

4.01

1,2,3-Triazoles

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4.01.1 INTRODUCTION

4.01.1.1 Historical

For the history of 1,2,3-triazoles and early reviews, see the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (84CHEC-I(5)669). 1,2,3-Triazoles and benzotriazoles have continued to

attract considerable attention in the past decade. An enormous number of publications and patents appear every year. The use of benzotriazole as a synthetic auxiliary in particular has been the focus of intensive studies since the start of the 1990s.

4.01.1.2 Relation to CHEC-I Chapter and Reviews

CHEC-I covered the literature to 1982. The second edition covers the literature from 1982 to early 1994. This chapter relates to Chapter 4.11 in CHEC-I. Section 4.01.3 (Structural Methods) in CHEC-I now becomes two different Sections (4.01.1.4 Theoretical Methods and 4.01.2 Experimental Structural Methods). Section 4.01.3 (Thermodynamic Aspects) is new. Sections 4.01.5–4.01.8 relate to 4.01.4 in CHEC-I. Sections 4.01.9 and 4.01.9 correspond to 4.01.4 in CHEC-I. Section 4.01.10 is new and 4.01.11 relates to 4.01.6 in CHEC-I.

The following are the most important reviews on 1,2,3-triazoles and benzotriazoles since 1982: <84JHC627, 84AHC(37)217, 84AHC(37)351, 86AHC(40)129, 88MI 401-01, 88BSB573, 90BSB281, 91T2683, 92AHC(53)85, 93AHC(56)49, 94MI 401-01, 94S445>.

4.01.1.3 Scope

This chapter covers literature published since 1982; early materials are included here only where needed as a basis for describing further developments or where not previously mentioned in CHEC-I <84CHEC-I(5)669>. The structural types surveyed here include 1,2,3-triazoles, benzotriazoles, their dihydro derivatives and carbocyclic fused compounds. Compounds with heterocyclic fused rings are not included. The nomenclature system was discussed in CHEC-I <84CHEC-I(5)670>.

4.01.1.4 Theoretical Methods

4.01.1.4.1 Semi-empirical methods

In the decade between 1985 and 1995, molecular orbital calculations using semi-empirical methods for 1,2,3-triazoles and benzotriazoles have received increasing interest. In particular, the semi-empirical methods AM1, PM3, and MNDO, have been widely used in theoretical calculations for 1,2,3-triazoles and benzotriazoles.

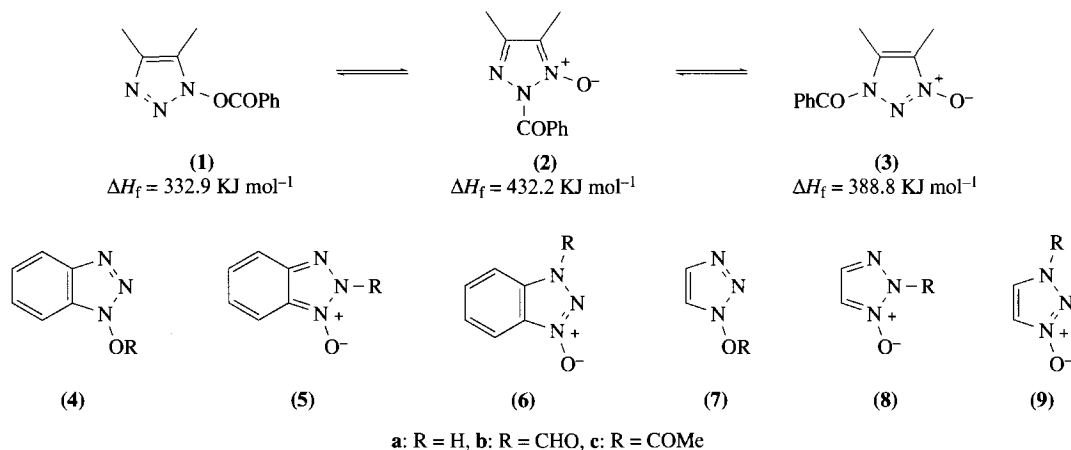
The reliability of semi-empirical methods (AM1, PM3, and MNDO) for the treatment of tautomeric equilibria has been tested in a series of five-membered nitrogen heterocycles, including 1,2,3-triazole and benzotriazole. The known tendency of MNDO to overestimate the stability of heterocycles with two or more adjacent pyridine-like lone pairs is also present in AM1 and to a somewhat lesser extent in PM3. Tautomeric isomers with a different number of adjacent pyridine-like nitrogens cannot be adequately treated by these semi-empirical methods. Both AM1 and PM3 represent major improvements over MNDO in the case of lactam–lactim tautomerism. The stability of *N*-oxides as compared to *N*-hydroxy tautomers is overestimated by the PM3 method. All three methods give reliable ionization potentials and dipole moments <90ZN(A)1328>.

Using AM1 methods, the relative stabilities of 1-benzoyloxy-4,5-dimethyl-1,2,3-triazole (**1**) and its corresponding *N*-acyl isomers have been obtained. Based on the heats of formations, the benzoyloxy structure (**1**) is more stable than the *N*-oxy forms (**2**) and (**3**) by 99.3 kJ and 55.9 kJ mol⁻¹, respectively <91JCR(S)104>. Prototropy of 1,2,3-triazol-1-ol has also been examined by the MNDO method <87MI 401-01>. Energy differences between 1-hydroxy-1,2,3-triazole and its *2H*- and *3H*-tautomers and the corresponding benzotriazole derivatives have been calculated by semi-empirical methods (AM1 and PM3). The results are shown in Table 1. The bond lengths and dihedral angles of these compounds are also calculated using AM1 and PM3. The PM3- and AM1-calculated energy differences of isomers (**4**), (**5**), and (**6**), and (**7**), (**8**), and (**9**) with various R groups (a, R = H; b, R = CHO; c, R = COMe) are mutually inconsistent (Table 1). AM1 predicts the isomers (**4**), whilst PM3 predicts isomers (**6**) to be the most stable. The errors in both methods are estimated by comparison with *ab initio* calculations. In almost all cases, the PM3 method yields results which are more reliable than AM1 <92JOC3698>. The AM1 semi-empirical method for calculating ΔH_f values of *N*-(α -aminoalkyl)benzotriazoles in nitromethane overestimates the stability of the N(1) isomers and does not accurately predict the order of ionization <93MI 401-01>. The PM3 method has been

compared with the AM1 method in the study of nitro-substituted 1,2,3-triazole and benzotriazole. The PM3 method is preferred over AM1 for the calculation of heats of formation. Adjacent lone pair–lone pair repulsion is better described at the PM3 level, although the PM3 method does not give the correct tautomeric predominance for the azoles <93MI 401-02>.

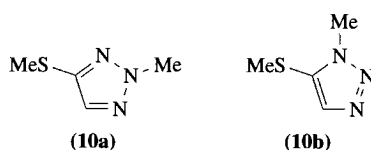
Table 1 Energies of substituted benzotriazoles and 1,2,3-triazoles and their relative stabilities (AM1 and PM3 results).

Structure	ΔH_f		Relative stabilities $\Delta\Delta H_f$	
	AM1	PM3	AM1	PM3
4a	106.1	81.8	0.0	0.0
4b	80.9	51.4	0.0	0.0
4c	76.2	43.3	0.0	0.0
5a	—	99.5	—	+17.7
5b	112.3	66.0	+31.4	+14.6
5c	—	58.1	—	+14.8
6a	121.9	82.2	+15.8	+0.4
6b	98.8	48.6	+18.9	-2.8
6c	89.6	39.4	+13.4	-3.9
7a	91.0	66.6	0.0	0.0
7b	67.6	36.0	0.0	0.0
7c	61.3	28.9	0.0	0.0
8a	107.1	74.8	+16.1	+8.2
8b	85.0	41.3	+17.4	+5.3
8c	79.9	33.1	+18.6	+4.2
9a	103.9	66.6	+12.9	0.0
9b	79.2	32.2	+11.6	-3.7
9c	72.4	24.0	+11.10	-4.9
1 <i>H</i> -1,2,3-triazole	86.4	67.9	0.0	0.0
2 <i>H</i> -1,2,3-triazole	92.3	70.7	+5.9	+2.8
1 <i>H</i> -benzotriazole	104.2	85.4	0.0	0.0
2 <i>H</i> -benzotriazole	117.0	93.2	+12.8	+7.8



A theoretical study of 1,1'- and 2,2'-bitriazole using the MNDO method with full optimization of the geometries shows the higher stability of orthogonal or near orthogonal conformations. The calculated dipole moments agree with experimental values <84CJC687>. MNDO calculations show that gaseous methylthiotriazoles (**10a**) and (**10b**) exist predominantly in a planar form for the (**10a**) isomer and in the nonplanar form for the (**10b**) isomer. The ΔH° for the rotameric equilibria is 2.7–4.2 kJ mol⁻¹ <83CJC1197>.

The reactivity and regioselectivity of the cycloaddition of 1-(*N*-phenacylidene)amino-1,2,3-triazoles with diphenyl nitrilimine (see Section 4.01.7.4) are examined on the basis of CNDO/2 calculations. The cycloaddition regioselectivity is HOMO_(dipole) controlled. The predominant orbital interaction shown in Figure 1 rationalizes the regioselective formation of 2*H*-1,2,3-triazoles



<90JHC735>. The polarizability and hyperpolarizability of 1,2,3-triazole have been computed by the Hartree-Fock perturbation theory on an extended basis CNDO method <90JPC1755>.

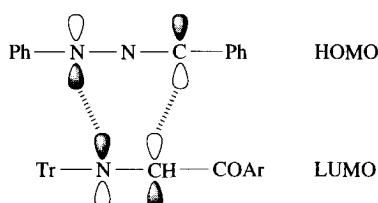


Figure 1 HOMO-LUMO Interaction between diphenylnitrilimine and 1-(N-phenylacylidene)aminotriazole.

INDO calculations with complete optimization of the geometries have been carried out on 1- and 2-aminotriazole and 1- and 2-aminobenzotriazole. The results are consistent with the available experimental evidence and provide a coherent picture of the conformation of the sp^3 amino group. Theoretical and experimental geometries of the amino groups of 2-aminobenzotriazole are listed in Table 2 <90JCS(P2)237>. The charge densities (atomic units) and the bond orders in the molecule of 2-phenyl-*N*-benzoyl-4,5-dimethyl-1,2,3-triazol-1-imine have been calculated by the MNDO method using bond lengths and angles obtained from x-ray analysis and are shown in Figure 2. The exocyclic nitrogen and oxygen carry considerable negative charge (-0.402 and -0.456) while C(2) is practically neutral. The significant contribution of N(4) atomic orbitals in the HOMO and C(2) atomic orbitals in the LUMO indicates that the molecule is a potential 1,3-dipole. From the bond order values it is concluded that there is significant electron delocalization in the triazole ring <92JOC2252>.

Table 2 Theoretical and experimental geometries of the amino groups of 2-amino-benzotriazole.

Bond lengths (Å)	Calc.	Exp.	Bond angles (°)	Calc.	Exp.
N(2)—N(8)	1.337	1.386	N(1)—N(2)—N(8)	119.5	121.1
N(8)—H(9)	10.72	0.897	N(3)—N(2)—N(8)	119.5	119.9
N(8)—H(10)	1.072	0.905	N(2)—N(8)—H(9)	110.8	109.0
			N(2)—N(8)—H(10)	110.8	110.1
			H(9)—N(8)—H(10)	107.9	115.2

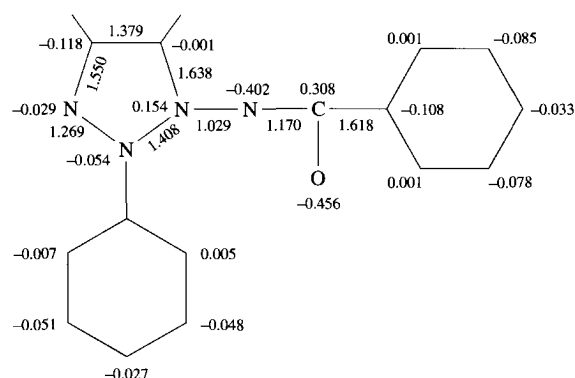


Figure 2 Charge densities and bond orders by MNDO method.

ASED (Atom Superposition and Electron Delocalization) molecular orbital calculations on the formation of monomeric 1-triazolylborane by the process $\text{BH}_3 + \text{triazole} \rightarrow \text{H}_2 + \text{H}_2\text{B(Tz)}$ indicate

that the reaction is energetically favorable and that the charge densities at the nitrogen atoms not involved in bonding to boron are essentially the same as those in the unsubstituted triazole. The calculated total energy for 1,2,3-triazol-1-ylborane is -506.70 eV and the energy change, ΔE , for the reaction is -0.78 eV. Molecular orbital calculations on the smoothed geometry of cyclo-tetrakis(triazolylborane) (see (184)) result in the highly symmetrical charge distributions and overlap populations shown in Figure 3 (91IC784).

For more semi-empirical molecular orbital calculations and comparison with experimental data, see Section 4.01.2. For MO calculations on aromaticity and tautomerization, see Section 4.01.3.

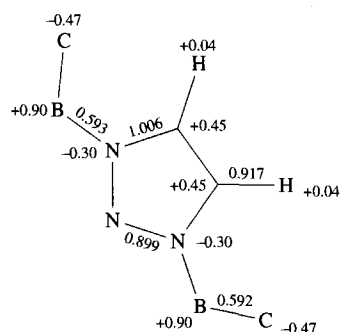


Figure 3 Calculated charge distribution and overlap populations for smoothed geometry of cyclo-tetrakis(triazolylborane).

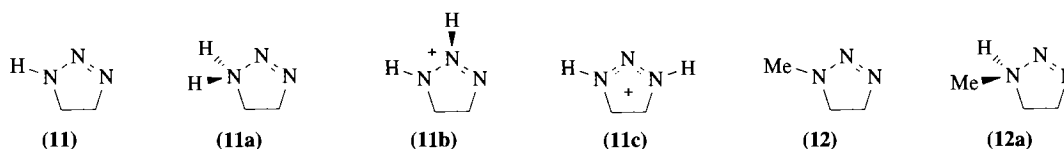
4.01.1.5 *Ab Initio* Methods

Fully optimized geometries have been calculated for the two tautomeric forms of 1,2,3-triazole at the Hartree-Fock SCF level employing a basis set of double zeta quality. The calculations show the 2H form to be the more stable, the energy difference being $\Delta E_{1H-2H} = -14.7$ KJ mol $^{-1}$ (88ACS(A)500). *Ab initio* molecular orbital calculations within the Hartree-Fock approximation have been used to investigate 1,2,3-triazoline (11) and related compounds. Moller-Plesset perturbation theory is used to study the effects of electron correlation on the energy of some configurations. Total energies calculated for neutral and protonated forms are listed in Table 3. The order of proton affinities for the various protonation sites is found to be $N_3 > N_1 \gg N_2$. No local minima are found in the region of the N_1 -protonated 1,2,3-triazoline at the 3-21G basis set level. Similar calculations are also performed on the neutral (12) and N_1 -protonated forms (12a) of 1-methyltriazoline (91JA7893). Hartree-Fock calculations with 3-21G(*) and 6-31G* basis have been performed to study the structure and energetics of Na^+ , K^+ and Al^+ -azole complexes. Structures have been fully optimized at the 3-21G(*) level. Calculated X^+ ($X = H, Li, Na, K, Al$) binding energies of 1,2,3-triazole show that cation association energies follow the sequence $Li^+ > Al^+ > Na^+ > K^+$, and all of them are much smaller than the corresponding protonation energies (92JPC3022).

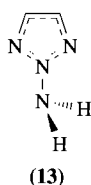
Table 3 Total energies calculated for neutral and protonated 1,2,3-triazolines.

Structure	SCF 3-21G	SCF 6-31G*	MP2 6-31G*	MP3 6-31G*	MP4(SDTQ) 6-31G*
1,2,3-triazoline (11)	-240.53891	-241.918832	-242.695354	-242.681168	-242.722110
N1-protonated (11a)	-240.90288 ^a	-242.258281	-242.996573	-243.021115	-243.063505
N2-protonated (11b)	-240.87511	-242.248118	-242.981686	-243.006938	-243.047585
N3-protonated (11c)	-240.91674	-242.286193	-243.016744	-243.041478	-243.080972
1-methyltriazoline (12)	-279.35591	-280.951644			
N1-protonated (12a)	-279.72077 ^a	-281.300788			

^a Unstable structure.



The geometries of four stationary structures of 2*H*-1,2,3-triazol-2-amine have been optimized with the 3-21G(N*) basis sets. The lowest energy and only equilibrium structure predicted by these calculations is the perpendicular C_s form (13). The NH-stretching vibrational frequencies and their spacing should be close to the corresponding values for 1*H*-pyrrol-1-amine. The calculations also suggest that the relative infrared (IR) intensity of the lower-frequency NH-stretching band for the structure (13) should be much greater than that of 1*H*-pyrrol-1-amine <89AJC433>. The equilibrium geometry and harmonic frequencies of 1,2,3-triazole anion have been calculated on three different levels: semi-empirical (MNDO), and *ab initio* (RHF/4-21G(N*) and MP2/6-31G*). The calculated harmonic frequencies are compared with FT-IR and FT Raman data. The results show that it is necessary to use a large basis set and to account for electron correlation. The absolute mean deviation between experimental and calculated MP2/6-31G* frequencies is found to be 2.9% <91JPC3119>. The equilibrium geometry and the harmonic force field of 1*H*- and 2*H*-triazole have also been calculated with MP2/6-31G* as the basis set. The rotational constants calculated from equilibrium geometries are consistent with experimental data of several isotopic species <91JPC3123>.



Ab initio calculations on the equilibrium between (14a) and (14b) are carried out with the 3-21G basis set. Figure 4 shows a plot of the calculated activation energy E_a vs. the reaction energy ΔE_r for the cyclization reactions. The plot is linear and provides a striking confirmation of Hammond's postulate. The cyclic structures (14b) are found to be planar, while the terminal =NH group in (14a) is ca. 50° out of the plane formed by the other atoms in (14a) <90CC882>. The gas phase basicity and acidity of 1,2,3-triazole have been calculated by *ab initio* methods (6-31G*//6-31G) and compared with experimental values <89MI 401-01>

For *ab initio* calculations on the aromaticity and tautomerization of 1,2,3-triazoles and benzo-triazoles, see sections 4.01.3.3 and 4.01.3.4.

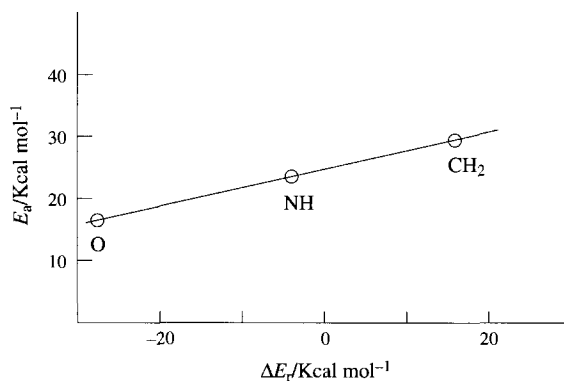
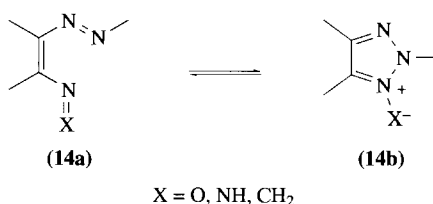


Figure 4 Plot of activation energy vs. reaction energy for the cyclization reactions.



4.01.1.6 Applications of molecular mechanics

A novel graph-theoretical approach based on the notion of ring-bond redistribution graphs (RBR graphs) has been used as a basis for the classification of a number of ring transformations in heterocycles, such as the Dimroth rearrangement. The vertices and edges of RBR graphs exclusively correspond to those atoms and skeleton bonds which are present in both the final and initial heterocyclic rings. Structurally similar reactions of the same level have the same RBR graphs and differ only by their labeling. This approach has been utilized in a computer program for the systematization of heterocyclic recyclization <93JA2416>.

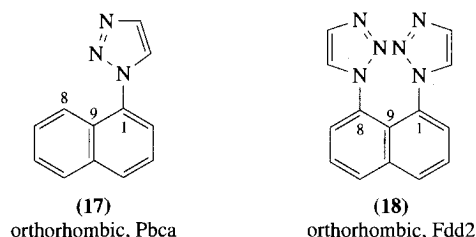
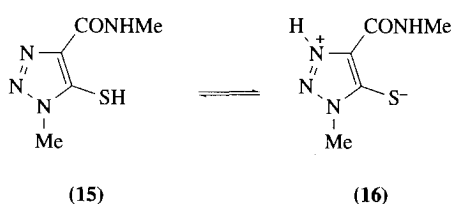
4.01.2 EXPERIMENTAL STRUCTURAL METHODS

4.01.2.1 X-Ray Analysis

Numerous 1,2,3-triazole and benzotriazole derivatives have had their crystal structures determined by x-ray since 1982. The structures of many triazoles and benzotriazoles discussed in the following sections have been determined by x-ray: (107–109), (169), (232) (R = naphthyl), (265), (276), (289), (420), (552), (566), (635) (R = Me), (636), (639), (674), (680), (682), (691), (700), (708), (718), (719), (770), (779).

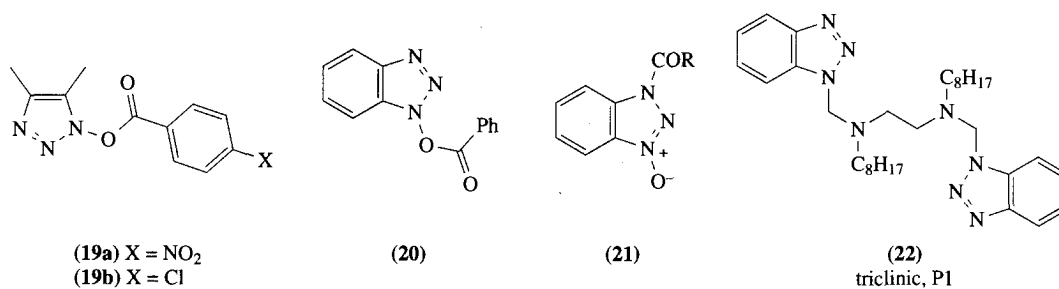
The experimental determination of geometry by x-ray has been carried out on 2-amino-benzotriazole with space group $P2_1/c$, $a = 11.590\ 0(5)$, $b = 4.603\ 1(8)$, $c = 12.559\ 1(8)$ Å, $\beta = 109.914(4)^\circ$. Disregarding the amino hydrogen atoms, the molecule is quite planar, with the amino group making an angle of $51(2)^\circ$ with the triazole ring. The amino hydrogen atoms are almost coplanar with the N(1) atom [N(1)—N(2)—N(8)—H(9)/H(10) = $135(2)/8(2)^\circ$] <86ICA235, 90JCS(P2)237>.

The x-ray data indicate a planar structure for the 5-thio-1*H*-1,2,3-triazole (15) with both an intramolecular hydrogen bond between sulfur and the hydrogen of the CONHMe group and a hydrogen attached to N(3) of the triazole ring, suggesting the mesomeric betaine structure (16) <93BSB1>. X-Ray analyses of 1-(1-naphthyl)-1*H*-1,2,3-triazole (17) and 1,1'-(1,8-naphthyl)di-1*H*-1,2,3-triazole (18) indicate that the naphthalene framework in (18) is distorted due to the steric repulsion between the two triazole rings <86AX(C)478>. The angle C(1)—C(9)—C(8) of (17) ($123.7(5)^\circ$) is significantly smaller than that of (18) (129.0°) because of less steric overcrowding in (17). The dihedral angle between the mean plane of the naphthalene ring and that of the triazole ring in (17) is $56.8(2)^\circ$. The crystal structure is stabilized mainly by van der Waals forces; the shortest intermolecular distance is 3.506 Å <87AX(C)147>.



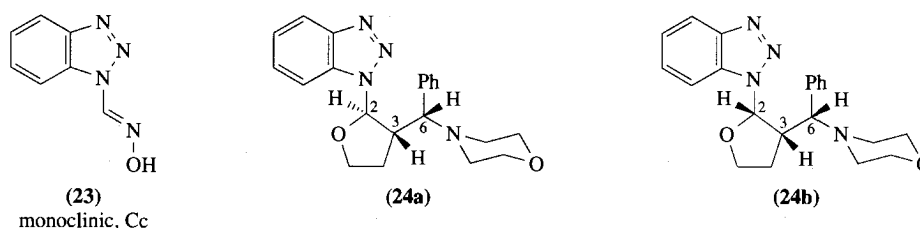
The isomerization between *N*- and *O*-acylated benzotriazol-1-ols and 1,2,3-triazol-1-ols has been extensively studied (see Section 4.01.7.1) in part by x-ray methods. The aroyl group position is established by x-ray crystallographic analyses because the *N*- and *O*-acylated forms are not readily distinguished by spectral methods. X-ray analyses of 1-(4-nitrobenzoyloxy)-1,2,3-triazole (19a) <93AX(C)49>, 1-(4-chlorobenzoyloxy)-1,2,3-triazole (19b) <88AX(C)1063>, and 1-benzoyloxy-benzotriazole (20) <77JCS(P2)224, 84LA1308> indicate that these compounds exist in the solid state as *N*-benzoyloxy esters. However, 3-acylbenzotriazole 1-oxides (21, R = Ar, R) are also isolated as demonstrated by x-ray analysis <85JOC2174, 88JOC205>. The space group of crystalline 3-(*N*^α-tritylmethionyl)benzotriazole 1-oxide is $P2_12_12_1$ <85JOC696>. *N*-(Dialkylaminomethyl)benzotriazoles exist as an equilibrium mixture of the 1- and 2-isomers in solution, but solely in the 1-substituted form in the crystalline state as proven by x-ray structural analysis of compound (22) <87JCS(P1)2673>.

The effect of the *N*-substituents on the geometry of the 1,2,3-triazole ring is studied by analyzing 35 x-ray crystal structures of substituted triazoles and benzotriazoles. The analyses employ least-squares estimation of parameters. Two models for the substitution effects on the endocyclic angles

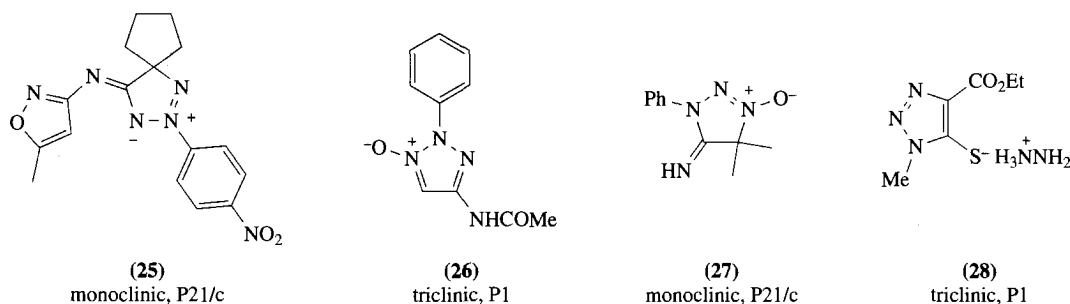


are analyzed. It is concluded that only the position of the *N*-substituent has a significant effect on the ring geometry (85ACS(A)259).

Benzotriazole-1-carbaldehyde oxime (**23**) is confirmed by x-ray analysis as the *trans* isomer, which exists in the solid state in an *anti* conformation about the N(1)—C(1) bond. The benzotriazole ring system is planar and is approximately coplanar with the oxime moiety. There is a system of intermolecular hydrogen bonding that interconnects the molecules in a three-dimensional network (93ACS167). The x-ray determination of 1,2-di(benzotriazol-1-yl)-1,2-diphenylethane reveals the structure to be the racemic isomer. The molecule exists in a staggered conformation with the pairs of phenyl rings and benzotriazole rings mutually gauche. The potential C₂ symmetry of the molecule is destroyed by small torsion angle differences. The phenyl and benzotriazole rings are all planar and exhibit normal bonding geometries (92JCS(P1)1111). The x-ray crystallographic data of compounds (**24a**) and (**24b**) confirms their structural and spectral assignments and also shows the configuration of the C(2), C(3) and C(6) atoms (92JOC4932).



Cyclotetrakis[dimethyl(1,2,3-triazol-1-yl)borane] crystallizes (see **184**) in the monoclinic space group C2/c. The individual molecules conform to C₂ symmetry; the symmetry axis passes through two of the four boron atoms. The space group of cyclotetrakis[dimethyl(benzotriazol-1-yl)borane] is P2₁/c with the individual molecules conforming to C_i symmetry (91IC784). The x-ray crystal structures of some mesoionic compounds (**25–28**) have been reported: (**25**) (90JCS(P1)2527); (**26**) (92TL7941); (**27**) (92MC131); (**28**) (89BSB415).



Structure and bonding in metal complexes of 1,2,3-triazoles and benzotriazoles have continued to receive much attention in the past decade. The solid-state structures of hydridotris(benzotriazol-1-yl)borate derivatives of group six metal carbonyls have been determined by x-ray diffraction, showing that the tridentate ligand contains the more hindered B—N bonds and that the metal coordination occurs at the 2-position of benzotriazole (89JOM(372)251). Diaqua-bis(1,2,3-triazole-4,5-dicarboxylato)copper(II) dihydrate crystallizes in the triclinic space group; the copper is in an elongated tetragonal geometry with equatorial coordination through two triazole nitrogens and two

water molecules <85ICA121>. Several benzotriazole and benzotriazolate complexes of rhodium have been studied by x-ray <85JOM(280)261>. The crystal structures of $\text{CdCl}_2(\text{BtH})_2$ and $\text{MnCl}_2(\text{BtH})_2$ were determined; octahedral coordination is completed by two metal—N(3) bonds with the plane of the benzotriazole ligand almost perpendicular to the plane of the metal and Cl atoms <84ACS(A)257>. For further x-ray crystal analyses of triazole and triazolate metal complexes, see the review by Moore and Robinson <88MI 401-01>.

4.01.2.2 Neutron and Electron Diffraction

The molecular structure and tautomer equilibrium of gaseous 1,2,3-triazole is determined by electron diffraction. The structural refinement of a planar C_{2v} model of the 2*H* tautomer is carried out based on the electron-diffraction data in combination with the measured rotational constants <88ACS(A)500>. 2-Methyl-4-trinitromethyl-1,2,3-triazole is studied by gas-phase electron diffraction. By using the valence force field, the mean amplitudes of the vibrations and shrinkage corrections are calculated. The geometrical parameters are obtained assuming C_{2v} molecular symmetry for the triazole ring (Table 4) <92JST(265)337>.

Table 4 Structural parameters of 1,2,3-triazoles by different methods.

<i>Molecule</i>	<i>C—C</i> (Å)	<i>C=N</i> (Å)	<i>N—N</i> (Å)	<i>Angle</i> (°) <i>N—N—N</i>	<i>Method</i>	<i>Ref.</i>
2 <i>H</i> -1,2,3-triazole	1.401(3)	1.347(3)	1.323(2)	117.3(2)	ED	88ACS(A)500
	1.406(2)	1.346(2)	1.323(1)	117.1(1)	ED-MW	88ACS(A)500
	1.413	1.317	1.349	114.05	<i>Ab initio</i>	88ACS(A)500
2-Me-4-C(NO ₂) ₃ -2 <i>H</i> -1,2,3-triazole	1.385(12)	1.358(5)	1.314(3)	117.6	ED	92JST(265)337
Derivatives of 1,2,3-triazole ^a	1.396	1.344	1.333	116.9	XD	85ACS(A)259

^a Average values for 1,2,3-triazole derivatives from x-ray diffraction data.

4.01.2.3 Microwave Spectroscopy

The microwave spectrum of the parent 1,2,3-triazole was interpreted in terms of the 1*H*-form <70SA(A)825>. The microwave spectrum of a highly enriched sample of *N*-deuterio-1,2,3-triazole was also assigned unambiguously, apparently to the 1-deuterio form <74CC605>. However, analysis of the microwave spectra of the parent molecule, the highly enriched ¹⁵N₃ species, and the *N*-deuterated derivative, reveals the molecule to exist as a mixture of two planar tautomers: a 1*H* form with C_s symmetry and a 2*H* form with C_{2v} symmetry. This is the first recorded microwave spectral line of the deuteriated 2*H* tautomer. The population ratio of the two tautomers, estimated from the analysis of the microwave spectrum of the triple ¹⁵N sample, is 1*H*:2*H* $\approx$ 1:1000 at room temperature. The dipole moments of the tautomers are measured as $\mu_{1H} = 4.38$ D and $\mu_{2H} = 0.218$ D for the 1*H* and 2*H* forms of the ¹⁵N₃ triazole, respectively <88ACS(A)500>.

The microwave spectra of 1*H*-benzotriazole and its *N*-D isotopomer have been studied in a heated cell. The molecule is planar. Due to the quadrupole coupling effects of the ¹⁴N nuclei, no hyperfine structures are observed. The dipole moment of benzotriazole obtained by microwave is 4.3 D, which is in agreement with the value determined in solution. The rotational spectrum is also assigned <93JSP(161)136>.

4.01.2.4 Molecular Dimensions as Summarized from Experimental Structural Methods

Table 4 presents molecular dimension parameters of 1,2,3-triazole and 2-methyl-4-trinitromethyl-2*H*-1,2,3-triazole based on electron diffraction (ED) data alone, joint analysis of electron diffraction and microwave spectral data (ED-MW), and *ab initio* calculations. The corresponding molecular dimensions of 1,2,3-triazoles in the crystalline state obtained by x-ray diffraction (XD) are the average values based on <85ACS(A)259>. Figure 5 shows the bond distances and angles of the crystal structure of 2-phenyl-4-chloro-1,2,3-triazole <84ACS(A)497>. As examples of 4,5-unsubstituted 1*H*-

and 2*H*-1,2,3-triazoles, the molecular dimensions of 1-picryl- and 2-picryl-1,2,3-triazole, obtained by x-ray <89JPC1000> are also summarized in Figure 5.

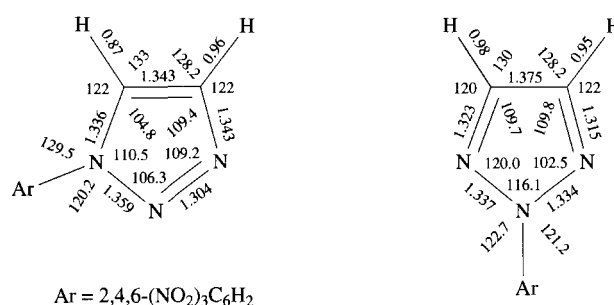


Figure 5 Molecular dimensions of 1,2,3-triazoles.

The corrected structural parameters of benzotriazole obtained from microwave spectroscopy are shown in Figure 6 <93JSP(161)136>. For comparison, the molecular dimensions measured by x-ray of crystalline benzotriazole-1-carboxamide <93ACS167> and 2-aminobenzotriazole, as an example of a 2-substituted benzotriazole, are listed in Figure 6 <90JCS(P2)237>.

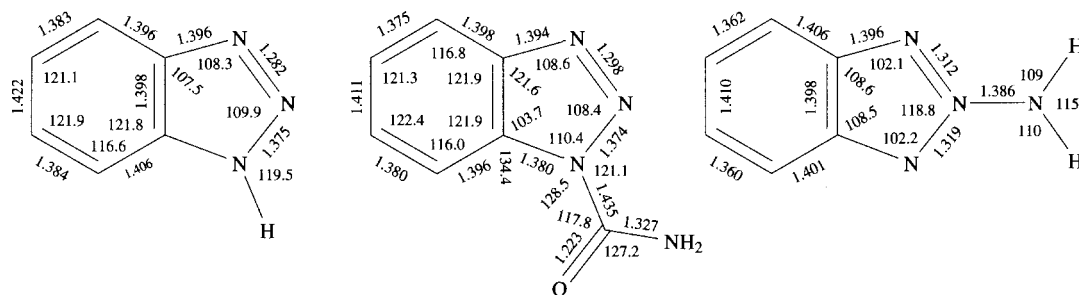


Figure 6 Molecular dimensions of benzotriazoles.

4.01.2.5 ¹H NMR Spectroscopy

The ¹H NMR spectral data of 1- and 2-substituted 1,2,3-triazoles have been described in detail in CHEC-I <84CHEC-1(5)678>. Some further data are summarized in Table 5. The ¹H NMR spectra of a large number of *N*-substituted benzotriazoles have been recorded. Spectral parameters for some benzotriazole ring protons are listed in Table 6. The electron-withdrawing groups generally shift all four benzotriazole ring protons downfield; however, the effect on 7-H is greater. The 7-H signals of 1-tritylbenzotriazole and 5,6-dimethyl-1-tritylbenzotriazole appear far upfield at δ 6.43 and δ 6.11, respectively. This suggests 7-H is in the shielding zone of one of the phenyl rings because of steric crowding <90JCS(P2)2059>. Solvent and temperature effects on the chemical shifts of benzotriazole ring protons have also been reported <89H(28)1121>.

Table 5 Proton NMR spectral data for triazoles (δ , ppm).

Substituent	Solvent	4-H	5-H	NH	R	Ref.
1-picryl	CD ₃ COCD ₃	8.29	8.98		9.33	89JPC1000
2-picryl	CD ₃ COCD ₃	8.23	8.23			89JPC1000
4-methoxyethyl	CDCl ₃		7.72	14.3		89CB911
1-CN	neat	8.18	7.27			67JA4760
4-COPh	CDCl ₃		8.39	16-10(br)		92JHC1203
4-SPh	CDCl ₃		7.69	15-10(br)		92JHC1203

The ¹H NMR spectra of 4,5-unsubstituted 1-alkyl-1,2,3-triazolines show two triplets for the CH₂ groups of C(4) and C(5) at ca 3.0 ppm and 4.1 ppm with rather large coupling constants ($J \approx 11$ Hz) <93JOC2097>. For 1-aryl-5-amido-1,2,3-triazolines, the 4-CH₂ protons appear as a multiplet and

Table 6 Proton NMR spectral data for *N*-substituted benzotriazole (δ , ppm).

Substituent	4- <i>H</i>	5- <i>H</i>	6- <i>H</i>	7- <i>H</i>	<i>R</i>	Ref.
1-Me	8.02	7.47	7.47	7.35	4.25	91RTC369
2-Me	7.85	7.34	7.34	7.85	4.50	91RTC369
1-Bu ^t	8.09	7.36	7.44	7.40	1.88(9H)	93H(36)1253
2-Bu ^t	7.88	7.36	7.36	7.88	1.83(9H)	93H(36)1253
1-CH ₂ Ph	8.04	^a	^a	^a	5.81, 7.40–7.20	90JCS(P2)2059
2-CH ₂ Ph	7.85	7.34	7.34	7.85	5.85, 7.40–7.30	90JCS(P2)2059
1-CPh ₃	8.05	^a	7.06	6.43	7.32–7.10	90JCS(P2)2059
2-CPh ₃	7.87	7.32	7.32	7.87	7.32–7.16	90JCS(P2)2059
1-CO ₂ Et	8.14	7.65	7.49	8.11	1.58, 4.70	93JPO567
1-CO ₂ Ph	8.18	7.52	7.48	8.14	7.48–7.27	93JPO567
1-CO ₂ NH ₂ ^b	8.25	7.71	7.54	8.19	8.31, 8.60	93ACS167
1-CN	8.23	7.64	7.64	7.8–7.9	–	91RRC573
1-CH ₂ Br	8.11	7.46	7.62	7.68	6.42	93ACS167
1-B(NMeR ₂) ₂	8.10	7.50	7.37	7.62	3.46, 2.68	90IC4693
1-CH ₂ CO ₂ H ^b	8.08	7.58	7.43	7.87	5.68	93T10205
1-CH=CHBt ^b	8.25	7.68	7.50	8.13	8.82	90JHC1543
1-CH(SiMe ₃)OMe	7.92	7.25	7.32	7.54	5.50, 3.18, 0.01	91JCS(P1)3295
1-SO ₂ Me ^b	8.30	7.83	7.65	8.02	3.87	92T7817
1-COMe	8.20	7.59	7.46	8.06	3.00	92T7817

^aOverlapped with signals of R group. ^bIn DMSO-*d*₆, all others in CDCl₃.

the ring 5-*H* as a doublet of doublets (92JOC3075). The ¹H NMR spectral data and detailed assignments of 5-amino-1-(2-nitroaryl)-1,2,3-triazolines (92JCS(P1)2709) and 4,5-dihydro-4-methylene-5-morpholinotriazole (86JCR(S)132) have also been reported.

NOE difference spectroscopy has been used for the unambiguous discrimination between H(4) and H(5) signals in 1-substituted 1*H*-1,2,3-triazoles (91T9783, 92JHC1203) and in the differentiation between regioisomeric 1,4-, 1,5- and 2,4-disubstituted 1,2,3-triazoles (Figure 7). The NOE experiment also supports the literature assignments with $\delta(H(5)) < \delta(H(4))$ in CDCl₃ and $\delta(H(5)) > \delta(H(4))$ in DMSO-*d*₆ for 1-substituted 1,2,3-triazoles (91T9783). The NOE method for discriminating between isomeric disubstituted 1,2,3-triazoles is illustrated by compounds (29)–(31). Simple NOE experiments allow the identification of (29); with this isomer only, an NOE enhancement of the triazole-*H* singlet is observed upon irradiation of the benzyl CH₂ group. Compound (30) can be distinguished from (31) by a moderate NOE enhancement between the NCH₂ and the ester group. NOE experiments have also been used to distinguish between isomeric benzotriazole derivatives (32) and (33) by irradiating the NH₂ group in (32) and the SO₂NH substituent in (33). Irradiation of the CH₃ group (2.46 ppm), in addition to the use of spin decoupling technology, was used to distinguish between (34) and (35) (92JOC190).

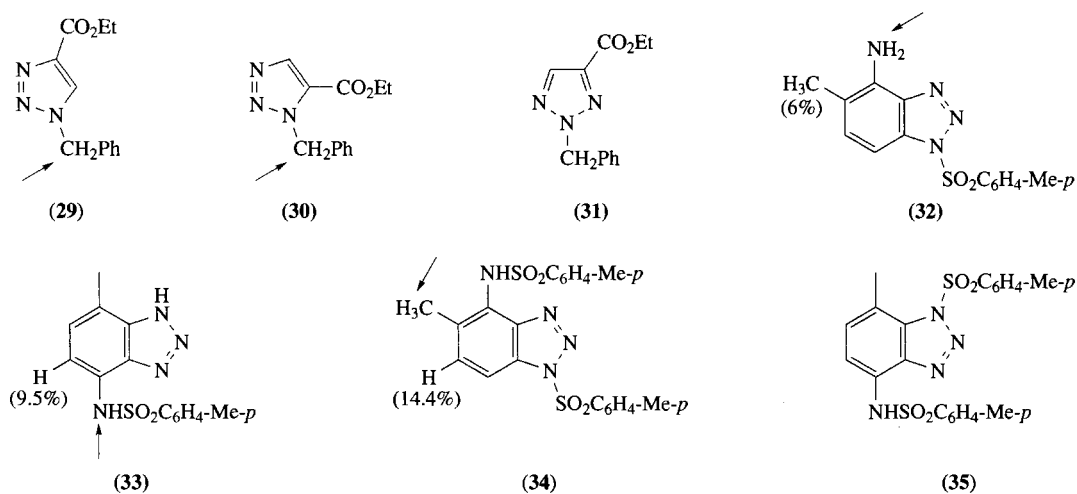
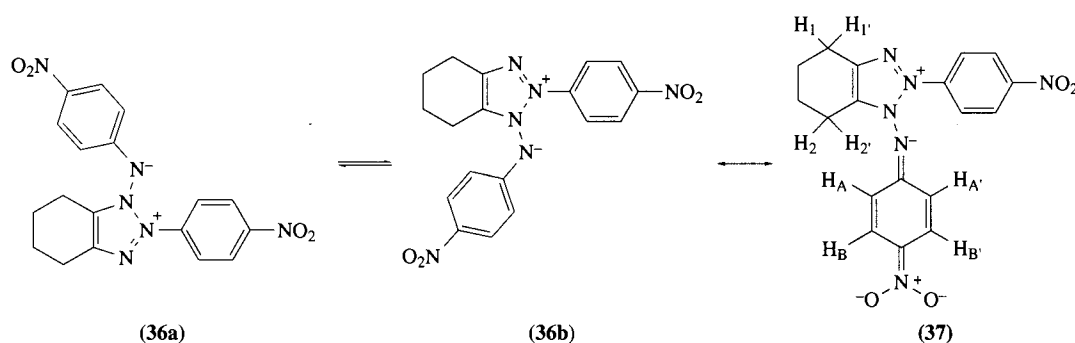


Figure 7 NOE Enhancement experiments (arrowed protons are irradiated and figures in parenthesis indicate NOE enhancement).

Variable-temperature NMR is a useful technique for studying rotational barriers and tautomeric equilibria. The rotation around the C—N bond between the dimethylamino group and the naphthalene ring in 1-(8-dimethylamino-1-naphthyl)-1*H*-1,2,3-triazole at 25°C gives rise to two sharp signals for the *N*-methyl protons ($\delta = 1.96$ ppm and 2.43 ppm), indicating nonequivalence of the two *N*-methyl groups. As the temperature is increased, line broadening occurs followed by coalescence at 371 K. At 393 K, the *N*-methyl signals become one peak. The activation parameters for internal rotation are $\Delta H^\ddagger = 63.7$ kJ mol⁻¹, $\Delta S^\ddagger = -26$ J mol⁻¹, $\Delta G^\ddagger = 73.2$ kJ mol⁻¹ <89CL939>. A degenerate rearrangement involving rapid exchange of aryl rings (**36a** $\rightleftharpoons$ **36b**) is studied by variable-temperature NMR between 120 and -83°C . A single exchange-narrowed AA'BB' spectrum for aromatic rings and an averaged signal for H₁H_{1'} and H₂H_{2'} is observed. As the temperature is lowered the signals are broadened. The coalescence temperature is 40°C and the rate of exchange at this point is 20 s⁻¹ in DMSO. By -46°C the exchange is frozen out and the spectrum is of form (**36b**) with two separate AA'BB' systems and two separate signals for H₁H_{1'} and H₂H_{2'}. Restricted rotation of the *N*-aryl bond in form (**37**) is also found at lower temperatures (-50 to -83°C) <87JCR(S)332>. The equilibrium between 1- and 2-(*N,N*-dialkylaminoalkyl)benzotriazoles has also been studied by variable-temperature ¹H NMR. The equilibrium constants, associated free energies for the equilibria, and free energies of activation for the isomerization, are calculated based on the coalescence (see also tautomerism, section 4.01.3.4) <89H(28)1121>. The low-temperature 300 MHz spectrum of 1,2,3-triazole in CD₂Cl₂ has been used in the study of tautomerism to determine the ratio of *s*- and *v*-tautomers. The rates and parameters of activation for this prototropic shift are also measured by NMR <84JCS(P2)1025>.



4.01.2.6 ¹³C NMR Spectroscopy

A large number of ¹³C chemical shifts of *N*-substituted 1*H*-1,2,3-triazoles, 2*H*-1,2,3-triazoles, 1*H*-benzotriazoles and 2*H*-benzotriazoles have been described. Some of these are listed in Table 7. As for the ¹H chemical shifts, *N*-substituents have little effect on the ¹³C chemical shifts of triazoles and benzotriazoles with a few exceptions. *N*-SnR₃ substituents exchange readily occurs between the different nitrogens of azoles. There is a parallelism with annular metallotropy; thus the chemical shifts of 1-tri-(*n*-butylstannyl)benzotriazole are quite different from others <88MRC134>. 1-Trifluoromethylsulfonyl-1,2,3-triazole does not exist as named but as its open-chain isomer, the diazoimine. Thus, the chemical shifts of C(4) and C(5) are 64.6 ppm and 172.6 ppm, respectively <88MRC134>. This is the normal behavior of 1-substituted 1,2,3-triazoles with strong electron-withdrawing groups, such as 1-cyano-1,2,3-triazole <81BSB615>. A multiple correlation analysis is carried out along with other azoles, and all give good correlation <88MRC134>. The C(4) and C(5) ¹³C chemical shifts of 1-alkyl-1,2,3-triazolines appear between 41–48 ppm and 63–66 ppm, respectively <93JOC2097>.

Some carbon-13 chemical shifts of benzotriazoles polysubstituted at both *N*- and *C*-atoms of the benzotriazole ring are listed in Table 8. They are generally assigned by comparison to literature values and by careful selective decoupling experiments. The contribution of *C*-substituents to the chemical shifts of benzotriazoles is much large than that of *N*-substituents.

¹³C NMR studies of various heteroaromatic nitriles, including 1*H*-1,2,3- and 2*H*-1,2,3-triazolyl nitriles, reveal a correlation between a value derived from the chemical shifts, δ_{CN} and $\delta_{\text{C-CN}}$, and the reactivity of nitriles in forming the corresponding enaminoketones via reactions with the enolate anion of acetone. Based on the correlation, a new reactivity index γ is proposed <82H(19)221>.

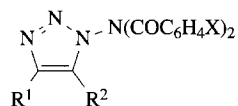
Table 7 ^{13}C Chemical shifts of *N*-substituted 1,2,3-triazoles and benzotriazoles.

Substituent	2H-triazole	1H-1,2,3-triazole			1H-benzotriazole						2H-benzotriazole		
	C-3,4	C-4	C-5	C-4	C-5	C-6	C-7	C-3a	C-7a		C-4(7)	C-5(6)	C-3a(7a)
Me	133.8	133.6	124.1	119.3	123.4	126.8	108.8	145.5	133.1		117.5	125.9	144.3
CH ₂ Ph	134.3	133.9	123.2	120.0	123.9	127.4	109.7	146.3	132.7		118.1	126.3	144.6
CH ₂ OH	135.0			120.0	124.5	128.1	109.8	146.3	132.5				
Ph	135.2	134.1	121.5	119.6	128.6	128.6	110.8	125.7	131.7		118.2	127.6	144.4
4-NO ₂ C ₆ H ₄	138.0	135.2	121.6	120.1	125.4	129.5	111.3	146.2	131.6		118.4	128.5	145.4
COMe	138.1	134.2	121.1	119.0	125.8	130.0	114.1	146.0	130.7				
CO ₂ Me	138.0	133.7	123.9	120.2	125.6	130.0	113.1	145.6	131.5				
NH ₂				119.2	124.0	127.2	110.6	144.1	132.5		116.4	125.0	141.9
NO ₂				121.3	127.5	132.7	112.4	144.3	127.0				
OMe		132.3	116.9	119.7	125.0	128.4	109.2	143.0	126.4				
SiMe ₃	135.9			119.8	123.4	127.0	111.1	146.6	137.8				
SO ₂ CF ₃		64.6	172.6	121.7	127.5	132.2	111.9	145.7	132.2				
Cl				120.5	125.1	129.3	109.3	144.1	134.1				
SnBu ₃	128.7			115.2	124.0	124.0	115.2	142.0	142.0				

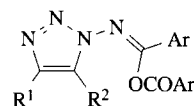
Table 8 ^{13}C Chemical shifts of polysubstituted benzotriazoles.

Substituents	C-4	C-5	C-6	C-7	C-3a	C-7a	Ref.
1,4,7-Me ₃	128.2	123.6	128.2	117.7	146.5	132.7	85H(23)2225
2,4,7-Me ₃	125.5	125.5	125.5	125.5	145.0	145.0	85H(23)2225
1H-5,6-Me ₂	119.8	123.8	127.2	109.1	144.2	133.1	93JPO567
2H-5,6-Me ₂	117.7	126.2	126.2	117.7	144.2	144.2	93JPO567
1,5,6-Cl ₃ -4,7-Me ₂	128.3	129.6	134.4	117.7	142.6	131.1	85H(23)2225
1-CO ₂ Me-5,6-Me ₂	124.5	131.4	131.4	124.5	143.6	143.6	85H(23)2225
1-CPh ₃ -5,6-Me ₂	119.0	133.3	136.8	113.0	145.7	133.4	90JCS(P2)2059
2-CPh ₃ -5,6-Me ₂	117.2	136.8	136.8	117.1	143.0	143.0	90JCS(P2)2059
1-CH(Ph)N(CH ₂) ₅ -5-NO ₂	116.9	144.2	122.8	110.7	144.4	136.4	89H(28)1121
1-OCOPh-6-NO ₂	119.8	121.7	147.7	105.9	128.3	145.4	91JCS(P2)1545

The ^{13}C NMR spectra of 1-(*N,N*-diaroyl)amino-1,2,3-triazoles (**38**) show that a methyl group at the 5-position ($\text{R}^2 = \text{CH}_3$) causes a downfield shift of 9.1 ppm for C(5) and an upfield shift of 1.4 ppm for C(4) with respect to the unsubstituted ($\text{R}^1 = \text{R}^2 = \text{H}$) parent molecule. For $\text{R}^1 = \text{R}^2 = \text{CH}_3$, both C(4) and C(5) are deshielded by 6.5 ppm and 5.0 ppm. In the 4-aryl-5-methyl derivatives, the aryl ring causes a downfield shift of 11.0 ppm for C(4) and an upfield shift of 4.0 ppm for C(5) with respect to the 5-methyl derivatives <85MRC585>. The chemical shifts of C(4) and C(5) in the triazole ring of 1-(α -aroyloxyarylideneamino)-1,2,3-triazoles (**39**) and the substituent effects are similarly described. The location of the methyl group at the 4- or 5-position can also be deduced from the carbon–proton coupling values involving C(4) and C(5) as well as CH₃(4) and CH₃(5) <84JHC1169>.



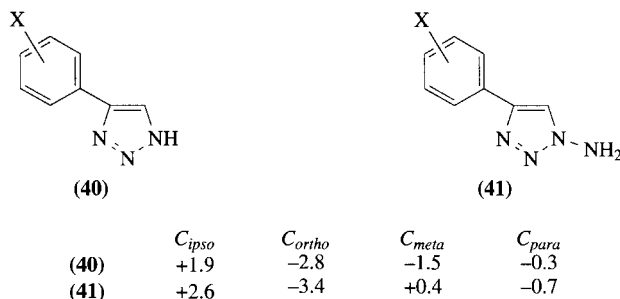
(38)



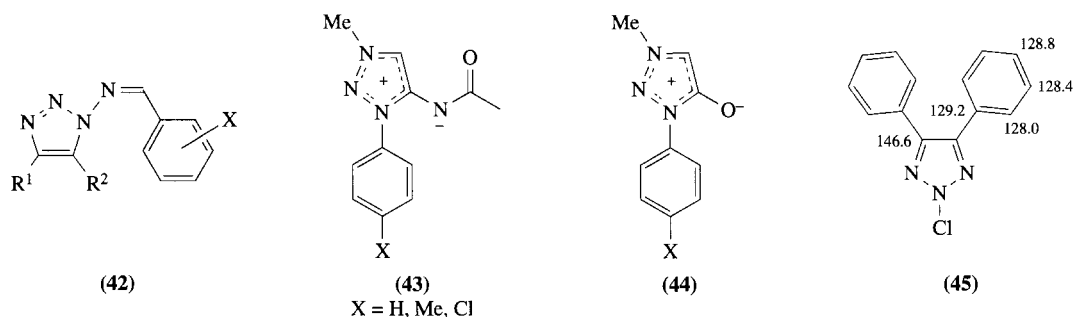
(39)

The effects of the 1,2,3-triazole and 1-amino-1,2,3-triazole heterocycles on the chemical shift of the carbon atoms in the phenyl ring of compounds (**40**) and (**41**) ($\text{X} = \text{H}$) are compared with the value for benzene. With regard to the effects of substituent X (*para* and *meta*) on the 1,2,3-triazole carbons, C(4) is deshielded by electron-withdrawing groups, whereas C(5) is shielded. Reasonable correlations with Hammett σ values are observed for the chemical shifts of both C(4) and C(5) of (**41**) <86MRC53>. The chemical shifts of C(4) and C(5) in 5-amino-1-aryl-1,2,3-triazoles are shifted upfield by ≈ 2 –5 ppm compared with the corresponding 5-anilino-1,2,3-triazoles. In 5-anilino-

triazoles, C(6) is shifted downfield by ca. 9 ppm ($-I$ effect), whereas C(7) and C(9) are shifted upfield by ≈ 7 –10 ppm, respectively ($+M$ effect) <86MRC809>.



The long-range influence of substituents on ^{13}C chemical shifts of triazole and $\text{C}=\text{N}$ carbon atoms in 1-(*N*-arylidene)amino-1,2,3-triazoles (42) is examined and a correlation between their δ values and net charge densities ($q_{\pi+\sigma}$) calculated by the CNDO/2 method is found. Thus, various carbon resonances, δ_{C} , can be expressed in relation to the calculated carbon net charge densities with δ_{C} (ppm) = $a \cdot q_{\pi+\sigma} + b$ where a and b are constants. The dependence of the coupling constants $^1J(\text{CH})$ for $\text{C}=\text{N}$ carbons on the substituents is better correlated using electron in bond values instead of charge densities <88JHC1161>. Similar correlations of ^{13}C resonances in mesoionic 1,2,3-triazol-4-ylacetamides (43) and 1,2,3-triazol-4-ones (44) with net charge densities are obtained <85MRC842>.



A ^{13}C NMR study of *N*-chloro derivatives of 4,5-diphenyl-1,2,3-triazole and 5,6-dichloro-4,7-dimethylbenzotriazole reveals that neither a rapid chlorotropy nor a slow chlorine equilibration takes place. The chlorination product of 4,5-diphenyl-1,2,3-triazole is (45); the ^{13}C NMR spectrum is assigned as shown <85H(23)2225>. The ^{13}C NMR spectra of 5-hydroxy- and 5-thio-1H-1,2,3-triazoles and their N(3) methylated and O/S alkylated derivatives have been analyzed, the results are summarized in Figure 8. The OH group exerts a downfield shift of 30.7 ppm on C(5) and an upfield shift of 18 ppm on C(4), while the SH group shifts both C(4) and C(5) downfield by 2.8–2.9 ppm. The two bond coupling constant (J^2) between C(5) and H(4) is diagnostic for 5-substituted triazoles <89ZN(B)587, 90BSB1007>. The ^{13}C chemical shifts of 1-ethyl-1,2,3-triazolium-3-dicyanomethylide and the analogous benzotriazole derivative are similar to those of the *N*-methyl quaternary salt <85MRC111>. The ^{13}C NMR assignments of an example of a (1,2,3-triazol-4-yl)iodonium salt are also shown in Figure 8 <92T3527>.

The ^{13}C chemical shifts of benzotriazole in the solid state are obtained using the CP-MAS technique. The chemical shifts are slightly different from those observed in DMSO-d_6 or CDCl_3 <83H(20)1713>. CP-MAS ^{13}C NMR spectroscopy is a powerful tool which enables determination of the tautomeric structure of benzotriazole in the solid state. Thus, the solid-state ^{13}C NMR spectra of some *N*-(dialkylaminomethyl)benzotriazoles support the existence of only the N(1) isomer <87JCS(P1)2673>.

4.01.2.7 ^{14}N and ^{15}N NMR Spectroscopy

^{14}N NMR spectroscopy has been described in some detail in CHEC-I <84CHEC-I(5)682>; however, no ^{15}N NMR spectra of 1,2,3-triazoles were reported before 1982 <84CHEC-I(5)684>. Since that time, ^{15}N NMR spectroscopy has been widely applied to triazole and benzotriazole compounds.

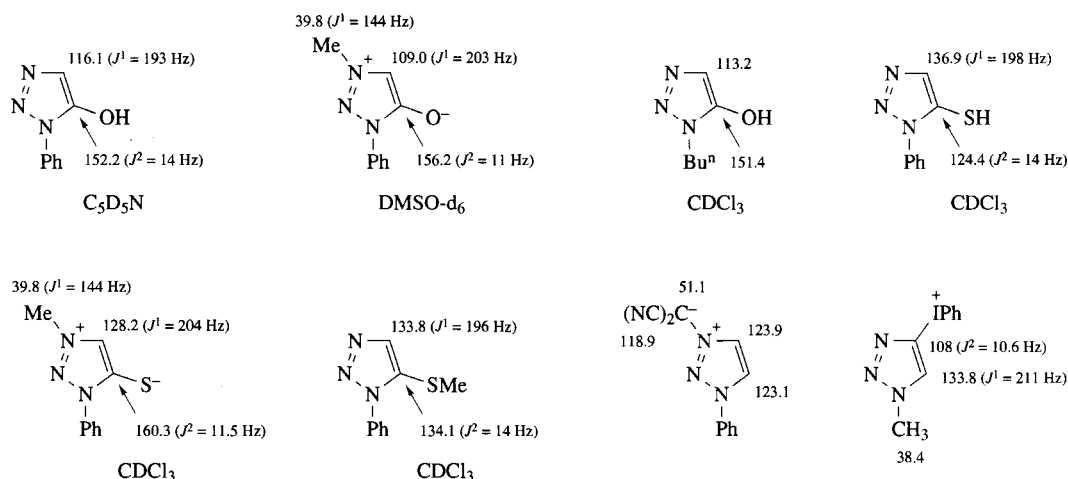
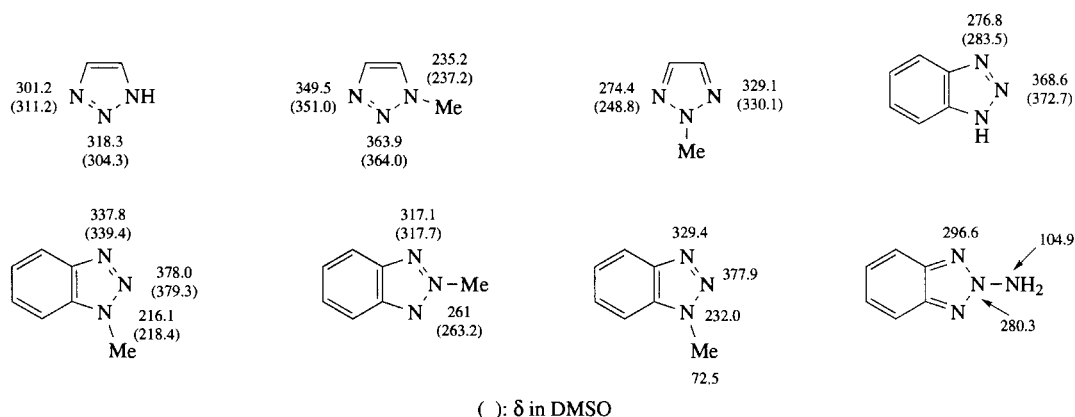


Figure 8 The ^{13}C chemical shifts of some 1,2,3-triazoles.

^{15}N NMR spectra of 1-methyl-1*H*- and 2-methyl-2*H*-1,2,3-triazole, 1-methyl- and 2-methyl-benzotriazole are measured at a standard concentration in a common solvent (0.5 M DMSO with a 0.01 M increment of $\text{Cr}(\text{acac})_3$ for each nitrogen atom present) to minimize the solvent effects on nitrogen nuclear shieldings. Signal assignments are assisted by the comparison with ^{14}N line widths, the use of $^2J(^{15}\text{N}^1\text{H})$ couplings, and shielding calculations obtained by the INDO/S-SOS approach. The shielding of pyrrole-type nitrogen is greater than that of pyridine-type nitrogen. When the pyridine-type nitrogen atom is connected to the pyrrole-type nitrogen atom, it is deshielded. Thus, the order of shielding in 1-methyl-1,2,3-triazole and 1-methylbenzotriazole is $\text{N}(1) \gg \text{N}(3) > \text{N}(2)$, and in the 2-methyl isomers, $\text{N}(2) > \text{N}(1)(\text{N}(3))$ $\langle 84\text{OMR}(22)215 \rangle$. The ^{15}N NMR chemical shifts of 1,2,3-triazole and benzotriazole and their *N*-methyl derivatives are determined in CDCl_3 and in DMSO with respect to external nitromethane and are corrected to external ammonia by the addition of 380.2 ppm. Solvent effects on chemical shifts are significant, particularly for unsubstituted triazole and benzotriazole. The large downfield shift of the pyridine-type nitrogen atoms is attributed to a large paramagnetic shielding term associated with the nonbonding electron pair. The detailed assignments are listed in Figure 9. The mole fractions of the prototropic tautomers can be obtained from the ^{15}N chemical shifts of the NH tautomers and the corresponding *N*-methyl derivatives. By this method, the average mole fraction for the 2-NH tautomer of benzotriazole is 0.02 in both CDCl_3 and DMSO, and that of 1,2,3-triazole is 0.34 in CDCl_3 and 0.55 in DMSO $\langle 82\text{JOC}5132 \rangle$.



(): δ in DMSO

Figure 9 The ^{15}N chemical shifts of 1,2,3-triazoles and benzotriazoles.

The ^{15}N chemical shifts and $^1J(^{15}\text{N}-^1\text{H})$ coupling constants of 1-amino- and 2-aminobenzotriazole in DMSO solution have been reported and the ^{15}N assignments are shown in Figure 9. There is a correlation between the ^{15}N chemical shifts of *N*-aminoazoles and *N*-methylazoles $\langle 90\text{JCS}(P2)237 \rangle$.

^{15}N NMR spectroscopy has been used to study the rearrangement of 1-benzoyloxybenzotriazoles to 3*H*-benzotriazole 1-oxides <85JOC2174>. The ^{15}N NMR spectrum of 1-(2-methylbenzoyloxy)-benzotriazole is recorded and the ^{15}N chemical shifts are close to that of 1-hydroxybenzotriazole, providing strong evidence for the structure <91JCS(P2)1545>, whereas the ^{15}N NMR spectra of 3-sorbylbenzotriazole 1-oxide and methyl β -methyl-3-benzotriazolepropionate 1-oxide show different chemical shifts (Figure 10) <85JOC2174>.

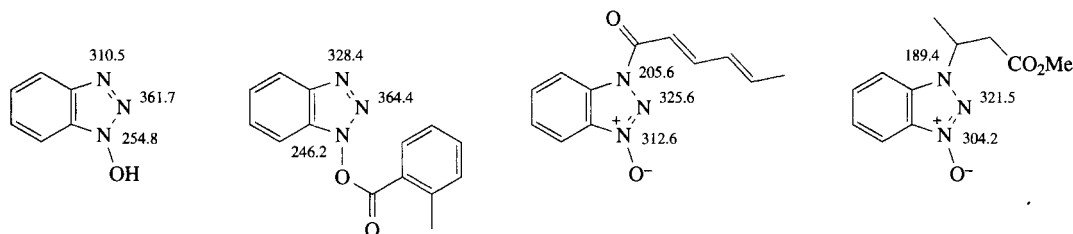


Figure 10 The ^{15}N signal assignments of 1-benzoyloxybenzotriazoles and benzotriazole-1-oxides.

A number of 5,5-dialkyldihydro-4*H*-1,2,3-triazole-4-ones and 5-amino-4,4-diphenyl-4*H*-1,2,3-triazoles have been studied by ^{15}N NMR spectroscopy. Their ^{15}N chemical shifts (corrected to the external standard of ammonia) are listed in Figure 11 <93CB103>. The ^{15}N NMR spectra of triazole and benzotriazole boron derivatives have been reported <89IC4022>. 4-(1-Azido-1-methylethyl)-1*H*-1,2,3-triazole shows ^{15}N chemical shifts (D_2O /pyridine, MeNO_2 external standard): δ – 284.6 (N α), δ – 161.5 (N γ), δ – 135.8 (N β), δ – 93.4, δ – 79.2, and δ – 60.4 ppm <89CB911>.

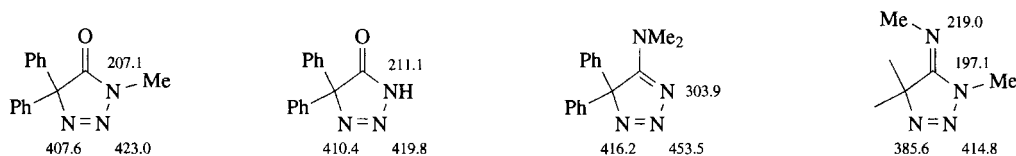
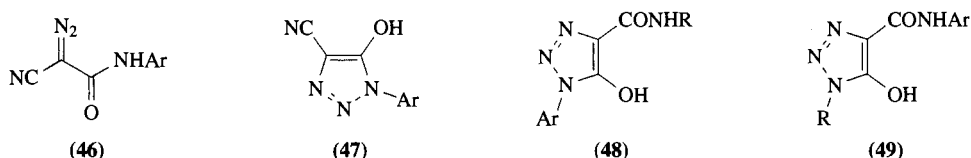


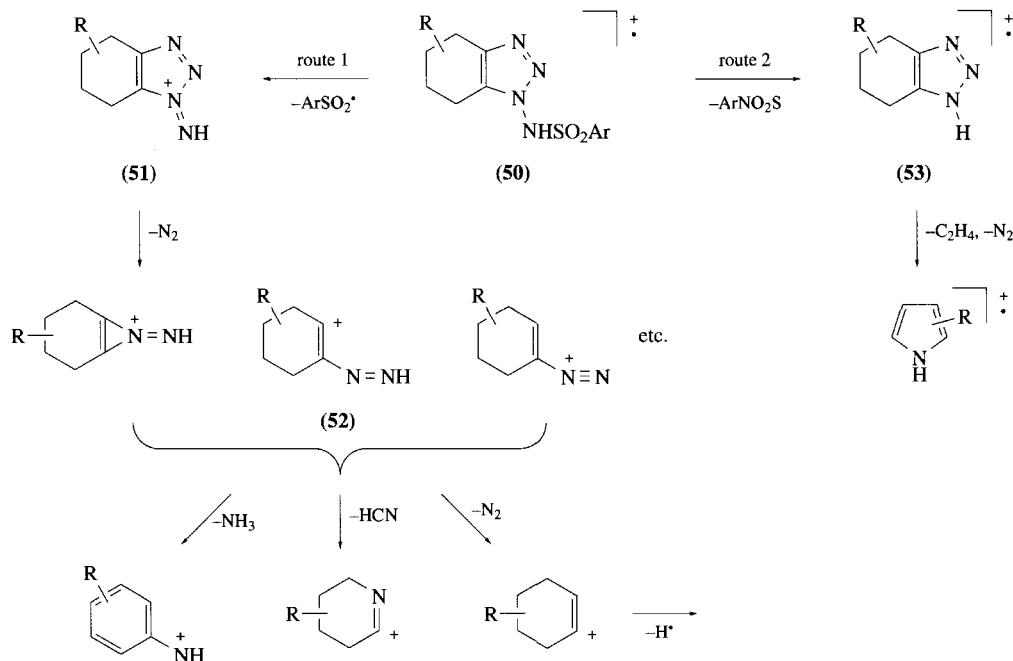
Figure 11 The ^{15}N chemical shifts of 5,5-dialkyldihydro-4*H*-1,2,3-triazole-4-ones.

4.01.2.8 Mass Spectrometry

The mass spectra of substituted 1,2,3-triazoles and benzotriazoles have continued to receive much attention since the mid-1980s. Mass spectroscopy has shown that 2-diazo-2-cyanoacetamides undergo cyclization in the presence of bases to form 4-cyano-5-hydroxy-1,2,3-triazoles. Thus, a simple comparison of the mass spectra of *N*-aryl-2-diazo-2-cyanoacetamides (**46**) and 1-aryl-4-cyano-5-hydroxy-2-triazoles (**47**) shows their identity and rationalizes the transformation of their $\text{M}^{+\bullet}$ ions into a common structure. The loss of nitrogen from both $\text{M}^{+\bullet}$ followed by fragmentation to the same ion peaks is clearly observed <88OMS(23)825>. The mass spectra of the isomeric 5-hydroxy-1,2,3-triazole-4-carboxamides (**48**) and (**49**) are characterized by the same array of common fragments with similar relative abundances. The spectra of the metastable ions are also almost identical. The structural changes in $\text{M}^{+\bullet}$ result in the complete transformation of one isomer into another. The main decomposition pathways of $\text{M}^{+\bullet}$ are the loss of nitrogen and a rearrangement leading to the molecular ion of a substituted aniline <90AJC2021>.



Unlike simple 1,2,3-triazoles, 1-sulfonylaminotriazoles (**50**) exhibit molecular ions of low abundance. The fragmentation of the fused triazoles follows two main pathways (Scheme 1). The first is initiated by the loss of an arylsulfonyl radical to give cation (**51**), which then eliminates nitrogen giving ions (**52**) followed by further fragmentation. The second pathway corresponds to the formal loss of ArNSO_2 , accompanied by hydrogen migration to give ions (**53**) and further decomposition <88OMS(23)794>.

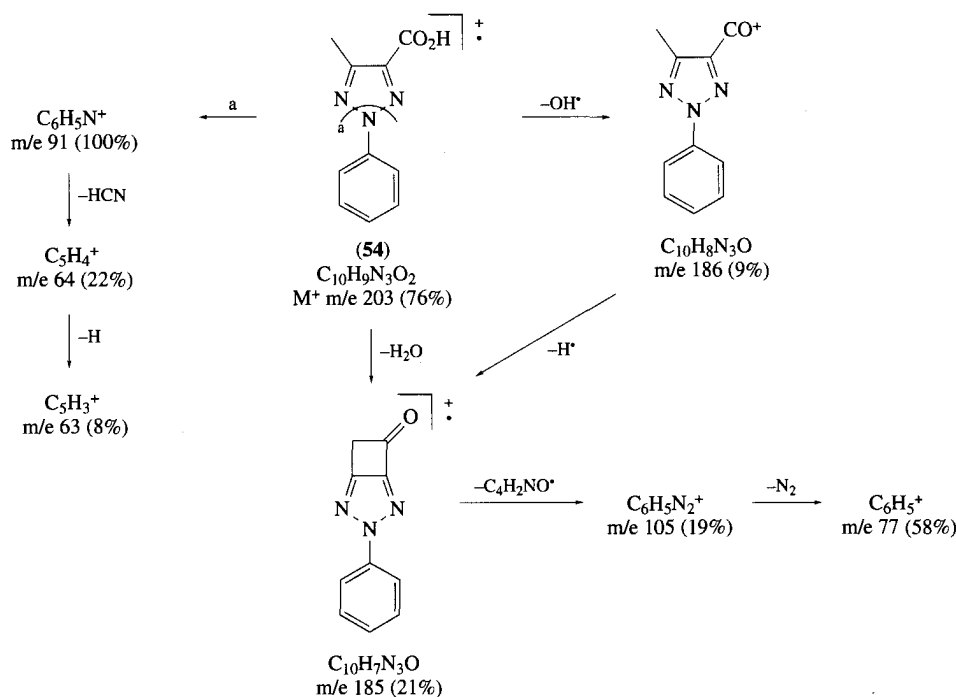


Scheme 1

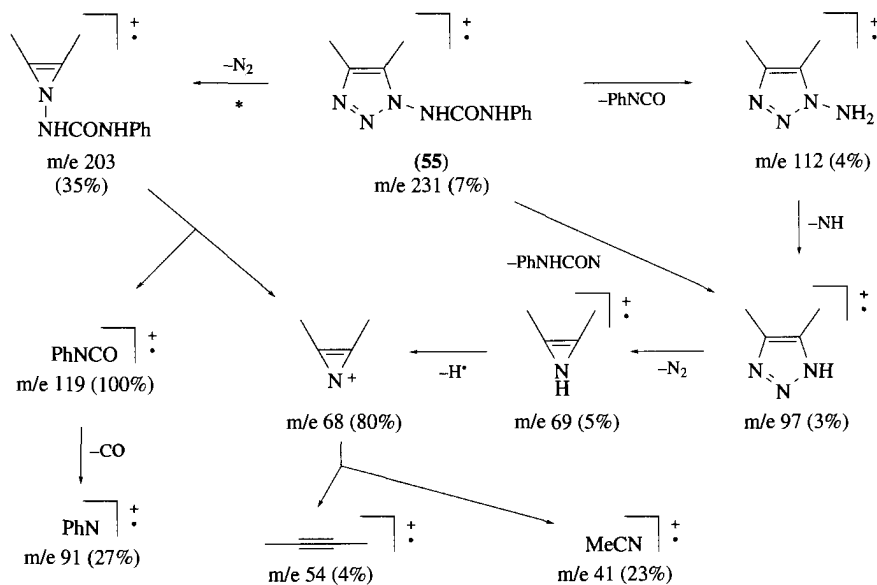
4-Carboxy-5-methyl-2-aryl-2H-1,2,3-triazoles (**54**) undergo considerable fragmentation on electron impact including loss of OH and H_2O from the molecular ions and rupture of the triazole ring. The base peak at m/z 91 is due to the species $\text{C}_6\text{H}_5\text{N}^+$ formed by cleavage of the triazole ring. The fragmentation pattern and relative abundances are indicated in Scheme 2. Conversely, 4-carboxy-5-phenyl-2-aryl-2H-1,2,3-triazoles show no loss of H_2O from the molecular ion <87JHC1029>. The fragmentation pattern upon electron impact at 70 eV of *N*-(1,2,3-triazol-1-yl)ureas and the corresponding *N'*-aryl derivatives (**55**) has been studied. The spectra examined either contained no molecular ion peak or the peak was of very low intensity. The ArNCO^+ ion gives rise to the base peak or one of the most prominent peaks. The principal fragmentation pathway is the loss of nitrogen (Scheme 3) <84JHC145>. The mass spectra of 1-arylamino-5-arylaminomethyl-1,2,3-triazoles have been reported <94JHC425>.

1-Arylideneamino-1,2,3-triazoles (**56**) show the general fragmentation pattern of other 1,2,3-triazoles. Thus, whilst the molecular ion peaks are of low intensity (0.2–12%), they all show the $\text{M}-28^+$ peak, which corresponds to nitrogen elimination from the molecular ion and is very characteristic of the 1-substituted-1,2,3-triazoles. The $\text{M}-28^+$ ions (**57**) are further split to azirine ions, acetylenes and nitriles (Scheme 4) <87JHC1461>. The mass spectra of 4,5-bis[5-aryl-1,3,4-oxadiazol-2-yl]-1-benzyl-1,2,3-triazole (**58**) show the expected fragmentation patterns of the 1,2,3-triazole and 1,3,4-oxadiazole rings. Thus, these compounds give peaks corresponding to $[\text{M}^\bullet]$, $[\text{M}-\text{N}_2]$ and $[\text{M}-\text{ArCNO}]$, as well as the fragments $[\text{ArCN}]$, $[\text{ArCNO}]$, $[\text{ArCO}]$, and $[\text{PhCH}_2]$ <90JHC1685>.

The electron impact mass spectrum of 1-vinylbenzotriazole displays the molecular ion at m/z 145 and intense fragment ion peaks at m/z 117 (loss of nitrogen), m/z 91 (consecutive loss of nitrogen and C_2H_2), m/z 90 (loss of nitrogen and HCN), and m/z 89 (loss of nitrogen, HCN and $\text{H}^\bullet$ in sequence). Collisional activation of the ion at m/z 91 shows that its structure is identical with the $[\text{M}-\text{N}_2]^+$ ion derived from the parent benzotriazole <88JCS(P2)1071>. Electron impact, field desorption, and field ionization mass spectrometry have been used to determine n in oligomer mixtures $[\text{R}_2\text{B}(\text{ut})]_n$ and $[\text{R}_2\text{B}(\text{bt})]_n$ (ut = 1,2,3-triazolate and bt = benzotriazolate) obtained from the reaction of R_2BX with *N*-(trimethylsilyl)-1,2,3-triazole or benzotriazole <89IC4022>.



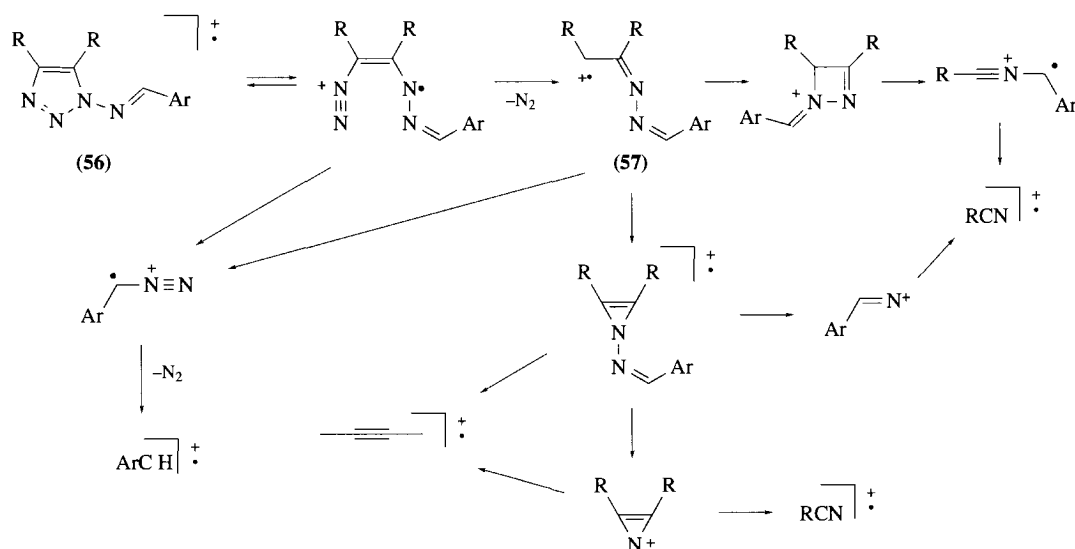
Scheme 2



Scheme 3

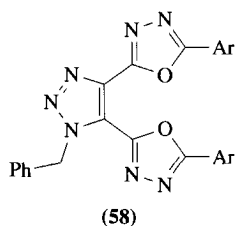
4.01.2.9 UV and Fluorescence Spectroscopy

For UV spectra of parent and substituted 1,2,3-triazoles and benzotriazoles, see CHEC-I (84CHEC-I(5)684). The UV spectra of benzotriazole, 1-methyl- and 2-methyl-benzotriazole in the gas phase at 90 °C have been recorded (94JOC2799). 1-Alkyltriazolines show two λ_{max} in acetonitrile, 239–242 and 263–266 nm, both with $\log \epsilon \approx 3.50$ (93JOC2097). The UV spectra of bicyclic triazolines (754) have been recorded (91JOC4463). The S_1 – S_0 electronic absorption spectrum of 1H-benzotriazole at 286 nm has been studied by computer simulation of the rotational contours. The result shows that the benzotriazole band is an almost pure type-B band (93JSP(158)399).



Scheme 4

The UV spectra of bisoxadiazolyltriazoles (**58**) consist of two main absorption bands. The first band with $\lambda_{\max}$ at 206–216 nm can be attributed to the 1,2,3-triazole ring. The other absorption band at longer wavelengths ($\lambda_{\max}$ 267–299 nm) is characteristic of 2-aryl-1,3,4-oxadiazoles. The results suggest that strong steric interactions probably prohibit conjugation between the triazole and the two oxadiazole rings. Compounds (**58**) also show strong fluorescence in ethanolic solution on stimulation by UV-irradiation which is detectable at concentrations as low as 10^{-7} M $\langle 90\text{JHC1685} \rangle$.

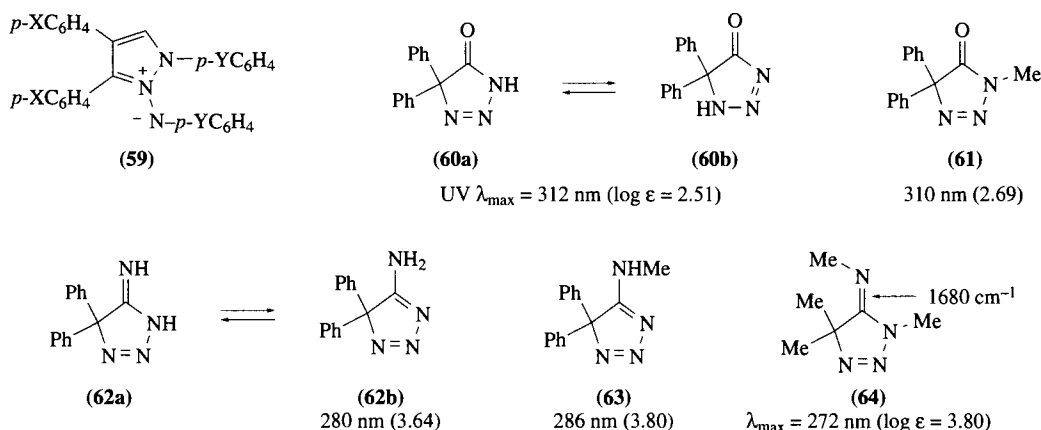


Ar	C ₆ H ₅	4-MeC ₆ H ₄	4-ClC ₆ H ₄	4-O ₂ NC ₆ H ₄	4-MeOC ₆ H ₄
$\lambda_{\max}$	214	209	214	206	216
log ϵ	(4.16)	(4.38)	(4.30)	(4.31)	(4.32)
$\lambda_{\max}$	267	281	270	266	299
log ϵ	(4.32)	(4.27)	(4.46)	(4.19)	(4.16)

1,2,3-Triazolium-1-imides (**59**) show an absorption band in the visible region ($\lambda_{\max}$ 400–500 nm) in acetone. By following the disappearance of this wavelength, the kinetics of the reactions of (**59**) with dipolarophiles can be measured $\langle 92\text{JCS(P2)1103} \rangle$. 4-Acetylamino-1-oxy-2-phenyl-2*H*-1,2,3-triazole (**26**) exhibits a UV absorption band at $\lambda_{\max}$ 285 nm ($\epsilon = 10400$) in methanol $\langle 92\text{TL7941} \rangle$. The UV spectra of some benzotriazoles bearing highly substituted 1-aryl groups have been reported $\langle 85\text{JCS(P1)2725} \rangle$. The UV spectra of some *N*-aminotriazoles have been described $\langle 85\text{TL335} \rangle$.

UV spectroscopy is of importance in studying the tautomerism of 5,5-diphenyl-4*H*-1,2,3-triazol-4-one and 5-amino-4,4-diphenyl-4*H*-1,2,3-triazole. The comparison of UV and other spectra of the tautomeric triazoles (**60**) and (**62**) with those of the *N*-methyl compounds (**61**) and (**63**) demonstrates that the tautomers (**60a**) and (**62b**) are strongly favored in solution $\langle 93\text{CB103} \rangle$. The UV absorption bands and IR spectrum of 1,4,4-trialkyl-4,5-dihydro-5-imino-1*H*-1,2,3-triazole (**64**) are also described $\langle 90\text{CB2195} \rangle$.

Some 2-(2'-hydroxyaryl)benzotriazoles are UV stabilizers and they have received much attention as a result of their UV and fluorescence properties; see review $\langle 89\text{MI 401-01} \rangle$. The UV spectra of benzotriazoles (**65b**, **c**) in heptane and methanol have been measured. The UV absorption of (**65c**) is markedly dependent on the solvent (340 nm in heptane and 280 nm in methanol) perhaps because of intermolecular hydrogen bonding. In contrast, the absorption spectrum of (**65b**) is relatively insensitive to solvents $\langle 81\text{AJC691} \rangle$. The absorption and fluorescence characteristics of 2-(2'-hydroxy-5-methylphenyl)benzotriazole (**65a**) and its sulfonated analog have been studied in a range of solvents (Table 9). The band near 340 nm is assigned to intramolecularly hydrogen bonded molecules. The excited state intramolecular proton transfer is strongly dependent on the hydrogen-bonding properties of the solvent $\langle 86\text{JPC5089} \rangle$. The effects of the solvent and the temperature, from



room temperature to 10K, on the electronic spectra and excited-state lifetimes of **(65a)** and its derivatives have been reported <87JPC1408>. The fluorescence lifetimes and rotational diffusion times of **(65a)** are measured in alcohol and ether solvents <87JPC4621>. The overall fluorescence quantum yield and the fluorescence decay time have also been measured from 350K to 12K. The fluorescence originates from the S_1 state of the proton transferred species of **(65a)** with an intact intramolecular hydrogen bond <88JPC1452>. Absorption spectra of 2,6-di(benzotriazol-2-yl)-1,3-dihydroxybenzene show a very high extinction coefficient, more than twice that of monobenzotriazolyl phenol. However, addition of a third benzotriazole ring does not significantly change the extinction coefficient <85MI 401-01>.

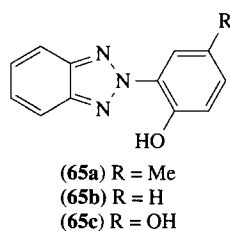


Table 9 Absorption, fluorescence and phosphorescence of benzotriazole **(65a)** <87JPC1408>.

Solvent	Wavenumber and ϵ of absorption maxima		Wavenumber of emission maxima	
	ν_1 , cm^{-1} (ϵ)	ν_2 , cm^{-1} (ϵ)	Fluorescence	Phosphorescence
MeOH	29850 (25200)	33900 (23400)	24400, 17250	21300, 19600
dioxane	29500 (17200)	33700 (14800)		
CHCl_3	29400 (18700)	33300 (15800)	16650	none

4.01.2.10 IR Spectroscopy

Complete assignments of IR spectra for the parent and substituted 1,2,3-triazoles are given in CHEC-I <84CHEC-I(5)685>. IR Spectra have been recorded for numerous 1,2,3-triazole and benzotriazole derivatives since the mid-1980s but generally no detailed assignments are given (see relevant sections).

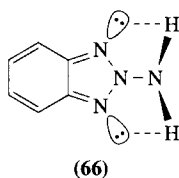
The IR and Raman spectra of benzotriazole, benzotriazole anion and its Cu(I) complex have been measured. The characteristic peaks in the IR spectrum of the triazole moiety in benzotriazole anion occur at 1163 cm^{-1} , 1134 cm^{-1} , and 1115 cm^{-1} . A broad band with a main peak at 1151 cm^{-1} occurs in the spectrum of the Cu(I)-BTA complex <85JST(100)571>. The chemisorption of benzotriazole on clean copper and cuprous oxide surfaces is investigated by combining XPS, UV-PE and IR reflection absorption spectroscopy (IRAS). Coordination geometry including the triazole-

N is confirmed by the absence of the 3400 cm^{-1} (N—H stretch) and 1210 cm^{-1} bands; both are characteristic of the benzotriazole molecule. The detailed assignments of the IR spectrum are given by Nilsson *et al.* <89MI 401-02>. The equilibrium geometry and harmonic frequencies have been calculated for the 1,2,3-triazole anion, and are compared with FT-IR and FT Raman data of the 1,2,3-triazole anion in aqueous NaOH solution at pH 12. The spectrum of the 1,2,3-triazole anion exhibits three bands at 1143 cm^{-1} , 1096 cm^{-1} , and 1086 cm^{-1} <91JPC3119>. A similar calculation is carried out with 1*H*- and 2*H*-1,2,3-triazole, which suggests that the IR spectral differences between the two forms occur in the $1550\text{--}1050\text{ cm}^{-1}$ range <91JPC3123>.

The N—H stretching frequencies of *N*-amino-1,2,3-triazoles and -benzotriazoles in CCl_4 are listed in Table 10. They show two N-H stretching frequencies, an intense νNH_{as} and a weak νNH_{s} . The results suggest that the amino group at the N(1) position lies in a plane orthogonal to the heterocyclic rings. The νNH_{as} of 2-amino-2*H*-benzotriazole and -naphthotriazole, however, are about 20 cm^{-1} higher than the *N*(1) derivatives and the νNH_{s} is more intense than the νNH_{as} bands. The different IR spectra may result from a change in geometry, and it is suggested that two intramolecular hydrogen bonds provide stabilization of the conformation (66) <88SA(A)283>.

Table 10 N-H Stretching vibrations of some *N*-amino 1,2,3-triazoles <88SA(A)283>.

Compound	νNH_{as}	ϵ_a	νNH_{s}	ϵ_a
4,5-dimethyl-1-amino-1,2,3-triazole	3371	73	3302	12
4,5-diphenyl-1-amino-1,2,3-triazole	3370	65	3297	15
1-aminobenzotriazole	3374	65	3301	5.9
7-methyl-1-aminobenzotriazole	3368	65	3300	7.0
5-methoxy-1-aminobenzotriazole	3373	60	3306	7.6
1-aminonaphtho[1,2- <i>d</i>]triazole	3372	57	3311	13
2-aminobenzotriazole	3390	48	3303	57
2-aminonaphtho[1,2- <i>d</i>]triazole	3380	21	3300	24



IR spectroscopy has been used to distinguish between 1- and 2-substituted benzotriazolyl derivatives <87JCS(P1)811, 63HCA1473>. The 1-isomers typically display two weak absorptions in the region $1630\text{--}1550\text{ cm}^{-1}$ due to the $\text{C}=\text{C}$ and $\text{C}=\text{N}$ stretching vibrations, whereas the 2-isomers show only one weak absorption in the same region. The IR spectra of a variety of *N*-(dialkylaminomethyl)benzotriazoles in bromoform or chloroform solution or as the neat liquid show three absorption bands. However, only two weak absorptions are observed in the solid state (in KBr disc or in Nujol dispersion). These results support the belief that *N*-(dialkylaminomethyl)benzotriazoles exist as a mixture of the N(1) and N(2) isomers in solution and in the neat liquid, but only as the N(1) isomer in the solid state <87JCS(P1)2673>. IR spectra have been used to differentiate between *N*- and *O*-acylated benzotriazol-1-ols <88JOC205, 91JCS(P2)1545>. The IR and far-IR ($500\text{--}100\text{ cm}^{-1}$) spectra of some metal complexes of benzotriazole have been recorded <83ICA109>.

4.01.2.11 Photoelectron Spectroscopy

Photoelectron spectroscopy has been used to study equilibria in the gas phase. Thus, the tautomerism of triazoline-5-thione is studied by variable temperature photoelectron spectroscopy <83CJC1197>. Photoelectron spectra of 1,2-dimethyltriazoline-5-thione (67a) calibrated with the $^2\text{P}_{1/2}$ and $^2\text{P}_{3/2}$ lines of argon and xenon are recorded with a resolution of 30 meV . The spectra of freshly evaporated material obtained with a P_1 probe indicate the presence of the unchanged thione even at 160°C . A spectrum recorded with a P_2 probe after heating the evaporated sample to 160°C exhibits an additional minor band at 9.40 eV which is most likely due to 2-methyl-4-methylthiotriazole (67b).

The presence of 1-methyl-5-methylthiotriazole (**67c**) could not be demonstrated since its bands would be masked by those of its isomer (**67b**). The ionization potentials are shown in Table 11.

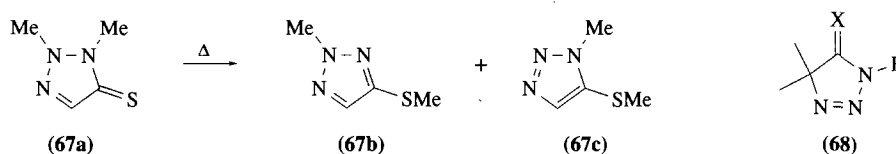


Table 11 Experimental ionization potentials (eV).

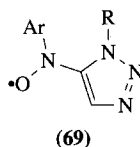
Compound	Ionization potentials						Ref.
1-methyl-4-methylthiotriazole	8.33	10.	10.37	10.75	11.4	12.1	83CJC1197
1-methyl-5-methylthiotriazole	9.30	9.70	10.40	10.65	11.55	12.45	83CJC1197
1-methyl-4-hydroxytriazole	9.1	10.3	10.8	11.8	12.9		89NJC551
1-methyl-4-methoxytriazole	8.7	9.9	10.4	11.8	12.7		89NJC551
2-methyl-4-hydroxytriazole	9.1	10.5	11.	11.9	12.9		89NJC551
1-methyl-5-hydroxytriazole	9.2	9.7	10.5	11.6			89NJC551
1-methyl-5-methoxytriazole	9.	9.6	10.5	11.6	12.4		89NJC551

The pyrolysis of 1*H*-1,2,3-triazole, carried out in a quartz tube containing cuprous oxide dispersed over quartz wool, is studied by photoelectron spectroscopy. Pyrolysis begins at 840K with the evolution of nitrogen and the formation of acetonitrile. At 970K, the reaction is complete with acetonitrile and nitrogen being the only products observed. The photoelectron spectroscopic experimental observations and the MNDO calculation both indicate that synchronous nitrogen extrusion and azirine ring formation is the energetically most favorable reaction pathway <83JA7681>. The flash pyrolyses of 4-hydroxy-1,2,3-triazole and its *N*-methyl derivatives, 4-methoxy-, and 5-methoxy-1-methyl-1,2,3-triazole are studied by photoelectron spectroscopy <89NJC551>. The ionization potentials are listed in Table 11.

The ionization potentials, measured by photoelectron spectra, of the 3,5-dihydro-4*H*-1,2,3-triazoles (**68**, X = O, NMe and CH₂, R = Me and CH₂Bu^t) have been assigned to specific molecular orbitals based on MNDO, AM1 and PM3 calculations. The most important occupied molecular orbitals are characterized as π_{NNN} , $\pi_{\text{C=N}}$, $n_{\text{N-3}}$, n_{NN}^+ , n_{NN}^- and n_x . The gas phase thermolyses of (**68**) are studied by photoelectron-controlled real-time gas analyses <93CB2683>.

4.01.2.12 Electron Resonance Spectroscopy

5-Anilino-1,2,3-triazoles are oxidized by RO₂[•] radicals to the corresponding nitroxyls (**69**). The electron resonance spectra indicate that the spin density is distributed in both the aryl and triazole rings. The *g*-factor for all these radicals is in the 2.0061–2.0065 interval. The influence of substituents at the N(1) position of the triazole ring on the values of a_{N} splitting constants can be mapped from the electron spin resonance (ESR) parameters of radicals (**69**) with R = aryl and R = alkyl groups. Substitution by a benzene ring increases the possibility of delocalizing the spin density within the triazole moiety of the radical. The ESR spectral parameters of nitroxyls (**69**) are compared with those of the diphenylnitroxyl radical <92CCC1065>.



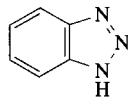
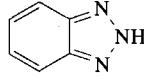
The ESR spectra of some copper complexes of benzotriazole, benzotriazolate, *N*-methylbenzotriazole, and 5-nitrobenzotriazole have been described. They show either isotropic *g* values or indications of axial or rhombic splittings. In no cases are copper hyperfine splittings observed. This indicates that the copper ions in the solid compounds are exchange coupled. The fact that the *g* values observed at X-band frequency differ from those obtained at Q-band frequency also indicates

the occurrence of magnetic exchange coupling $\langle 83\text{ICA}109 \rangle$. The experimental and calculated ESR spectra of a mixed-valence (benzotriazolato) copper (I, II) cluster, $\text{Cu}_5(\text{BTA})_6(\text{RNC})_4$, at different temperatures are studied. The magnetic parameters including the line width, line shape, and hyperfine line width, and the g and A values are nearly independent of temperature $\langle 85\text{JPC}1976 \rangle$.

4.01.2.13 Dipole Moments

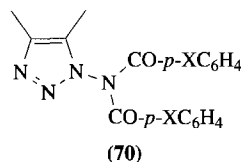
The dipole moments of 1,2,3-triazole, benzotriazole and their *N*-methyl derivatives have been described in CHEC-I $\langle 84\text{CHEC-I}(5)672 \rangle$. The experimental dipole moment in benzene for the tautomeric mixture of 1*H*- and 2*H*-1,2,3-triazole is 1.85 D at 25°C and 2.08 D at 45°C $\langle 73\text{JCP}(70)1483 \rangle$. The experimental microwave dipole moment for 1*H*-1,2,3-triazole is 4.1 D and for 2*H*-1,2,3-triazole is 0.37 D $\langle 74\text{CC}605 \rangle$. There is an excellent correlation between the experimental microwave dipole moments of a variety of azoles and those calculated by the *ab initio* method at 6-31G**//6-31G level: $\mu_{\text{exp}} = 0.942 \mu_{\text{cal}} + 0.008$ $\langle 86\text{JPC}5597 \rangle$. With this equation, the experimental values for 1*H*- and 2*H*-1,2,3-triazole are predicted as 4.35 D and 0.32 D, respectively $\langle 89\text{MI} 401-01 \rangle$. Experimental and calculated dipole moments for all tautomers of 1,2,3-triazole and benzotriazole are shown in Table 12. Generally, the agreement between theoretical, either semi-empirical or *ab initio*, and experimental dipole moments is satisfactory. Thus, quantum chemical calculations are a valuable aid in estimating tautomeric equilibria by dipole moment studies $\langle 90\text{ZN(A)}1328 \rangle$.

Table 12 Comparison of calculated dipole moments (Debye) with experimental results.

Compound	Method	Dipole moment	Ref.
	AM1	4.10	90ZN(A)1328
	PM3	4.35	90ZN(A)1328
	MNDO	4.03	90ZN(A)1328
	STO-3G//STO-3G	4.13	89MI 401-01
	6-31G**//6-31G	4.61	89MI 401-01
	3-21G//3-21G	4.87	89MI 401-01
	experiment	4.38	89MI 401-01
	AM1	0.12	90ZN(A)1328
	PM3	0.30	90ZN(A)1328
	MNDO	0.24	90ZN(A)1328
	STO-3G//STO-3G	0.06	89MI 401-01
	6-31G**//6-31G	0.33	89MI 401-01
	3-21G//3-21G	0.45	89MI 401-01
	experiment	0.22	89MI 401-01
	AM1	3.65	90ZN(A)1328
	PM3	3.75	90ZN(A)1328
	MNDO	3.56	90ZN(A)1328
	6-31G//6-31G	4.64	90ZN(A)1328
	6-31G**//6-31G	4.25	78JST(43)203
	experiment	4.15	78JST(43)203
	AM1	0.13	90ZN(A)1328
	PM3	0.33	90ZN(A)1328
	MNDO	0.18	90ZN(A)1328
	6-31G//6-31G	0.78	90ZN(A)1328
	6-31G**//6-31G	0.55	78JST(43)203
	experiment (N-Me)	0.49	78JST(43)203

Experimental dipole moments of 1-(*N,N*-diaroyl)amino-1,2,3-triazoles (**70**) are determined at 25°C in benzene solution by the Guggenheim-Smith method. Theoretical dipole moments are calculated by vector addition of all possible conformations of the imide group which can be derived by rotating the aryl groups around the $\text{C}_7\text{—N}_6$ and $\text{C}_8\text{—N}_6$ bonds at angles from 0 to 360° $\langle 83\text{JHC}1469 \rangle$. Another report describes the dipole moments of 1-methyl-3-aryl-1,2,3-triazol-4-ylacetamides (**43**, X, μD : H, 6.39; Me, 6.40; Cl, 6.80) and 1-methyl-3-(4-tolyl)-1,2,3-triazol-4-one (**44**, $\mu\text{D} = 5.98$) in benzene solution $\langle 85\text{JCS(P2)}1123 \rangle$. These values are higher than those of the triazole

ring system by 1 D <79JHC571>. The dipole moments calculated by the CNDO/2 method are higher than the experimental data by ca. 30%, but this deviation is within the range of the accuracy of the methods. The dipole moment of (43c, X = Cl) calculated by vector addition of the moment vector of (43a, X = H) is 4.96 D, which agrees well with the experimental value of 4.83 D <85JCS(P2)1123>.

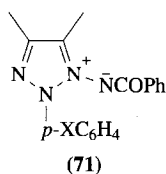


X	H	Me	OMe	Cl	NO ₂
μD	4.64	4.83	5.11	3.77	3.97

The experimentally determined electronic dipole moments of the zwitterionic 2-aryl-*N*-benzoyl-4,5-dimethyl-1,2,3-triazol-1-imines (71) are in the range of 3–5 D in CCl₄ solution. These values follow a good linear correlation with σ^+ substituent constants of slope $\rho = 1.851$. Dipole moments of compounds (71) are also calculated using MNDO, AM1 and PM3 and are listed in Table 13. When the computed dipole moments are compared with the experimental ones, good to fair correlations are found <93JHC1121>. The dipole moments calculated by MNDO using the MOPAC package for 5-mono- and difluoro-substituted 1,2,3-triazoles are described and their data are shown in Figure 12 <88H(27)1803>.

Table 13 Experimental (CCl₄, 25°C) and calculated dipole moments for (71).

<i>X</i>	$\alpha_d[b]$	$\alpha_n[b]$	<i>Exp.</i>	<i>MNDO</i>	<i>AM1</i>	<i>PM3</i>
MeO	6.94	0.97	3.09	2.35	2.68	2.26
Me	7.41	0.99	3.12	3.35	2.77	2.69
H	9.87	0.74	3.63	3.45	3.00	2.61
Cl	8.81	0.86	4.10	4.04	3.74	2.52
NO ₂	15.60	0.88	4.96	6.65	7.74	6.29

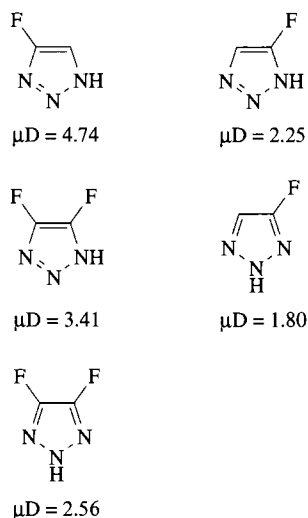


4.01.3 THERMODYNAMIC ASPECTS

4.01.3.1 Boiling Points and Melting Points

The melting point of the parent 1*H*-1,2,3-triazole is 23–25°C, and the boiling point is 205–206°C. The melting point of benzotriazole is 100°C. Melting points or boiling points of some substituted 1,2,3-triazoles and benzotriazoles are listed in Table 14. Generally, the less-symmetrical 1-substituted 1,2,3-triazoles and benzotriazoles have higher melting points and/or boiling points than the symmetrical 2-substituted analogs. In many cases, 1-alkylbenzotriazoles are crystalline whereas the 2-alkylbenzotriazoles are oils (see Table 14).

1,2,3-Triazoles

**Figure 12** The calculated dipole moments of fluoro-substituted 1,2,3-triazoles.**Table 14** Melting points or boiling points of 1,2,3-triazoles and benzotriazoles.

Substituent	m.p. (°C) or b.p. (°C/mmHg)	Ref.	Substituent	m.p. (°C) or b.p. (°C/mmHg)	Ref.
1,2,3-triazoles					
1-Me	223–225/760	59ACS888	1-Ac	60–62	^a
2-Me	102–103/760	59ACS888	2-Ac	33–36	^a
1-Ph	56	^a	1-Me-4-OH	135	^a
2-Ph	43–44	86ACS(B)262	2-Me-4-OH	99–100	^a
1-Cl	104–106	69JCS(C)1474	1-Me-4-CO ₂ Me	157–158	87CB159
4-Ph	143–145	90CL453	4-CH ₂ OH	58–59.5	89CB1963
2-Me-4-CO ₂ Me	63–64	87CB159	1-Bz-5-OH	159–160	84JHC1603
			4,5-Ph ₂	139–140	93TL1055
benzotriazoles					
1-Me	64–66	91RTC369	1-CH ₂ NC	99–101	89TL6657
2-Me	44–45/0.03	94LA7	1-CH ₂ F	119–120	93PJC1243
1-Et	100/0.03	94LA1	1-SO ₂ Ph	124–126	92T7817
2-Et	55/0.03	94LA7	1-COMe	51–52	92T7817
1-CH ₂ Ph	114–116	85H(23)2895	1-CN	73–76	91RRC573
2-CH ₂ Ph	oil	85H(23)2895	1-NH ₂	84	69JCS(C)742
1-allyl	161/15	38CB596	2-NH ₂	121–122	69JCS(C)742
2-allyl	127/15	38CB596	2-Ph	109–110	89AJC441
1-CHPh ₂	154–155	90JCS(P2)2059	1,4,7-Me ₃	68–70	85H(23)2225
2-CHPh ₂	87–88	90JCS(P2)2059	2,4,7-Me ₃	65–67	85H(23)2225
1-CPh ₃	218–220	90JCS(P2)2059	1-OH	159–160	^a
2-CPh ₃	196–198	90JCS(P2)2059	1-Cl	104–106	^a
1-CH ₂ Ph-5,6-Me ₂	165–166	93JPO567	1-F	oil	91T7447
2-CH ₂ Ph-5,6-Me ₂	oil	93JPO567			

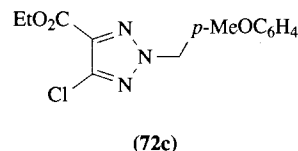
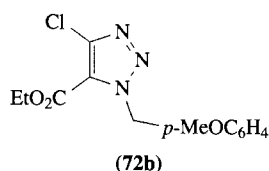
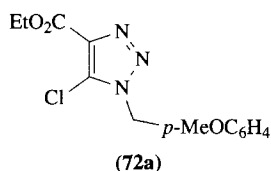
^a Dictionary of Organic Compounds, 5th edn. Chapman and Hall, New York, 1982.**4.01.3.2 Solubilities and Chromatographic Behavior**

1,2,3-Triazoles and benzotriazoles are generally soluble in many common organic solvents. For example, the solubilities of benzotriazole and 1-methylbenzotriazole in benzene, alcohol or chloroform are all > 10%. Similarly, 1,2,3-triazole has good solubility in H₂O, alcohol, acetic acid, and ether <B-85MI 401-02, B-85MI 401-03>.

Mixtures of 1- and 2-substituted benzotriazoles are readily separated by column chromatography. For instance, mixtures of N(1) and N(2) isomers of *N*-benzyl-, *N*-diarylmethyl-, and *N*-tritylbenzotriazole are separated by flash column chromatography on silica gel with CH₂Cl₂ or hexane–CHCl₃–CH₂Cl₂ as eluent <90JCS(P2)2059>. Mixtures of 1- and 2-alkylbenzotriazoles are similarly

separated <91RTC369>. In most cases, the more symmetrical and less-polar 2-substituted benzotriazoles elute first <85H(23)2225>.

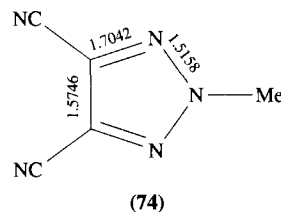
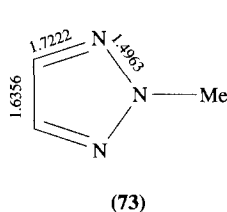
The reaction of 4-methoxybenzyl-1,2,3-triazole with PCl_5 gives three isomeric products (**72a–c**). These isomers are readily distinguished by their high-pressure liquid chromatography (HPLC) behavior. Compounds (**72b**) and (**72c**) almost coelute on HPLC. However, repeated chromatography on silica gel eluting with CHCl_3 –light petroleum gives pure samples of (**72b**) and (**72c**) <82JCR(S)292>.



4.01.3.3 Aromaticity

Aromaticity as a qualitative concept is very well established in organic and particularly in heterocyclic chemistry. It is also well recognized that aromaticity is not only a qualitative but also a quantitative concept. Much effort has been devoted towards developing experimental methods and molecular orbital calculations to obtain a quantitative measure of aromaticity in heterocyclic compounds <89JA7>. Aromaticity and antiaromaticity are generally evaluated by energetic, structural, and magnetic criteria. The concept of aromaticity in heterocyclic chemistry has been summarized in two reviews <91H(32)127, 93AHC(56)303>.

An aromaticity index based upon the statistical degree of uniformity of the bond orders of the ring periphery has been introduced. The aromaticity index I is calculated for a wide range of five-membered heterocycles: $I = 100(1 - V/V_k)$ where V is the coefficient of variation for the bond orders. In the case of a fully delocalized heterocycle, V will have the value 0, whereas for a non-delocalized Kekulé form the value depends upon the type of ring system. Thus, for a five-membered heterocyclic ring, $V_k = 35$, for a six-membered heterocyclic ring, $V_k = 33.3$. The I values of 88 and 73 assigned to $2H$ - and $1H$ -1,2,3-triazole respectively correctly identify the former tautomer as the preferred species <85T1409>. The aromaticity is evaluated for 2-methyl-1,2,3-triazole (**73**) and 4,5-dicyano-2-methyl-1,2,3-triazole (**74**) based on the bond order between atoms shown. Compound (**73**) poses some interesting questions because the orders of the ring bonds, except those to N(1), are of the correct magnitudes for a highly aromatic system. However, the bonds to N(1) are orders corresponding more to single bonds suggesting localization of the lone pair on N(1). This could suggest that (**73**), in an unperturbed state, would not show aromaticity. If the hydrogens on C(4) and C(5) are replaced by cyano groups, the molecule (**74**) is aromatic, as shown by the bond orders <91H(32)2023>.



The relative stability of 1,2,3-triazole and benzotriazole tautomers can be rationalized based on the concept of aromaticity. The aromaticity of both 1,2,3-triazole tautomers probably being similar, the lone–lone pair repulsion accounts for the lower stability of $1H$ -1,2,3-triazole. In the case of benzotriazole, the aromaticity of the benzenoid $1H$ -benzotriazole has been considered greater than that of the quinonoid $2H$ -benzotriazole <89JA7348>. However, great care must be taken in measuring the difference in aromaticity between the two tautomers because this will depend strongly on the dielectric constant of the medium.

4.01.3.4 Tautomerism

Tautomerism was only treated briefly in CHEC-I <84CHEC-I(5)671> under the section of thermal and photochemical reactions. Tremendous effort has been devoted to the study of the tautomerism, both prototropic and ring chain, of 1,2,3-triazoles and benzotriazoles. Therefore, tautomerism is described in considerably more detail in CHEC-II. For tautomerism of 1,2,3-triazolines, see Section 4.01.5.

4.01.3.5 Annular Prototropic Tautomerism

The annular prototropic tautomerism of the parent 1,2,3-triazole and benzotriazole are described in CHEC-I <84CHEC-I(5)691> and was reviewed earlier <76AHCS295>.

Tautomerism in 1,2,3-triazole has been extensively investigated using various spectroscopic methods. Microwave and photoelectron spectroscopy studies conclude that in the gas phase the 2H tautomer strongly dominates <81ZN(A)34, 81ZN(A)1246> (see Section 4.01.2.3). In solution, both the 2H and the 1H tautomer are observed. Early evidence was obtained from the determination of averaged proton-carbon coupling constants in NMR spectra. Accordingly, the more stable *s*-isomer (60%) and the *v*-isomer (40%) were assigned <74CC702>. Other ¹H NMR studies in CD₂Cl₂ indicate that both tautomers are present in solution with their relative proportion depending upon temperature and concentration <84JCS(P2)1025>. A ¹⁵N study provides similar results, i.e. 1*H*-1,2,3-triazole is more stable (66%) in CDCl₃, but in DMSO-*d*₆ the 2*H*-1,2,3-triazole is favored (55%) <82JOC5132>. In aqueous solution, however, the 2H tautomer is favored over the 1H tautomer by a factor of about two based on arguments from basicity and partitioning <89JCS(P2)1903>.

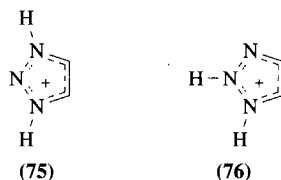
The tautomeric equilibrium of unsubstituted benzotriazole has been studied extensively and has been summarized in several reviews <63AHC(2)27, 76AHCS295>. The 1H form predominates strongly under all conditions studied. Thus, in the crystalline state the sole existence of 1*H*-benzotriazole is demonstrated by x-ray <74AX(B)1490>, by ¹³C NMR <83H(20)1713>, and by microwave spectra <93JSP(161)136>. The gas phase UV spectra show, however, both 1H and 2H tautomers in the approximate ratio 80/20 <94JOC2799>. Both semi-empirical methods (PM3, AM1 and MNDO) and *ab initio* calculations predict a large energy preference for the 1H over the 2H form (Table 15) <90JOC5683, 94JOC2799>. The reason 1*H*-benzotriazole is the dominant tautomer is probably related to (i) its high dipole moment which favors interactions with itself (solid) or with the solvent (solution) <94JOC2799> and (ii) the aromaticity <89JA7348>.

Table 15 Differences in energy (kcal mol⁻¹) of benzotriazole, triazole, and (dimethylamino)methylbenzotriazole tautomers.

Method	1 <i>H</i> -triazole over 2 <i>H</i> -triazole	1 <i>H</i> -benzotriazole over 2 <i>H</i> -benzotriazole	1- <i>Me</i> ₂ <i>NCH</i> ₂ <i>Bt</i> over 2- <i>Me</i> ₂ <i>NCH</i> ₂ <i>Bt</i>
6-31G**/3-21G	-4.73	2.71	0.47
3-21G	-3.94	5.51	0.28
6-31G*		4.84	
MNDO//MNDO	-4.93	11.11	9.83
AM1//AM1		12.75	13.13
PM3//PM3		7.75	9.23

Calculations at the 6-31G level indicate that in the gas phase, 2*H*-1,2,3-triazole is more stable than 1*H*-1,2,3-triazole by about 4.5 kcal mol⁻¹. In solution, the 1H isomer becomes the more stable species because the large difference in dipole moments favors the more polar tautomer. The triazolium ion (**75**) is predicted to be more stable than (**76**) by about 13.5 kcal mol⁻¹ <89MI 401-01>. 2*H*-1,2,3-Triazole represents more than 99.9% of the equilibrium mixture in the gas phase. However, the *ab initio* calculated proton affinity of 1*H*-benzotriazole is 10.2 kcal mol⁻¹ larger than that of 2*H*-benzotriazole, which is consistent with ICR measurements (1-methylbenzotriazole is 10 kcal mol⁻¹ more basic than 2-methylbenzotriazole). Measurements of enthalpies of solution, vaporization, sublimation and solvation in water, methanol and DMSO confirm the predominance of the 1H tautomer in solution <89JA7348>. The energy difference between the tautomers of 1,2,3-triazole has also been estimated at the 6-31G**(MP2)//3-21G level including zero-point effects. The

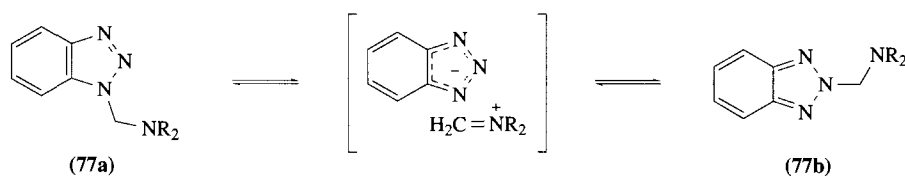
results confirm that only the 2H tautomer is expected to be observed in the gas phase. In aqueous solution the free-energy separation of the tautomers is considerably reduced. These calculations agree with the experimental findings that both tautomers are observed in a polar solvent <90JPC5499>.



4.01.3.6 Cationotropic Tautomerism of *N*-Substituted Triazoles and Benzotriazoles

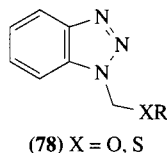
Migrations of acyl, trimethylsilyl, and trialkylstannyl groups between nitrogens in 1,2,3-triazoles are well known <66CB2512, 70TL5225, 72JOM(44)117>. Migration of the *p*-methoxybenzyl group during the conversion of (72a) to a mixture of (72b) and (72c) has also been described <82JCR(S)292>. A similar rearrangement of 1-benzyloxymethyl-4,5-bismethoxycarbonyl-1,2,3-triazole to the 2-benzyloxymethyl isomer is dissociative and intermolecular, as evidenced by complete crossover between the ^{15}N -labelled and isotopically normal moieties <87JCR(S)396>.

N-(*N*',*N*'-Dialkylaminomethyl)benzotriazoles usually exist in the crystalline state solely as the N(1) isomers, but in solution they form equilibrium mixtures of the N(1) and N(2) isomers (77a) and (77b) <75JCS(P1)1181, 87JCS(P1)2673>. The N(1) and N(2) isomers are of nearly equal stability in nonpolar solvents and in the gas phase (2 : 1 ratio on statistical grounds). Polar solvents favor the 1- and 3-substituted forms over the 2-substituted, and conversely substituents at positions four and seven favor the 2-substituted form. The interconversion of these N(1) and N(2) isomers proceeds intermolecularly, as demonstrated by crossover experiments, by a dissociation–recombination mechanism involving the formation of intermediate iminium cations and the benzotriazole anion <87JCS(P1)2673>. The equilibrium constants, associated free energies for the equilibrium mixtures and free energies of activation for the isomerization process are calculated from the variable temperature ^1H NMR spectra. The greater the stabilization provided to either of the intermediate ions, the lower the energy barrier. The greater the polarity of the solvent, the lower the value of $\Delta G^\ddagger$. The bulkier the dialkylaminoalkyl substituent, the more abundant the 2-isomer. In extreme cases the 2-isomer becomes the predominant component <89H(28)1121>. *Ab initio* and semi-empirical calculations on the tautomeric equilibrium of *N*-(dimethylamino)methylbenzotriazole have been carried out. The *ab initio* results correctly predict the almost equal stability of the two forms (77a) and (77b), whereas the semi-empirical methods significantly overestimate the relative stability of (77a) <90JOC5683>.



While most *N*-(*N*',*N*'-dialkylaminomethyl)benzotriazoles undergo rapid equilibration in solution, the N(1) and N(2) isomers of the corresponding sulfur and oxygen analogs (78), interconvert less rapidly and can be separated. The higher energy barriers for these interconversions are ascribable to the lower stability of the positively charged sulfur and oxygen intermediates ($\text{R}^1\text{CH}=\text{S}^+\text{R}^2$, and $\text{R}^1\text{CH}=\text{O}^+\text{R}^2$) compared with $\text{R}^1\text{CH}=\text{N}^+\text{R}^2\text{R}^3$. The isomerization rates of *N*-[α -(alkylthio)alkyl]benzotriazoles in solvent and in the absence of solvent depend on the number of H atoms attached to the C—N(1) or C—N(2): tertiary (no hydrogen) > secondary (1 hydrogen) > primary (2 hydrogen) <89JOC6022, 91HCA1936>. Mixtures of benzotriazole and carbonyl compounds exist in equilibrium with their isomeric N(1) and N(2) adducts. In general the N(1) adducts predominate over the N(2) isomers <90JCS(P2)921>. The thermal isomerizations of *N*-benzyl-, *N*-diarylmethyl- and *N*-trityl-benzotriazoles have been studied. In all cases, the N(1) isomer predominates over the N(2) isomer at thermodynamic equilibrium. The rate of attainment of equilibrium depends on the

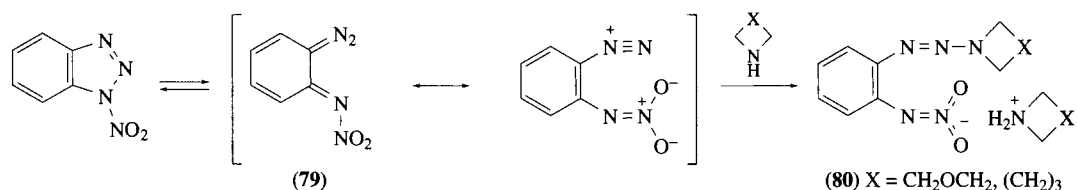
electronic effects of the substituents, both in the benzotriazole ring and in the migrating group. These results, in conjunction with a crossover experiment, support a mechanism involving heterolytic N—C bond cleavage followed by intermolecular rearrangement $\langle 90\text{JCS(P2)2059} \rangle$.



4.01.3.7 Ring-Chain Tautomerism

Ring-chain equilibria of 1,2,3-triazoles and benzotriazoles with the isomeric α -diazo imines result in the well-known Dimroth rearrangement (see Section 4.01.4.1.1).

1-Nitrobenzotriazole is in equilibrium with the isomeric α -diazo 1-nitroimine (79) as a result of the opening of the 1,2,3-triazole ring. In the presence of nucleophiles such as piperidine, this open-chain isomer can be trapped by attack at the diazo group. A second molecule of the amine acts as a base to afford the piperidinium salt (80). Eventually, crystallization forces this ring-chain equilibrium to the right resulting in the observed high yields of (80) $\langle 84\text{JOC2197} \rangle$. The ring-chain equilibrium of 1-cyanobenzotriazole with the isomeric α -diazo imines in polar solvents or on melting shows reversible thermochromic behavior and was reported earlier $\langle 67\text{JA4760} \rangle$. Similar equilibria of 1,2,3-triazoles with strong electron-withdrawing group, such as $-\text{CN}$ and OSO_2CF_3 are also known.



Scheme 5

1,2,3-Triazolium-1-imides are in equilibrium with 1,2-*cis*-bis(aryloxy)ethenes, which have been investigated by variable-temperature NMR $\langle 87\text{JCR(S)332} \rangle$ (see Section 4.01.2.5) and by *ab initio* calculations $\langle 90\text{CC882} \rangle$ (see Section 4.01.1.5).

4.01.4 REACTIVITY OF FULLY CONJUGATED RINGS

4.01.4.1 Unimolecular Thermal and Photochemical Reactions

4.01.4.1.1 Dimroth rearrangement

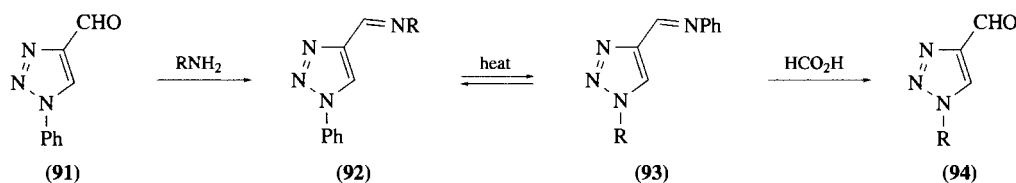
Dimroth rearrangements constitute an important part of the thermal ring-transformation reactions of 1,2,3-triazoles, and have received much attention in the past decade from 1985 to 1995. A 1990 review on this subject $\langle 90\text{BSB281} \rangle$ is a good supplement to previous works $\langle 74\text{AHC(16)33}$, 84JHC627 , $84\text{CHEC-1(5)694} \rangle$. A variety of known Dimroth rearrangements of 4- and/or 5-substituted 1,2,3-triazoles (81) involving intermediates of type (82) is summarized in Scheme 6.

The interconversion of 5-amino-1-aryltriazoles (81, $\text{R}^1 = \text{aryl}$, $\text{R}^5 = \text{NH}_2$) to 5-anilino-1-triazoles (83, $\text{R} = \text{H}$) via α -diazoamidines (82, $\text{R}^5 = \text{NH}_2$) was discovered by Dimroth $\langle 09\text{AC(R)183} \rangle$. The equilibrium position is shifted towards the acidic form (83, $\text{R} = \text{H}$) as the electron-withdrawing capacity of the R^1 -substituent increases. Basic solvents such as pyridine also favor the acidic 1*H*-triazole (83) $\langle 82\text{JOC5132} \rangle$. When $\text{R}^1 = \text{Ts}$, the rearrangement is so fast that the cycloaddition of tosyl azide to aroyl ketene *S,N*-acetal gives only the Dimroth rearrangement product, 5-tosylamino-1-triazole (87) (Scheme 7) $\langle 88\text{S851} \rangle$. When the R^5 substituent is NHCONHR , the same product (89) is obtained by treatment of the triazole isomers (88) and (90) with isocyanates (Scheme 8) $\langle 85\text{AHC(38)299} \rangle$. 5-Hydrazinotriazoles (81, $\text{R}^5 = \text{NHNH}_2$), generated *in situ* from 5-chlorotriazoles

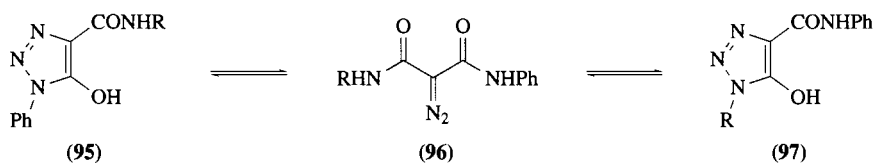

$$\text{TsN}_3 + \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}=\text{C}-\text{R}^1 \\ | \\ \text{MeS} \quad \text{NHR}^2 \end{array} \xrightarrow[\text{-MeOH}]{\text{NaOH, EtOH, } 0^\circ\text{C to RT}} \left[\begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{N} \quad \text{COR}^1 \\ \diagdown \quad \diagup \\ \text{N} \quad \text{NHR}^2 \\ | \\ \text{Ts} \end{array} \right] \longrightarrow \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{N} \quad \text{COR}^1 \\ \diagdown \quad \diagup \\ \text{N} \quad \text{NHTs} \\ | \\ \text{R}^2 \end{array} \quad (87)$$

Scheme 7



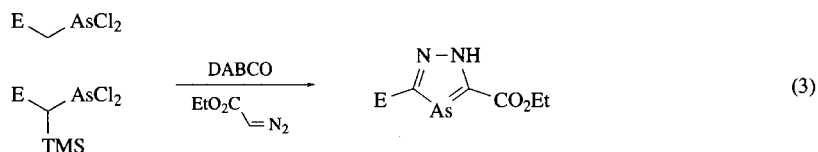
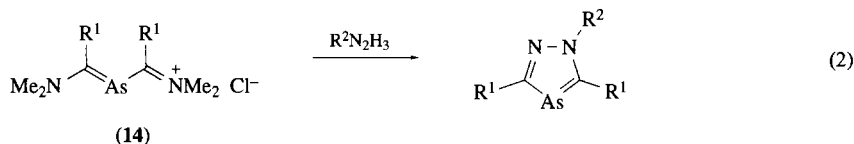
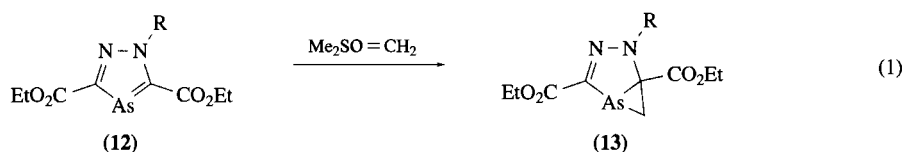


Scheme 9

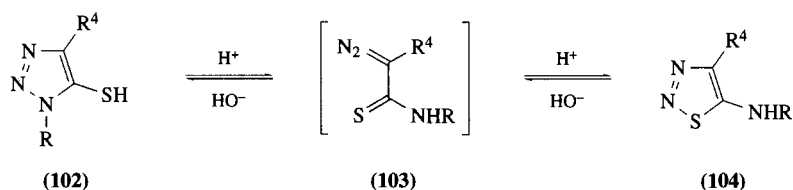


Scheme 10

1,2,3-Triazoles can rearrange to other heterocyclic ring systems. For instance, tetrazoles (99) are obtained from 5-hydroxy-4-phenylazotriazoles (98) and glacial acetic acid (Equation (1)) <58AC51236>. 5-Azidotriazoles (100) are in equilibrium with tetrazoles (101) (Equation (2)) <83BSB913, 85T4621, 88T3617>. The thermal rearrangement of 5-azidotriazoles (100) depends on the nature of the R⁴ substituent, i.e., rearrangement to tetrazoles (101) occurs when R⁴ = CO₂Me or other electron-withdrawing groups, decomposition to alkylidenetriazenes (112) occurs when R⁴ = Ar <88T3617, 89T749>. 5-Azido-4-methoxycarbonyl-1-phenyltriazole is also thermolyzed in acetonitrile and benzonitrile yielding imidazotetrazoles <85T4621>. 1-Alkyl- (102, R = alkyl) or 1-amino-5-thio-1,2,3-triazoles (102, R = NH₂) rearrange into 5-alkylaminothiadiazoles (104) and 5-hydrazinothiadiazoles (104, R = NH₂) via intermediates (103) in acidic solution (Scheme 11) <89T7329, 89JHC1811>. However, the reverse reaction is more favorable in the presence of base <84JHC627, 89BSB415, 89JHC1811>. The rearrangement of (102) to (104) is much faster for R⁴ = CO₂Et than for R⁴ = H or Ph. The hydrazone (106) is obtained from (105) and benzaldehyde through a Dimroth rearrangement (Equation (3)) <89JHC1811>.

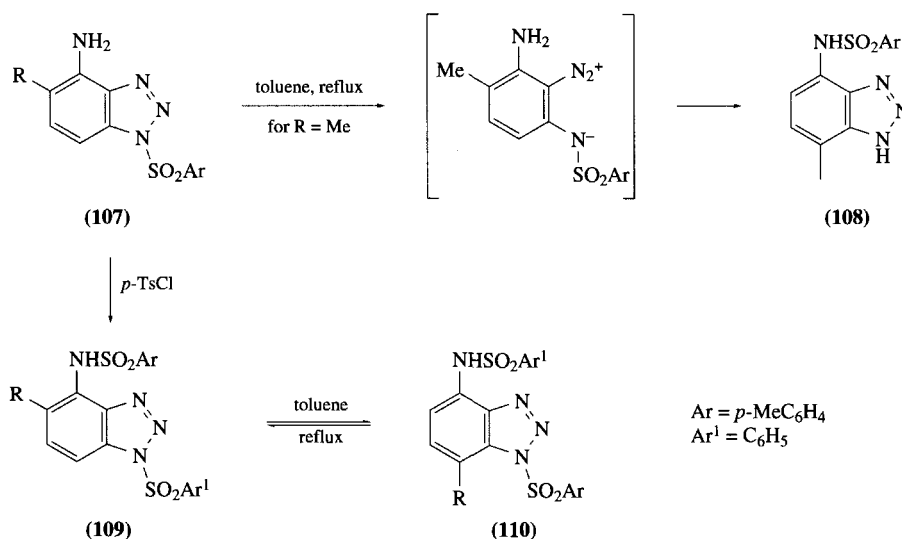


Dimroth rearrangements of 4-amino- or 4-imino-benzotriazoles were unknown until the mid-1980s, although similar rearrangements were known for 1,2,3-triazolo fused pyrimidines <86BSB679> and triazines <88BSB179>. The benzotriazole ring is more stable and less susceptible to ring opening. Thermal rearrangements of 4-aminobenzotriazoles only occur when the N(1) substituent is strongly



Scheme 11

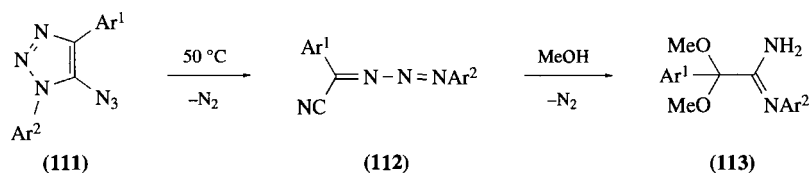
electron withdrawing. Thus, 4-amino-1-(4-toluenesulfonyl)benzotriazole (**107**, R = Me) is completely converted to 7-methyl-4-[(4-toluenesulfonyl)amino]benzotriazole (**108**) and the reverse rearrangement is not observed (Scheme 12). The bis-tosylates (**109**) are relatively stable and their rearrangements are slow, especially in nonpolar solvents. Compounds (**109**, R = Me) and (**110**) interconvert but can be separated from the equilibrium mixture and identified by NMR, IR, and x-ray. When R = H, the rearrangement is so fast that it can only be studied by NMR. Crossover experiments support an intramolecular mechanism ^[92JOC190].



Scheme 12

4.01.4.2 Thermolysis

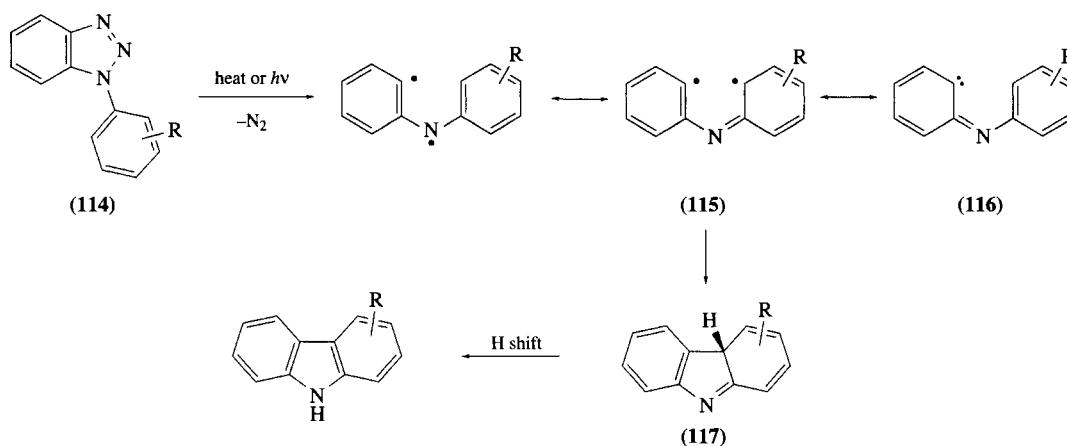
The gas-phase pyrolysis of 1*H*-1,2,3-triazole is studied by photoelectron spectroscopy. 2*H*-Azirine is the main product with some acetonitrile formed in addition to nitrogen which is evolved at 515K ^[83JA7681]. 5-Azido-4-aryl-1,2,3-triazoles (**111**) decompose thermally with loss of nitrogen at 50°C to form alkylidene triazenes (**112**) which react further with methanol undergoing additional elimination of nitrogen to give compounds (**113**) (Scheme 13) ^[88T3617, 89T749].



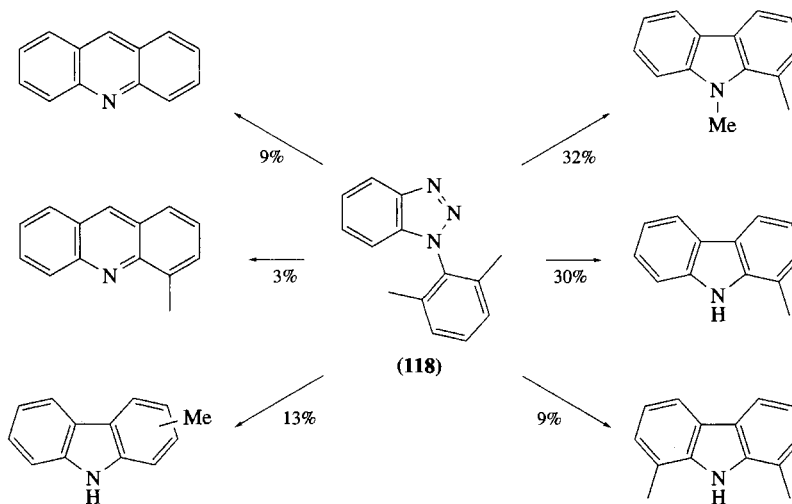
Scheme 13

Thermal or photochemical extrusion of nitrogen from 1-arylbenzotriazoles (**114**) leads to the formation of carbazoles (Scheme 14). The mechanism is believed to involve cyclization of a diradical (**115**) or an iminocarbene (**116**) to the 4*aH*-carbazole (**117**) followed by an aromatizing hydrogen

shift. The flash vacuum pyrolysis of benzotriazoles (**118**) in which both *ortho*-hydrogens of the 1-aryl substituent are replaced by methyl groups gives complex products as shown in Scheme 15; the major products are mono- and dimethyl-carbazoles. All of these products can be rationalized by the generation of a 4*aH*-carbazole intermediate of type (**117**) followed by thermally-allowed sigmatropic rearrangements. The pyrolysis of 1-(pentamethylphenyl)benzotriazole (**120**) yields an even more complex mixture from which only the two carbazoles (**119**) and (**121**) can be identified (Scheme 16) <85JCS(P1)2725>. Flash-vacuum pyrolyses of 1-vinylbenzotriazoles at 500–650 °C give *N*-phenylketenimines from the loss of nitrogen. At higher pyrolysis temperatures 1-vinylbenzotriazole affords indole via isomerization of the ketenimine <88JCS(P2)1071>. 1-Vinylbenzotriazoles give indoles on flash pyrolysis at 600 °C/10⁻² Torr. However, depending on the vinyl substituents, side reactions leading to *N*-phenylketenimines or benzonitrile are also observed <90JCS(P1)485>.



Scheme 14



Scheme 15

The vapor-phase pyrolysis of 4-hydroxy-1,2,3-triazole and its *N*-methyl derivative affords methanimine and its *N*-methyl analog. Analysis of the reaction path by the MNDO method shows the presence of two stable or metastable isomers, (1*H*)-4-hydroxy-1,2,3-triazole and its ketone protomer <89NJCS51>. 4-Diazo-1,2,3-triazoles (**122**) thermolyze or photolyze in benzene to 4*H*-1,2,3-triazolyldenes (**123**) which convert benzene to 4-phenyl-1,2,3-triazoles and/or isomerize to α -diazonitriles (**124**). Intermediates (**124**) react with benzene via a carbene to give addition, ring expansion or substitution products (Scheme 17) <82TL5115>. The similar thermolysis of diazotriazoles in substituted benzene gives complex mixtures in which all of the components are sometimes impossible to isolate and identify <90AHC(48)65>.

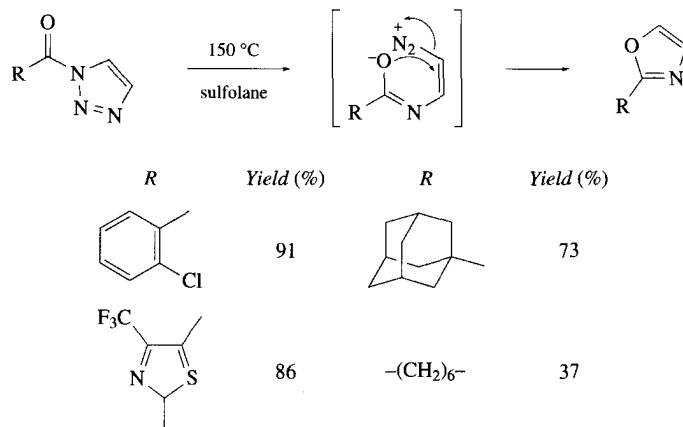
Triazole amides, when heated to 150 °C in sulfolane, rearrange with the elimination of nitrogen

Scheme 16

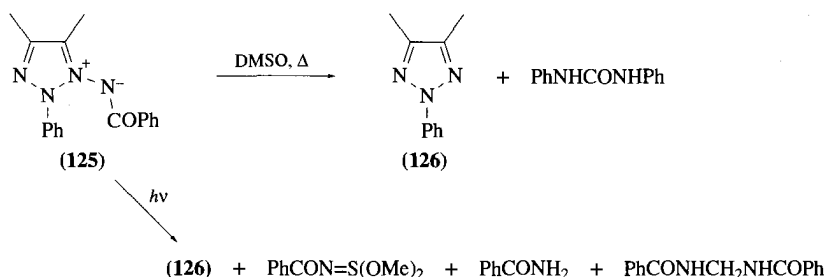
Scheme 17

Scheme 18

In a photolytic decomposition, triazol-1-imine (**125**) affords (**126**), benzamide, *N*-benzoyl



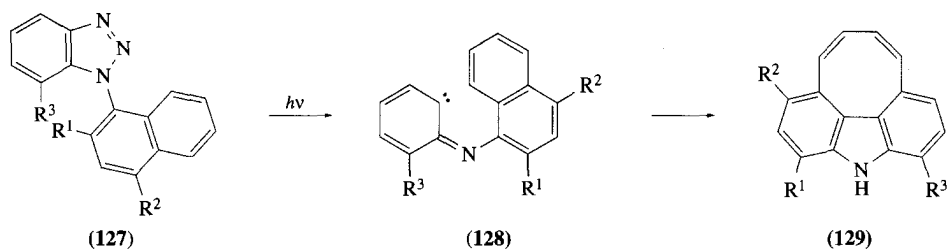
Scheme 19



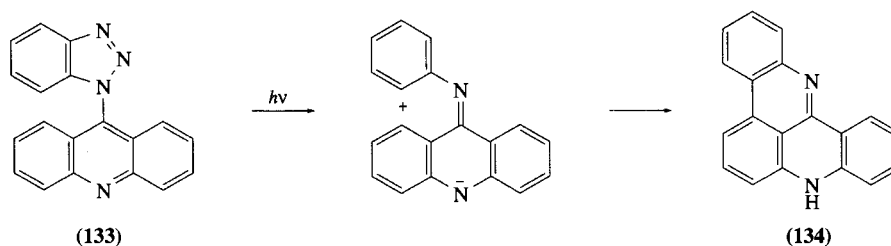
Scheme 20

dimethylsulfoximine, and methylene bisbenzamide. These results parallel the benzophenone-sensitized irradiation of benzoyl azide and indicate that nitrene is likely involved (92JOC2252).

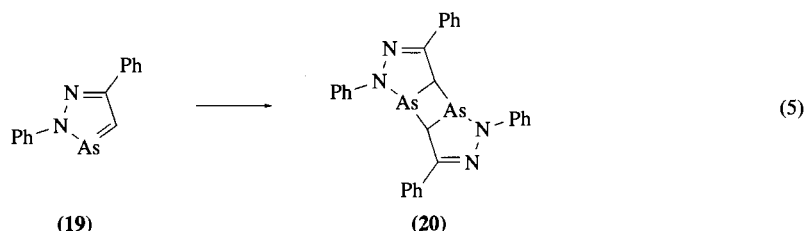
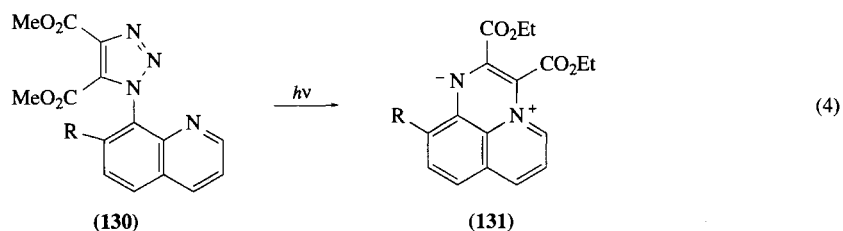
It is well known that the photolysis of 1-arylbenzotriazoles affords a high yield of the corresponding carbazoles (81AHC(28)231). The study has been extended to more complex systems; the photolysis of 1-(1-naphthyl)benzotriazoles (127) gives (i) cycloocta[def]carbazoles (129) by collapse of an intermediate carbene (128) on to the naphthalene ring junction followed by ring expansion, and (ii) the 6a*H*-benzo[*a*]carbazole (117) and its photo-rearrangement product (Scheme 21). The substituents can be H, Me, Cl, Br, and SiMe₃ (85CC652, 85JCS(P1)2733). On similar photolysis, the quinolinyltriazoles (130) give the stable ylides (131) (Equation (4)) (87JCS(P1)403). In contrast with its thermolysis, photolysis of 1-(2,6-dimethylphenyl)benzotriazole (118) in acetonitrile at 254 nm gives only cyclopentaquinoline (132) in 46% yield (Equation (5)). The photolysis of acridinylbenzotriazole (133) yields the quinocridine (Scheme 22) (134) (85JCS(P1)2725, 87JCS(P1)403).



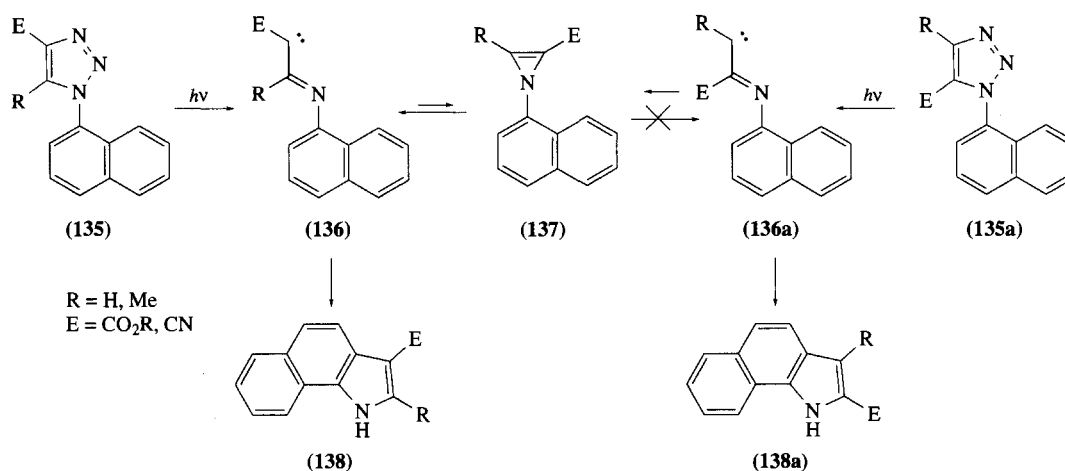
Scheme 21



Scheme 22



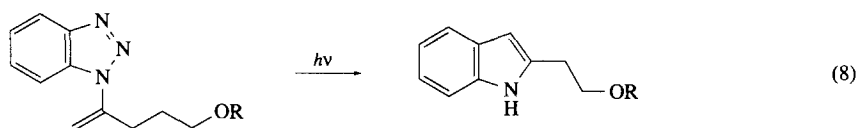
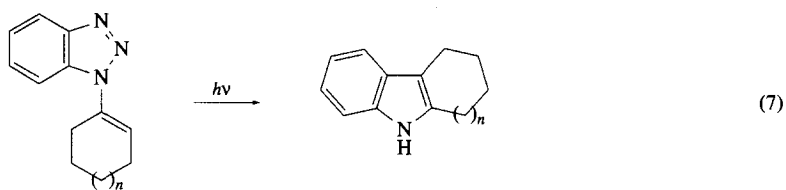
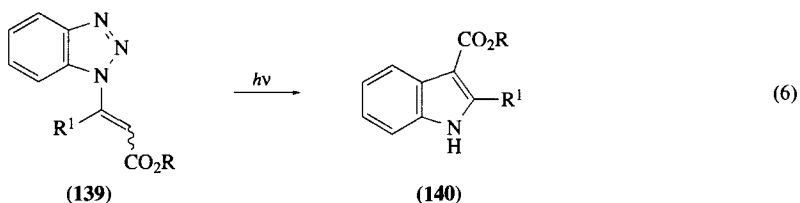
The photolysis of 1-(1-naphthyl)-1,2,3-triazoles (135) which have electron-withdrawing groups on at least one carbon atom of the triazole ring gives the appropriately substituted benzo[*g*]indoles (138) and (138a) (Scheme 23), arising from attack of the intermediate carbenes (136) and (136a) at the naphthalene 2-position. Isomeric carbene (136a) can rearrange to (136) via azirine (137); however, this process is irreversible. Thus, photolysis of (135) with one electron-withdrawing group at the 4-position affords only the corresponding indoles (138), while that of (135a) with an EWG at the 5-position gives a mixture of indoles (138) and (138a). Photolysis of 1-phenyltriazoles with electron-withdrawing groups at the 4- or 5-positions follows the same pattern <86CC399, 87JCS(P1)413>.



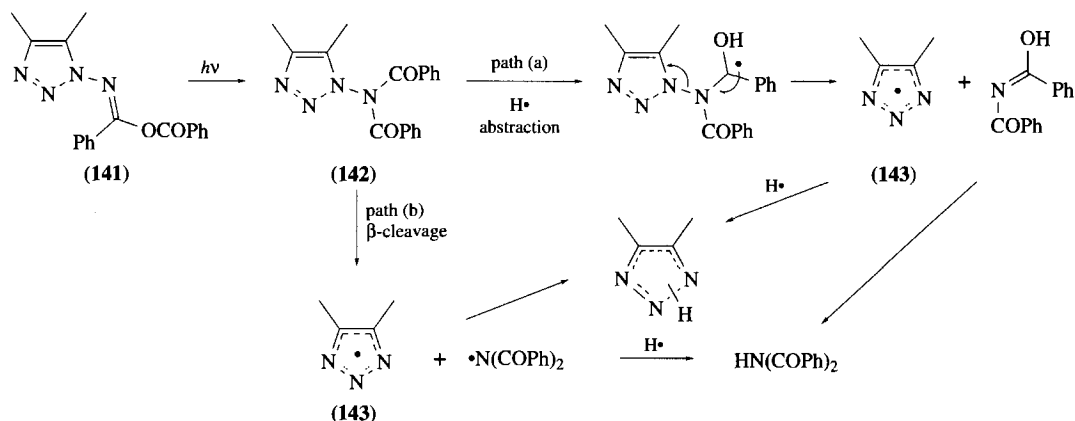
Scheme 23

The corresponding photochemistry of 1-alkenylbenzotriazoles has received only limited attention. However, by analogy to the 1-arylbenzotriazoles, cyclization to indoles is observed, albeit in

variable yield <79HCA2129>. The photolysis of 1-alkenylbenzotriazoles (**139**) gives 3-alkoxycarbonyl substituted indoles (**140**) in good yield. A number of 2- or 3-substituted and 2,3-disubstituted indoles are synthesized from the photolysis of 1-alkenylbenzotriazoles (Equations (6)–(8)) <86T2985>.

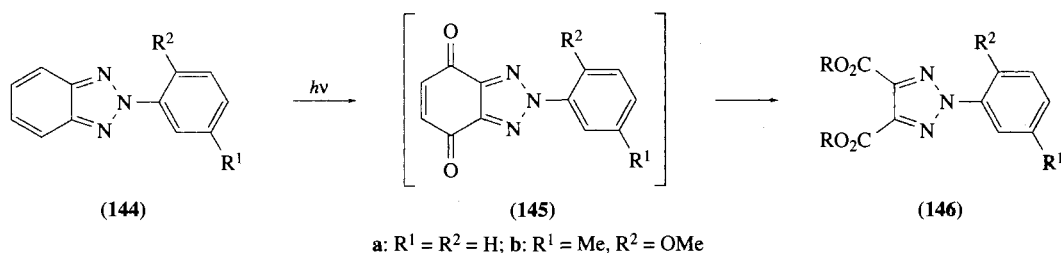


The photoinduced β -elimination of 1,2,3-triazole from 1-(*N,N*-bisacyl)amino-1,2,3-triazoles (**142**), itself formed from the photochemical isomerization of triazoles (**141**), proceeds either via an intra- or intermolecular hydrogen abstraction or electron-transfer mechanism followed by homolytic cleavage of the *N,N*-bond (path a); or via π^* -assisted β -cleavage of the same weak bond (path b). The composition of the products suggests that in all cases a σ -type 1,2,3-triazolyl radical (**143**) is eliminated which is further quenched by hydrogen abstraction as shown in Scheme 24 <93JHC1301>.



Scheme 24

UV irradiation of 2-arylbenzotriazoles (**144**), including the commercially available photostabilizer Tinuvin P, in an aerated solvent results in oxidation of the benzo ring to give the 2-aryl-1,2,3-triazole-4,5-dicarboxylic acid (**146**), possibly via the intermediate 2-arylbenzotriazole-4,7-dione (**145**) (Scheme 25). Indeed, when the independently synthesized 1-phenyl-2*H*-benzotriazole-4,7-dione (**145**, $R^1 = R^2 = H$) is irradiated under the same conditions, compound (**146**; $R^1 = R^2 = H$) is formed, and the reaction is completed within 30 min <89AJC441>.



Scheme 25

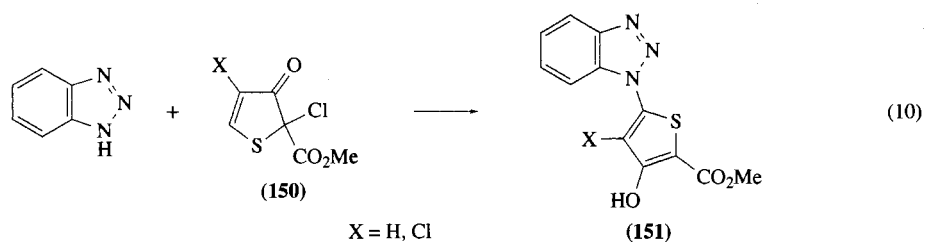
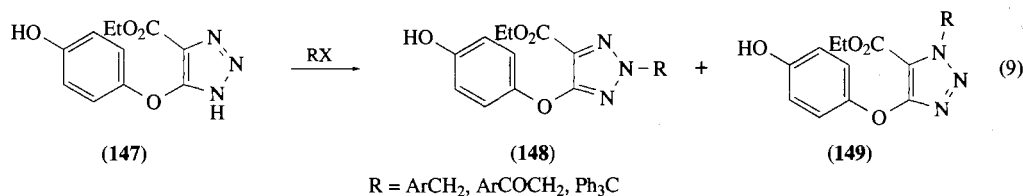
4.01.4.4 Electrophilic Attack at Nitrogen, Acidity and Basicity

For acidity and basicity of azoles, see Catalan *et al.* <87AHC(41)187>.

4.01.4.5 Alkylation and Acylation Reactions

N-Alkylation of 1,2,3-triazoles and benzotriazoles is readily achieved using (i) alkyl halides, dialkyl sulfates, diazoalkanes, and *p*-tosylates or (ii) the Mannich reaction. For early works, see CHEC-I <84CHEC-I(5)697> and Katritzky *et al.* <91RTC369>. When alkyl halides are used sodium alkoxide, sodium hydride <93T10205> or sodium hydroxide <92LA843> is usually employed as the base. The *N*-alkylation of benzotriazole with alkyl halide proceeds efficiently using powdered NaOH as the base in DMF. The highest yields (80–100%) of the alkylated benzotriazoles are obtained when a fourfold excess of NaOH is employed <91RTC369>. *N*-Alkylbenzotriazoles have been prepared from benzotriazole and alkyl halides using phase-transfer catalysts, e.g., KOH/benzene/tetrabutyl ammonium salts <85H(23)2895>, KOH/benzene/polyethylene glycol <90JCS(P2)2059>. *N*-Alkylbenzotriazoles can also be synthesized as mixtures of the N(1) and N(2) isomers by the reaction of benzotriazole with the corresponding aryl- or diaryl-methanols in benzene in the presence of TsOH <90JCS(P2)2059>. Alkylation of benzotriazole has been performed either in basic media under solvent-free phase-transfer catalysis conditions or in the absence of base by conventional and microwave heating <94H(38)793>. Most methods generate *N*-alkylbenzotriazoles as mixtures of the N(1) and N(2) isomers which can be separated by column chromatography.

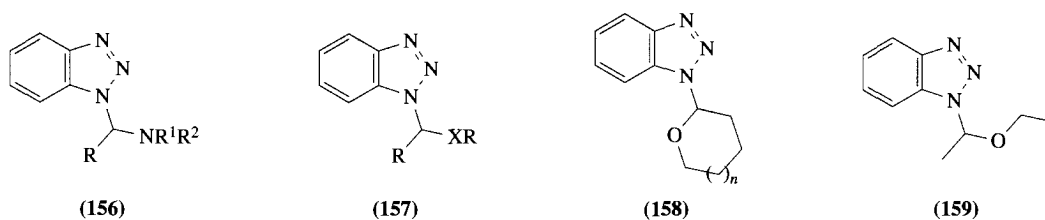
The alkylation of 5-(4-hydroxyphenoxy)-1*H*-1,2,3-triazoles (147) under alkaline conditions exclusively yields the isomeric N(2) and N(3) alkylation products (148) and (149) (Equation (9)). For $R = PhCH_2$, the N(2) and N(3) isomers are obtained in almost equal amounts, but for $R = Ph_3C$, only 1% of the N(3) isomer is formed because of steric hindrance. No N(1) alkylation is observed. Acylation and sulfonation of (147) under similar conditions results in attack at the phenolic oxygen <82JHC1147>. Reaction of benzotriazole with 2-chlorothiophen-3-ones (150) in acetic acid gives 5-(benzotriazol-1-yl)-3-hydroxythiophene-2-carboxylates (151) (Equation (10)) <87JHC1301>.



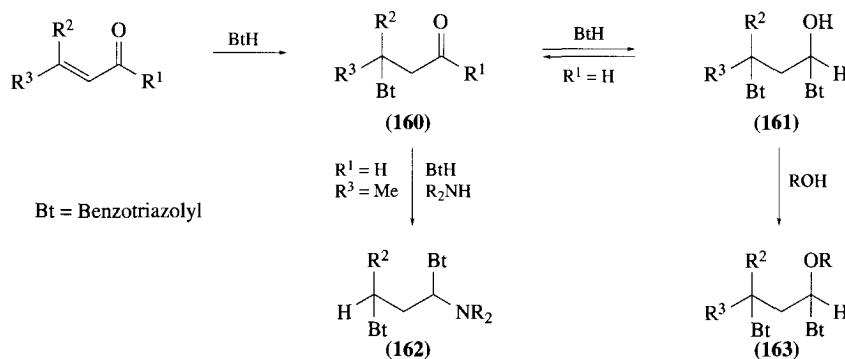
(152) + $\xrightarrow{\text{toluene}}$ (153) (11)



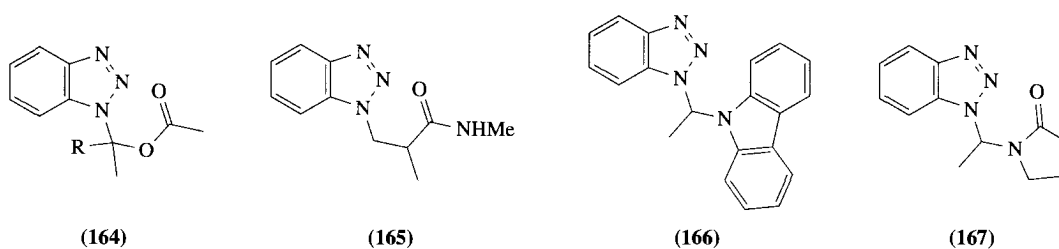
Benzotriazole and aldehydes react reversibly to give addition products. In most cases α -(hydroxyalkyl)benzotriazoles can be obtained in good yields $\langle 87\text{JCS(P1)791, 90JHC1543} \rangle$. Benzotriazole undergoes condensation with amines and perfluoroaldehydes $\langle 91\text{JFC(51)33} \rangle$. In the presence of amines, amides, and other NH compounds, water is eliminated to form **156** ($\text{R}^1 = \text{alkyl, aryl, NHR, COR, CSR, SO}_2\text{R, NOH}$; $\text{R}^2 = \text{alkyl, aryl, H}$). The similar oxygen and sulfur derivatives (**157**, $\text{X} = \text{O, S}$) are also easily prepared $\langle 87\text{JCS(P1)791, 89\text{JOC6022}} \rangle$. The condensation of benzotriazole with aldehydes in the presence of SOCl_2 gives 1-(α -chloroalkyl)benzotriazoles $\langle 87\text{JCS(P1)811, 91S69} \rangle$. For further details, see Section 4.01.7.



Benzotriazole readily adds to vinyl ethers to form the corresponding α -benzotriazolyl saturated ethers (e.g., (158) and (159)) $\langle 90\text{JCS(P1)1717} \rangle$. Addition of benzotriazole to α,β -unsaturated aldehydes and ketones gives β -benzotriazolyl-aldehydes (160, $\text{R}^1 = \text{H}$) and -ketones (160, $\text{R}^1 = \text{alkyl}$) in high yield (Scheme 27); (160) can react with a further equivalent of benzotriazole to give 1,3-bis(benzotriazolyl)alkanols (161). In the presence of amines or alcohols, 1,3-bis(benzotriazolylalkyl)amines (162) or ethers (163) are formed respectively $\langle 92\text{PJC1633} \rangle$. Benzotriazole also undergoes addition to alkynoates $\langle 86\text{T2985} \rangle$, vinyl acetates $\langle 90\text{JCS(P1)1717} \rangle$, acrylamides $\langle 93\text{JHC1261} \rangle$, enamines, and enamides to give the corresponding adducts (e.g. (139) and (164)–(167). For details, see also Section 4.01.7.

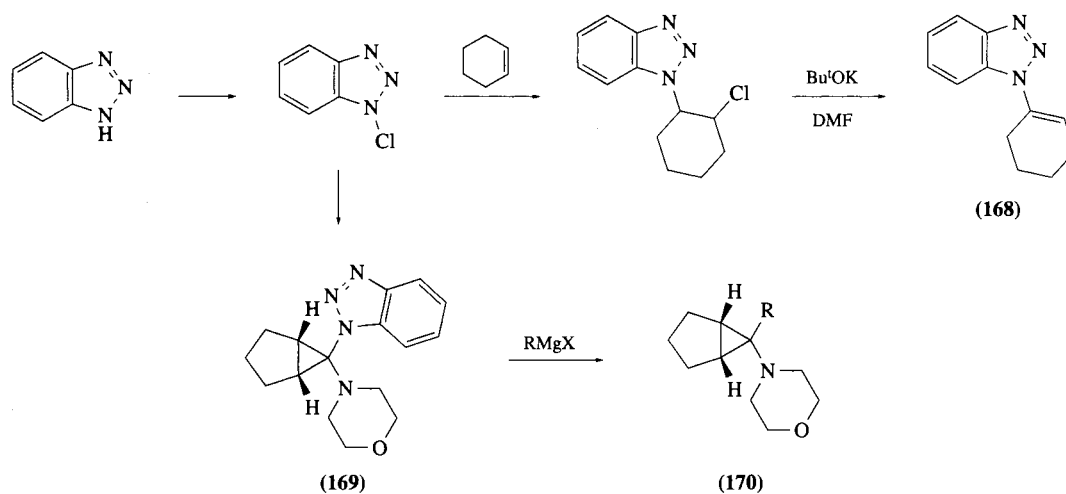


Scheme 27

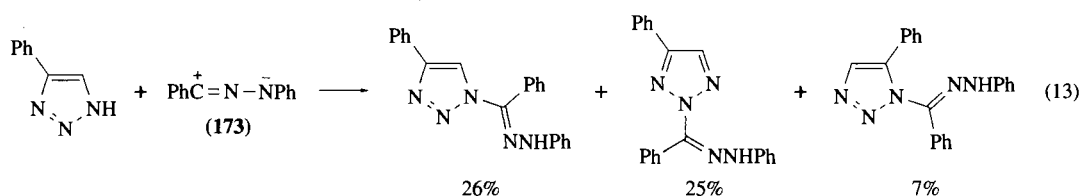
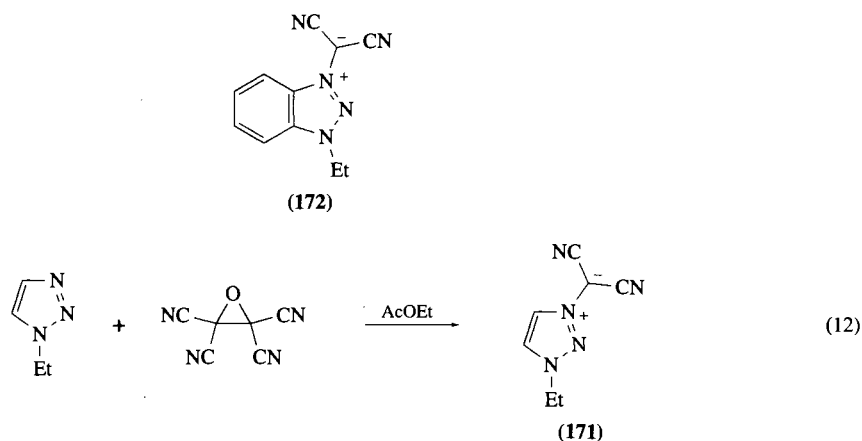


1-Chlorobenzotriazole reacts with alkenes to provide addition products $\langle 69\text{JCS(C)1474} \rangle$. Thus, 1-chlorobenzotriazole adds to cycloalkenes, then undergoes subsequent dehydrohalogenation with Bu^tOK in DMF to give 1-cycloalkenylbenzotriazoles (168) (Scheme 28) $\langle 86\text{T2985} \rangle$. Reaction of 1-chlorobenzotriazole with 4-(cyclohexen-1-yl)morpholine in the presence of triethylamine gives bicyclic compound (169). Treatment of (169) with Grignard reagents produces substitution of the benzotriazolyl moiety by a phenyl or benzyl group to give (170) $\langle 94\text{H(38)319} \rangle$.

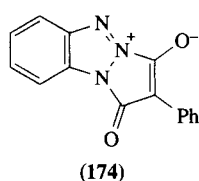
Tetracyanoethylene oxide reacts with equimolar amounts of 1-ethyl-1,2,3-triazole in ethyl acetate to give the 3-dicyanomethylide derivative (171), and with 1-ethylbenzotriazole to give the 3-dicyanomethylide product (172). However, the similar reaction with 2-ethylbenzotriazole does not occur $\langle 82\text{JOC4409} \rangle$. Reaction of phenyltriazole with diphenylnitrilimine (173) gives three hydrazonotriazoles (Equations (12) and (13)) $\langle 88\text{JCS(P1)3233} \rangle$. 4,5-Dimethyl-1,2,3-triazole undergoes a similar reaction to yield N(1) and N(2) hydrazone derivatives $\langle 90\text{JHC231} \rangle$. The analogous reaction between benzotriazole and (173) gives 1- and 2-arylhydrazonylbenzotriazoles $\langle 85\text{H(23)2779} \rangle$.

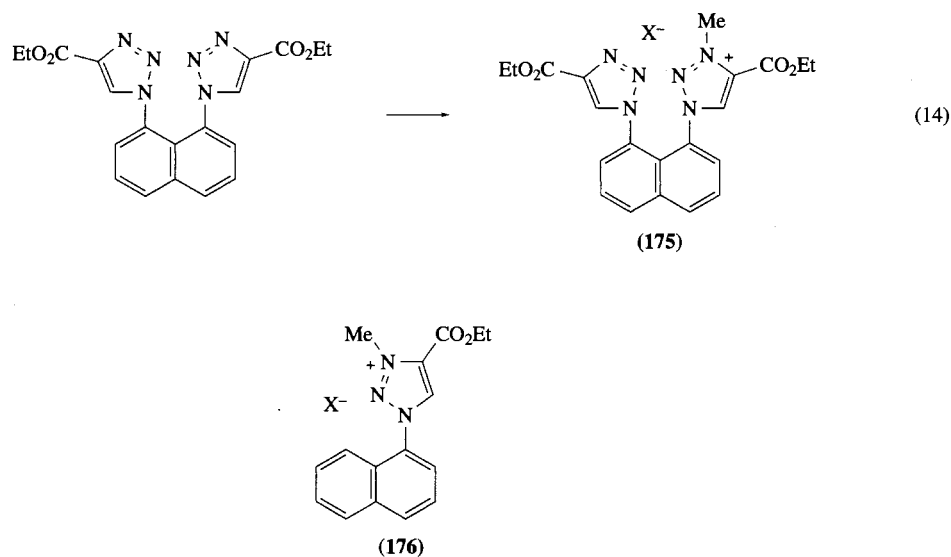


Scheme 28



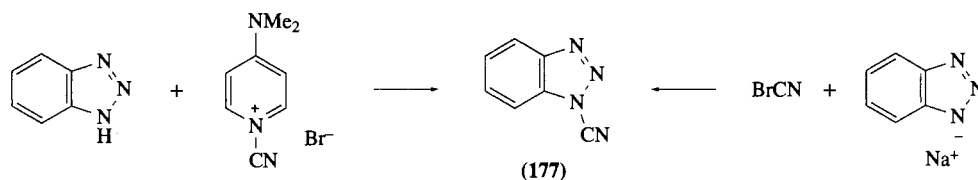
Quaternization of 1-alkyl-1,2,3-triazoles and -benzotriazoles is readily achieved by treatment with alkyl halides ^{<88BSB573>} or alkyl sulfates ^{<87H(26)1751>}. Benzotriazoles react with phenyl-(chlorocarbonyl)ketene to give (174) ^{<88JOC2889>}. Controlled *N*-methylation of bistriazolyl-naphthalene with methyl *p*-toluenesulfonate gives selectively the *N*-methyltriazolium tosylate salt (175). The monotriazolium salt (176) is similarly synthesized. Treatment of (175) and (176) with ion-exchange resins affords the corresponding triazolium halides (Equation (14)). The H-D exchange of mono *N*-methyltriazolium (175, X = Cl, Br) and (176) in D₂O are studied by proton NMR spectroscopy. The reaction rates of (175) are much faster than those of (176), suggesting that the triazole ring in (175) interacts sterically with the *N*-methylated triazole ring to accelerate the H-D exchanges ^{<91H(32)1709>}. Quaternary triazolium ions have been used for the selective introduction of substituents into the 4- or 5-position; see Sections 4.01.4.8–4.01.10.





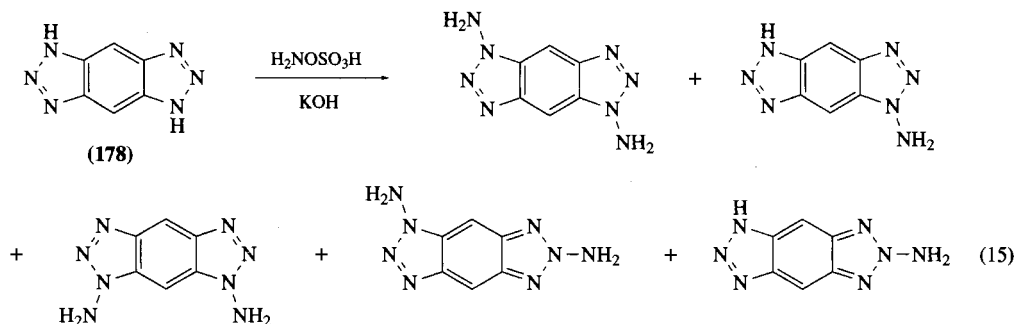
4.01.4.6 Other Electrophilic Attack at Nitrogen

Benzotriazole reacts with 1-cyano-4-dimethylaminopyridinium bromide to give 1-cyano-benzotriazole (177) (Scheme 29) <88S470>. 1-Cyanobenzotriazole is also prepared in a more convenient way from cyanogen bromide and the sodium salt of benzotriazole in 90% yield under carefully controlled conditions <91RRC573>. Benzotriazole can be chlorinated at the N(1) position by NaOCl <85H(23)2225>. *N*-Fluorination of benzotriazole with caesium fluoroxysulfate gives 1-fluorobenzotriazole in 25% yield <91T7447>.



Scheme 29

Direct amination of benzo[1,2-*d*:4,5-*d'*]bistriazole (178) in aqueous base with hydroxylamine-*O*-sulfonic acid gives a mixture of three diamino derivatives and two monoamino derivatives (Equation (15)). The combined yields of diamino and monoamino products are 45% and 48%, respectively. The three diamino derivatives can be separated by fractional crystallization from ethanol <86JOC979>. *N*-Amination of triazoles can also be achieved by treatment with NaH in DMF followed by *O*-amino-2,4-dinitrophenol <85TL335> or *O*-(mesitylsulfonyl)hydroxyamine <91JCS(P1)2045>.



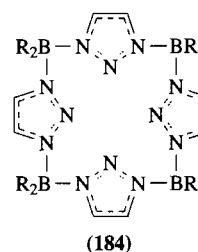
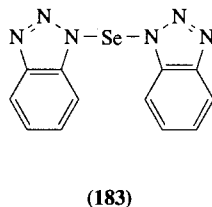
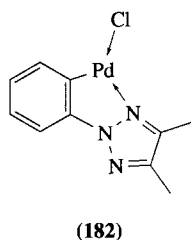
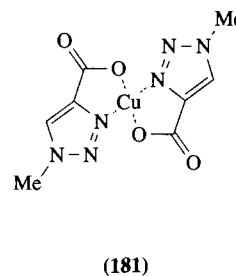
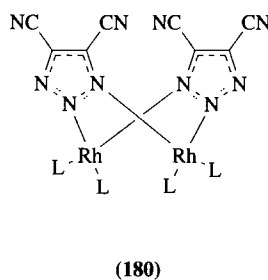
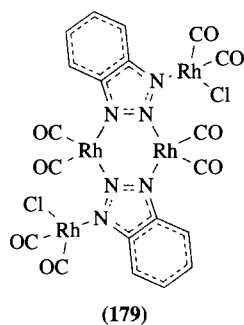
1-Substituted 1,2,3-triazoles are oxidized by *m*-chloroperoxybenzoic acid at the more basic N(3) to give the corresponding triazole *N*-oxides. The yield is lower if an electron-withdrawing substituent is present at the C(4) or C(5) position <87ACS(B)724>. 2-Alkyl-1,2,3-triazole-1-oxides are produced from the oxidative cyclization of alkyl hydrazono oximes <86ACS(B)262>; see Section 4.01.8.1.

4.01.4.7 *N*-Metallation Reactions

1,2,3-Triazole and benzotriazole are both weak acids and are capable of coordinating with a metal in anionic as well as neutral form. Transition-metal derivatives of triazoles and benzotriazoles have been reviewed <88MI 401-01>. Adducts of triazoles with transition-metal salts are usually prepared by direct reaction of the two components and frequently precipitate or crystallize spontaneously from the reaction mixture <83ICA109, 84ACS(A)257>. The generally preferred coordination positions appear to be N(3) for triazoles and N(1) for triazolate anions <83CJC2520, 88MI 401-01>.

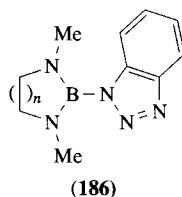
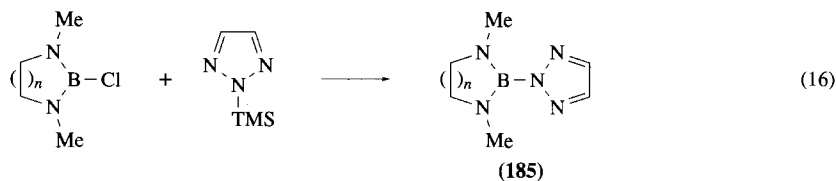
Complexes of triazoles and benzotriazoles with various transition metals have been reported: titanium and manganese <83ICA109>, molybdenum <77IC3372, 89JOM(372)251>, iron <83CJC2520>, cobalt <87ZN(B)55>, nickel <83ICA109>, palladium <83CB269, 83ZN(B)546, 87ZN(B)55>, platinum <85ICA173>, copper <83JST(100)571, 83ICA109, 85ICA173>, zinc <81ACS(A)739>, cadmium, and mercury <83ICA109>.

The preparation and properties of mono- and di-nuclear rhodium(I) complexes of benzotriazole with the general formula $\text{RhClL}_2(\text{BtH})$, $\text{Rh}(\mu\text{-Bt})\text{L}_2$, $\text{Rh}(\mu\text{-Bt})(\mu\text{-N}_3)(\text{L}_2)_2$, and $\text{Rh}_2(\mu\text{-Bt})(\mu\text{-SCN})(\text{COD})_2[\text{L}_2 = \text{dialkene}, (\text{CO})_2 \text{ or } (\text{CO})(\text{PPh}_3)]$ are described. For example, the complex (179) is prepared by the reaction of $\text{RhCl}(\text{CO})_2\text{BtH}$ and $\text{Rh}[\text{acac}(\text{CO})]_2$ <85JOM(280)261>. Binuclear rhodium(I) 4,5-dicyano-1,2,3-triazolate complexes (180) are obtained by treating $[\text{Rh}_2(\mu\text{-Cl})_2(\text{dialkene})_2]$ with dicyanotriazole <88JOM(338)411>. This rhodium triazole complex undergoes further reactions with various ligands leading to the cleavage of triazol bridges and the formation of new complexes. The synthesis and characterization of various copper(II) complexes of 1,2,3-triazolecarboxylic acids (e.g., (181)) are reported <85ICA121>. The triazole cyclopalladated complex (182) undergoes halogenation in the *ortho* position <85S233>. The reaction of bisallylselenide and *N*-chlorobenzotriazole affords 1,1'-bisbenzotriazolylselenide (183) <92TL2129>.



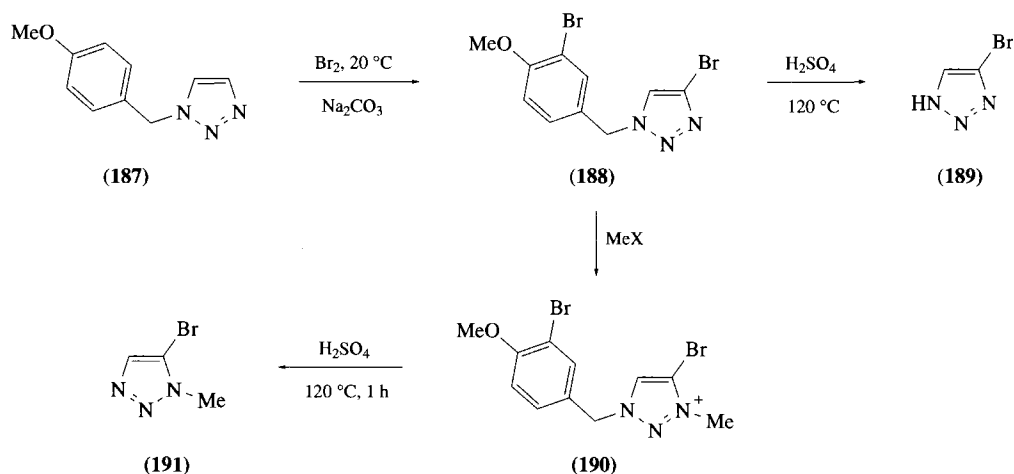
When 1-(trimethylsilyl)-1,2,3-triazole is treated with halodiorganylboraness R_2BX ($\text{X} = \text{Br}, \text{Cl}$), a cyclic tetramer (184) is obtained exclusively. Only one resonance is observed for the triazole rings in both the ^1H and ^{13}C NMR spectra of (184). The reaction of $\text{Me}_3\text{N-BH}_3$ with benzotriazole or trimethylsilylbenzotriazole gives the tetramer $[\text{H}_2\text{B}(\text{Bt})]_4$ with a cyclic structure analogous to (184) <89IC4022>. *N*-Bonded boron derivatives of triazole (185) containing trigonal boron have been prepared from the reaction of 2-chloro-1,3,2-diazaboracycloalkanes with 2-(trimethylsilyl)-1,2,3-

triazole via Si–N cleavage (Equation (16)). The benzotriazole boron derivative (**186**) is similarly obtained <90IC4693>.



4.01.4.8 Electrophilic Attack at Carbon

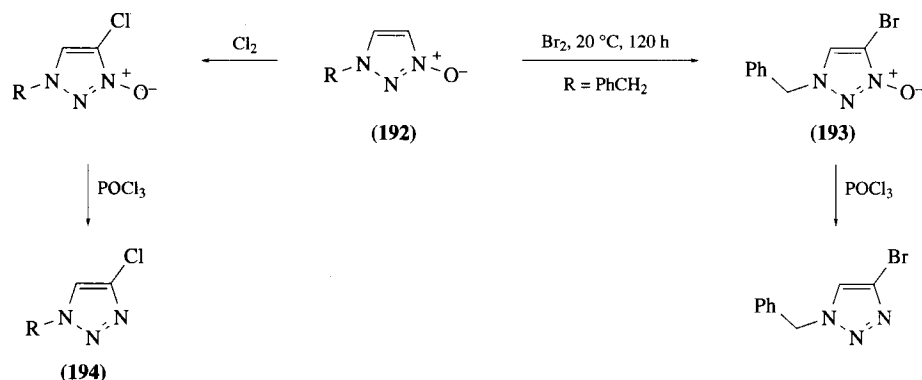
The following are reviews on this subject: <88BSB573, 92H(33)1129>, and <93AHC(57)291>. 1,2,3-Triazoles are considerably less reactive towards electrophilic attack at carbon than benzene. Thus, halogenation of both 1- and 2-phenyl-1,2,3-triazole occurs at the *para*-position of the phenyl group <63CJC2380, 87ACS(B)724>. Bromination of the parent 1,2,3-triazole gives only the 4,5-dibromotriazole. The 4-position of 1-substituted 1,2,3-triazoles is more reactive than the 5-position. Therefore, electrophiles attack only at the C(4) position with no dibromotriazole being formed <93AHC(57)291>. 1-Benzyltriazole is completely brominated to the 4-bromo derivative in seven days at 20 °C <87ACS(B)724>. 4-Bromo-1*H*-1,2,3-triazole (**189**) and 1-substituted 5-bromo-1,2,3-triazole (**191**), both inaccessible by direct electrophilic substitution, can be prepared by introducing a removable group to the N(1) position as shown in Scheme 30. 1-(4-Methoxybenzyl)-1,2,3-triazole (**187**) is brominated to give the dibromo intermediate (**188**) which undergoes quaternization with an alkyl halide to afford (**190**). Removal of the protective group by treatment with conc. H₂SO₄ results in 4-bromotriazole (**189**) from (**188**) and 1-methyl-5-bromo-1,2,3-triazoles (**191**) from (**190**), respectively <88BSB573>.



Scheme 30

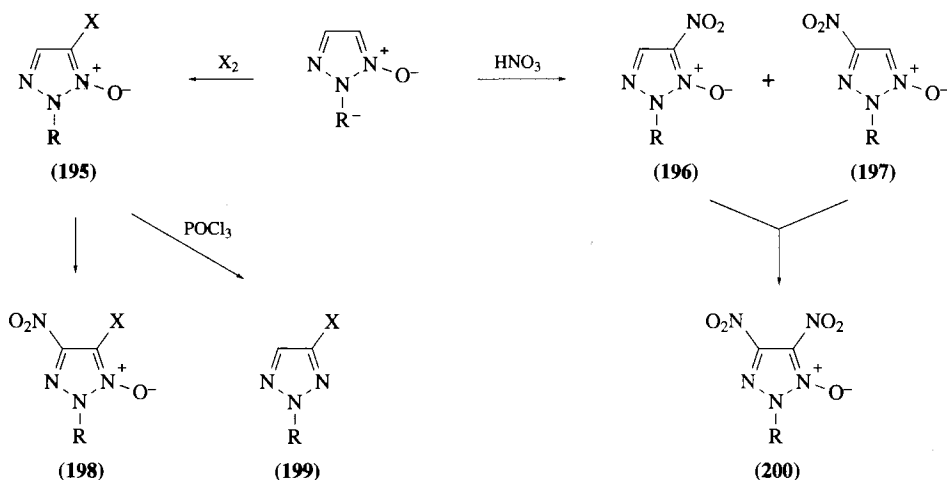
Triazoles can be activated towards electrophiles by the introduction of an *N*-oxide group. *N*-Oxidation gives rise to better activation of the 5-position than the 4-position. Thus, bromination of 3-benzyl-1,2,3-triazole 1-oxide (**192**, R = PhCH₂) requires only 120 h at 20 °C and affords the 5-bromo compound (**193**) in quantitative yield <87ACS(B)724>. 3-Phenyl-1,2,3-triazole 1-oxide is

selectively brominated or chlorinated to give the 5-halo-1,2,3-triazole without attack on the phenyl group. Therefore, the selective halogenation of (**192**, R = Ph) followed by deoxygenation with POCl_3 is a useful method to prepare the otherwise difficult to access 1-phenyl-4-halo-1,2,3-triazoles (**194**, R = Ph). 1-Alkyl-4-halo-1,2,3-triazoles (**194**, R = alkyl) can be similarly obtained (Scheme 31) $\langle 87\text{ACS}(\text{B})724 \rangle$.



Scheme 31

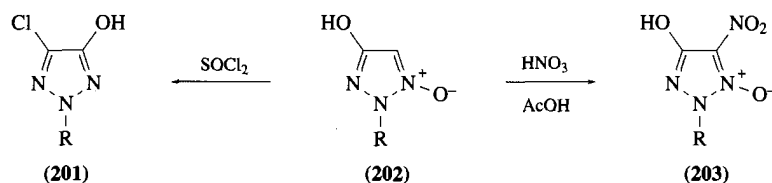
2-Alkyltriazole 1-oxides are halogenated to the 5-halo-1,2,3-triazole 1-oxides (**195**), and no 4-halogenation is observed (Scheme 32). However, both the C(4) and C(5) positions are attacked during nitration to form a mixture of mononitro derivatives (**196**) and (**197**). These 4- and 5-substituted 2-alkyltriazole 1-oxides (**195**) to (**197**) undergo further nitration to give disubstituted derivatives (**198**) or (**200**). However, the nitro group attacks the *para*-position of the phenyl group in the case of 2-phenyltriazole 1-oxide. Again, the triazole *N*-oxides (**195**) are readily deoxygenated by POCl_3 to give 2-alkyltriazoles (**199**). Conversely, the nitro derivatives (**198**) and (**200**) can not be deoxygenated $\langle 86\text{ACS}(\text{B})262 \rangle$.



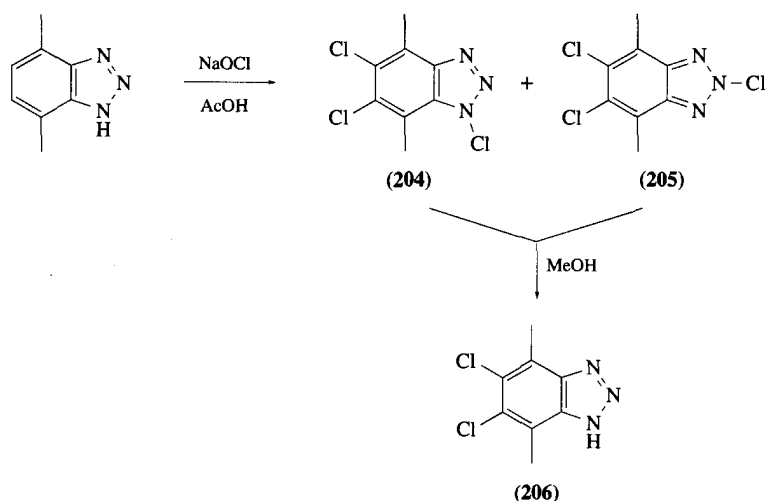
Scheme 32

4-Hydroxy-2-phenyl-1,2,3-triazole is brominated in chloroform to give 5-bromotriazole in 91% yield. Similarly, nitration with nitric acid in glacial acetic acid affords the 4-hydroxy-5-nitro-2-phenyltriazole in 60% yield $\langle 88\text{JOU}589 \rangle$. 5-Chlorotriazole-4-carboxaldehydes are prepared by the Vilsmeier-Haack reaction of 1,2,3-triazol-5-ols using POCl_3 and DMF $\langle 84\text{JHC}1603 \rangle$. The 2-alkyl-4-hydroxytriazole 1-oxide (**202**) is chlorinated at the 5-position with accompanying deoxygenation to form triazole (**201**) upon treatment with thionyl chloride (Scheme 33). The nitration of (**202**) gives the 5-nitro derivative (**203**) $\langle 88\text{JOU}589 \rangle$. Chlorination of 4,7-dimethylbenzotriazole with sodium hypochlorite in acetic acid affords a 3:2 mixture of the trichlorobenzotriazoles (**204**) and (**205**) (Scheme 34). Dechlorination of this mixture with methanol results in the dichlorobenzotriazole (**206**) $\langle 85\text{H}(23)2225 \rangle$.

2-(2',4',6'-Trinitrophenyl)-1,2,3-triazole undergoes nitration at the 4-position. The 1-isomer does



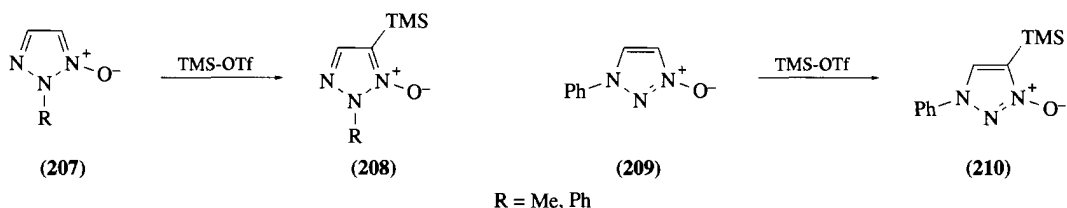
Scheme 33



Scheme 34

not undergo nitration [71JHC51]. The nitration of 2-methyltriazole can proceed stepwise through 2-methyl-4-nitrotriazole to 2-methyl-4,5-dinitrotriazole which is thermally stable above its melting point [86ACS(B)262]. Nitration of benzotriazole by mixed acid gives 4-nitrobenzotriazole, while 5-methylbenzotriazole affords 5-methyl-4-nitrobenzotriazole [92JOC190].

2-Methyl- and 2-phenyl-triazole 1-oxide (207) are silylated selectively at the 5-position with trimethylsilyl triflate to afford stable 5-trimethylsilyl derivatives (208) (Scheme 35). If the 5-position is blocked with a substituent, the 4-position is silylated. Thus, 5-chlorotriazole 1-oxide is converted to 5-chloro-4-trimethylsilyl-1,2,3-triazole 1-oxide in the presence of lithium tetramethylpiperidine. 3-Phenyl-1,2,3-triazole 1-oxide (209) is selectively silylated at C(5) to afford (210) by treatment with trimethylsilyl triflate and diisopropylethylamine. If the C(5) position is blocked, electrophilic attack occurs at the C(4) position [93JCS(P1)625].

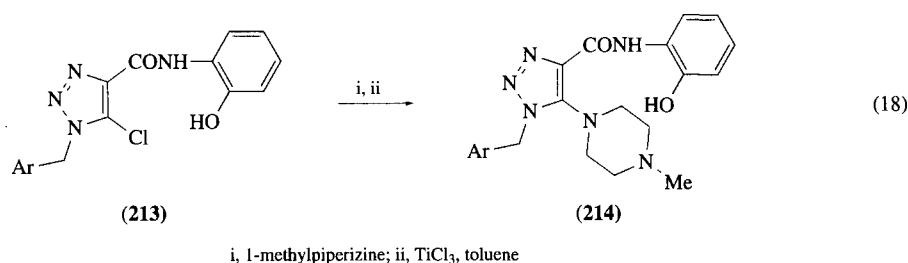
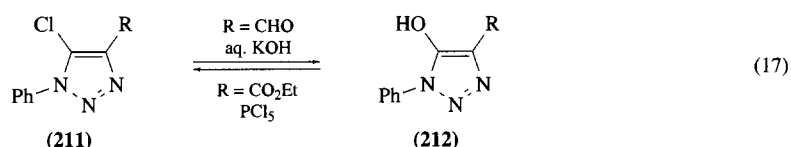


Scheme 35

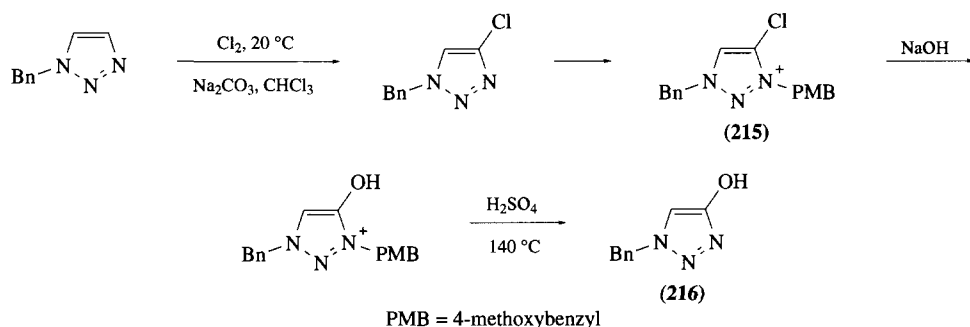
4.01.4.9 Nucleophilic Attack at Carbon and Nitrogen

The C(5) position of 1-substituted 1,2,3-triazoles is activated towards nucleophilic attack by a pyridine-like nitrogen, and the equivalent C(4) and C(5) positions of 2-substituted 1,2,3-triazoles are weakly activated. However, a suitable leaving group, such as a halogen, is generally required for nucleophilic substitution [88BSB573].

5-Chloro-1*H*-1,2,3-triazole-4-carboxaldehydes (**211**, R = CHO) are readily hydrolyzed to the corresponding 5-hydroxytriazoles (**212**) in aqueous media (Equation (17)) <84JHC1603>. On the other hand, 5-hydroxytriazoles (**212**, R = CO₂Et) are converted to their 5-chloro derivatives (**211**, R = CO₂Et) on refluxing with PCl₅ in toluene <82JCR(S)292, 85JHC1693>. Nucleophilic substitution of the halogen in triazole rings with cyanide and amines is known, for example, the chlorine at the 5-position of triazole (**213**) is readily displaced by *N*-methylpiperazine to give the amino derivative (**214**) (Equation (18)) <85JHC1693>, and by phenols to afford 5-phenoxy-1,2,3-triazoles <82JHC1147>. However, the initially formed product of the reaction of 1-aryl-5-chloro-1,2,3-triazoles with hydrazine undergoes a Dimroth rearrangement to 1-amino-5-(substituted)amino-1,2,3-triazoles <89BSB343>. The amino group of aminotriazoles can be replaced by hydroxy or halogen substituents via diazotization <89BSB419, 89BSB343>.



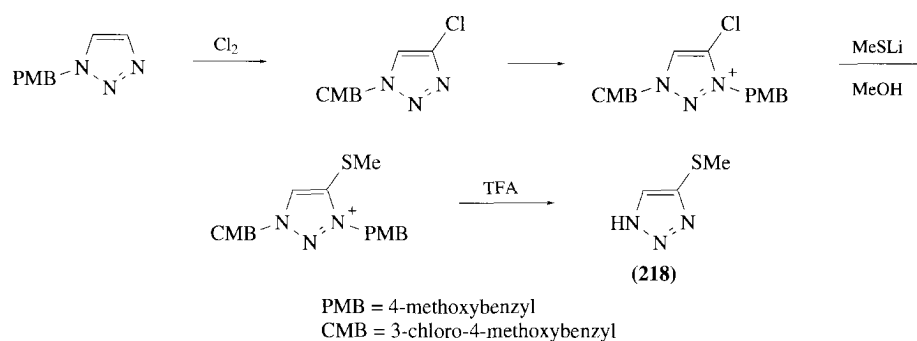
Quaternization of triazole nitrogen atoms causes the ring to become positively charged and activated towards nucleophilic attack. Thus, the synthetic strategy shown in Scheme 36 can be applied to the preparation of 1-benzyl-4-hydroxy-1,2,3-triazole (**216**) using *p*-methoxybenzyl as a removable activating group. Generally, this synthetic sequence can be used for the preparations of 1-alkyl-4-substituted triazoles (**217**) by reaction of the intermediate (**215**) with various nucleophiles, followed by removal of the activating group <88BSB573>. 4-Substituted 1*H*-triazoles (**219**) can be prepared by the introduction of two removable *N*-substituents to triazole as illustrated by the synthesis of 4-methylthio-1,2,3-triazole (**218**) in Scheme 37. Although the protecting group (PMB) is also chlorinated, the deprotection is not affected. Both activating groups (CMB and PMB) are removed by treatment with trifluoroacetic acid <88BSB573>. 4,5-Disubstituted 1-alkyl-1,2,3-triazoles (**220**) are similarly prepared from 4,5-dihalo triazoles by the introduction of the PMB activating group as outlined in Scheme 38.



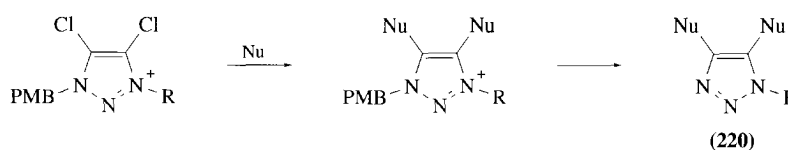
PMB = 4-methoxybenzyl

Scheme 36

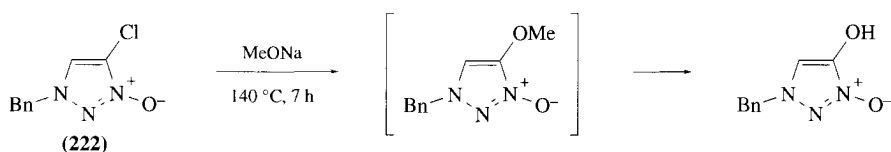
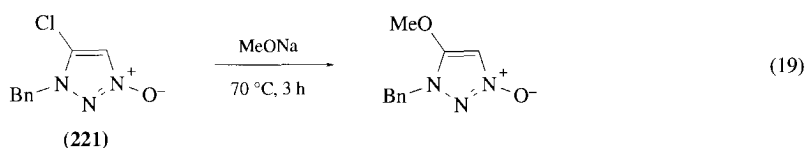
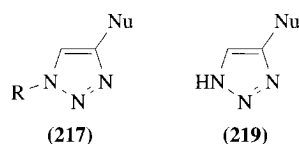
The nucleophilic substitution of 1,2,3-triazole is also activated by *N*-oxidation. In 3-substituted 1,2,3-triazole 1-oxides, a halogen substituent at C(4) is more reactive than one at C(5) <87ACS(B)724>. Therefore, the C(4) chlorine of compound (**221**) (Equation (19)) is displaced by methoxide under much milder conditions than the corresponding C(5) chlorine of (**222**) (Scheme 39), and the only C(5) bromine is displaced in the case of 4,5-dibromotriazole 1-oxide <88BSB573>.



Scheme 37



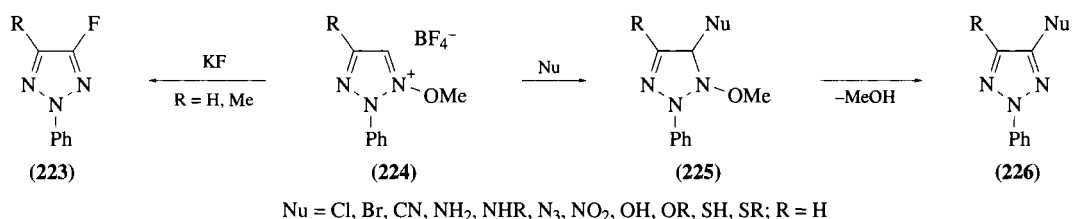
Scheme 38



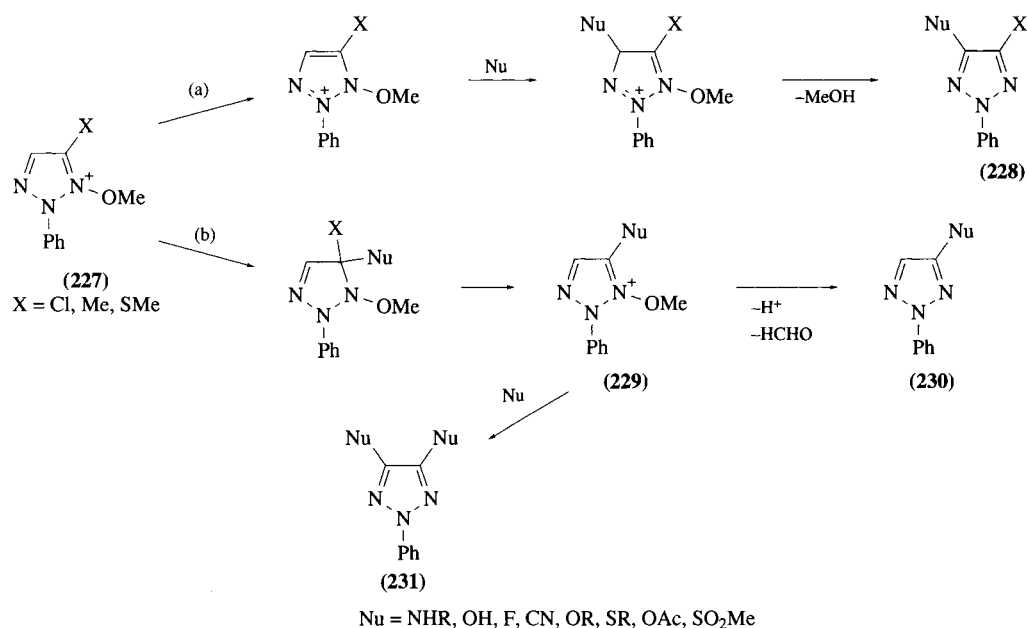
Scheme 39

The reaction of KF with 1-methoxy-2-phenyl-1,2,3-triazolium salts (**224**), which are obtained in quantitative yield by alkylation of the *N*-oxide with trimethyloxonium tetrafluoroborate, gives the 5-fluoro products (**223**) <77BSF171>. Compounds (**224**) react with a variety of nitrogen, halogen, carbon, sulfur, and oxygen nucleophiles to afford substituted products (**226**) via nucleophilic addition and subsequent elimination of methanol from the intermediate (**225**) <88BSB573>. The reactions of 5-substituted 2-phenyl-*N*-methoxytriazolium salts (**227**) with nucleophiles are more complex. There are two major paths depending on the nature of the 5-substituent, the nucleophile and the reaction conditions. When X = CH₃, nucleophilic attack at C(4) is followed by the elimination of methanol to give the unsymmetrical disubstituted triazoles (**228**) in good yield (path a). There are a few exceptions in which substitution at the methyl group via an elimination–addition mechanism is observed (Scheme 41). When X = Cl, a good leaving group, displacement of chlorine to give 5-substituted 1-methoxytriazoliums (**229**) and the corresponding elimination products (**230**) is the sole or predominant process for most nucleophiles (path b). When X = SMe, however, both pathways are operational and all products (**228** and **229**) are obtained. A symmetrical disubstituted

triazole (**231**) is formed on treatment with MeSNa. Strong nucleophiles favor the displacement of SMe <82JCS(P1)2749>.

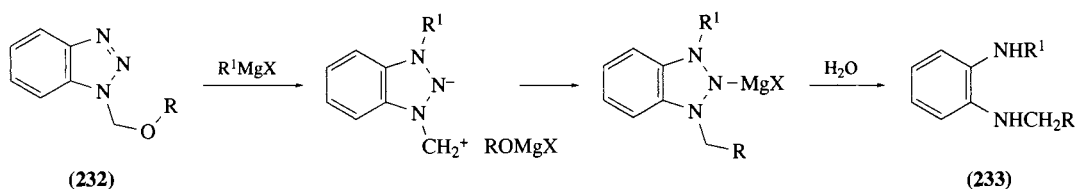


Scheme 40



Scheme 41

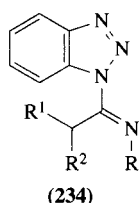
There are a few examples in which the pyridine-like nitrogen atoms of the benzotriazole ring undergo nucleophilic attack by organometallic reagents. Thus, the N(3) atom is attacked by Grignard reagents in (benzotriazol-1-yl)methylethers (**232**) (Scheme 42) <89JOC6022> and in (benzotriazol-1-yl)methyl ammonium salts to give *o*-phenylenediamines (**233**) in 10–40% yield <89JHC1579>. Grignard reagents attack 1-imidoylbenzotriazoles (**234**) at the imidoyl carbon atom and also at the benzotriazolyl-N(2) and N(3) atoms leading to complex reaction products <90CB1545>.



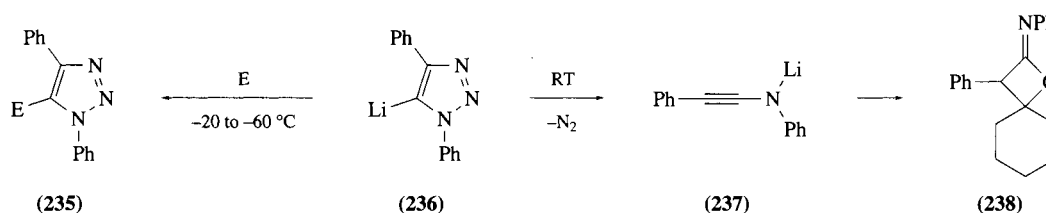
Scheme 42

4.01.4.10 Nucleophilic Attack at Hydrogen

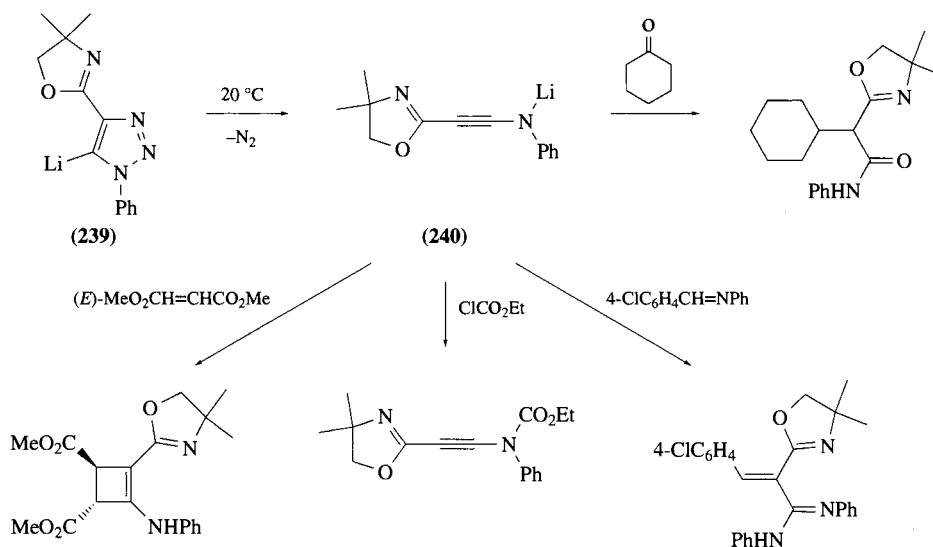
For reviews of this subject, see Begtrup <88BSB573> and Rewcastle and Katritzky <93AHC(56)155>. 1-Substituted 1,2,3-triazoles undergo lithiation with *n*-butyllithium at -20 to -60°C and reaction



with electrophiles at the 5-position to give substituted triazoles (**235**) (Scheme 43). However, the lithiated intermediate (**236**) rapidly undergoes fragmentation at room temperature to nitrogen and lithium ketenimine (**237**). The metallation of 1-phenyl-5-methyltriazole occurs at the methyl group <71CJC1792>. The lithium alkynylamides (**237**) react with carbonyl compounds to give oxetanes (**238**) <74LA1655>. The lithium salt (**240**) derived from 4-(dihydrooxazol-2-yl)triazole (**239**) undergoes simple substitution or [2 + 2] cycloaddition with a variety of electrophiles, such as ethyl chloroformate, Schiff bases, alkenes, and ketones to give interesting products (Scheme 44) <91JCS(P1)775>.



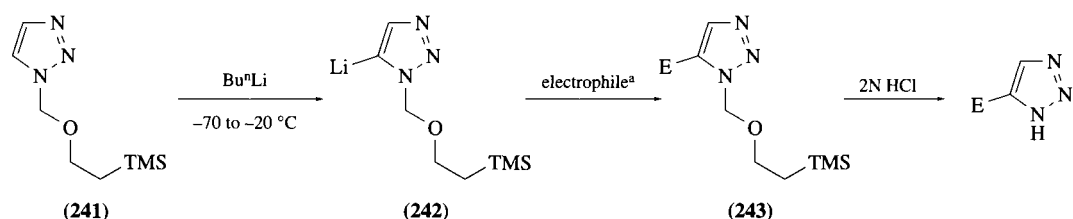
Scheme 43



Scheme 44

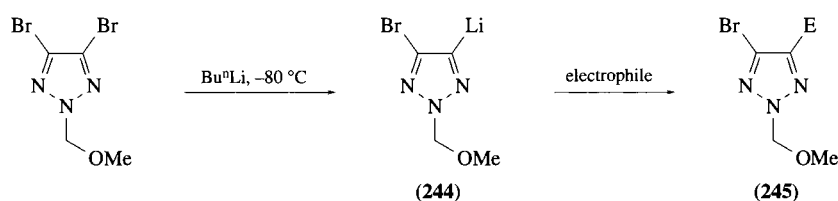
2-(Trimethylsilyl)ethoxymethyl (SEM) has been used as a protective group in the lithiation of 1-SEM-1,2,3-triazole (**241**) is accomplished by treatment with *n*-butyllithium in THF at -70°C and allowing the mixture to warm to -20°C before adding the electrophile to the re-cooled solution of the resulting lithio-intermediate (**242**) (Scheme 45). Removal of the protecting group from intermediate (**243**) by the action of aqueous HCl leads to the appropriate 4-substituted 1*H*-1,2,3-triazoles <92JHC1203>.

The direct lithiation of a 2-substituted 1,2,3-triazole has not been reported. Halogen-metal exchange of 4,5-dibromotriazole with *n*-butyllithium at -80°C occurs smoothly and the subsequent reaction of the lithium intermediate (**244**) with various electrophiles except aldehydes gives the 4-bromo-5-substituted triazoles (**245**) (Scheme 46). The corresponding 1-substituted 4,5-dibromo-1,2,3-triazole undergoes a similar reaction at the 5-position <B-88MI 401-02>.



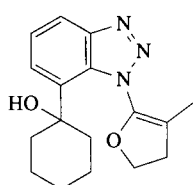
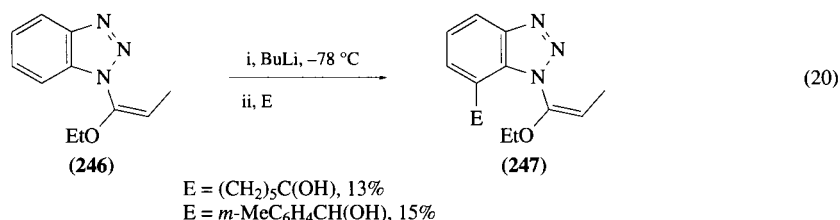
^a PhCHO, PhCO₂Et, MeI, PhSSPh, Cl₃CCl₃, TMS-Cl

Scheme 45

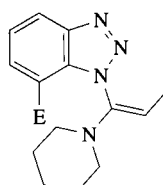


Scheme 46

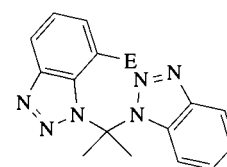
The benzo ring in benzotriazole is strongly deactivated by the electron-withdrawing nitrogen atoms. Lithiation of the benzotriazole ring is considered to be extremely difficult. The reactivity and the selectivity depend critically upon the presence of an *O*- or *N*-containing directing group in the substrate. Lithiations of the benzo ring fail for most oxygen- and nitrogen-containing groups, such as —CH(OMe)₂, —CH₂NEt₂, —CMe₂OMe, and —CO₂Li (decomposed or lithiated at the directing group). However, it is found that a double bond conjugated with the benzotriazole ring is able to stabilize the *ortho*-lithiated product, and lithiation does occur at the 7-position, although in low yields. For example, treatment of benzotriazole (246) with butyllithium in THF followed by reaction with electrophiles gives (247) (Equation (20)). The 7-substituted benzotriazoles (248)–(250) are similarly prepared in 11–18% yields <95H(41)131>.



(248) 18%

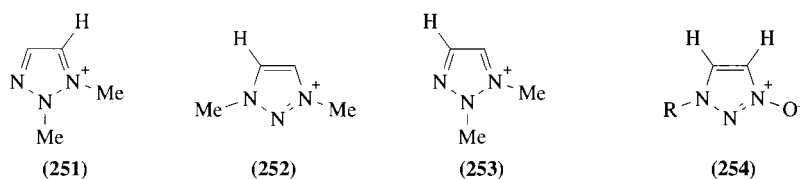


(249) E = (CH₂)₅C(OH), 16%
E = *m*-MeC₆H₄CH(OH), 11%

(250) E = (CH₂)₅C(OH), 18%

By converting triazoles to the corresponding triazolium, the deprotonation becomes much more facile. The relative acidity of the different protons in triazolium ring systems (251)–(253) is estimated from their base-catalyzed exchange with deuterium. The carbanion, generated by deprotonation with NaH in DMF, may be reacted with carbon, halogen, sulfur, and oxygen electrophiles <75CC334, 88BSB573>.

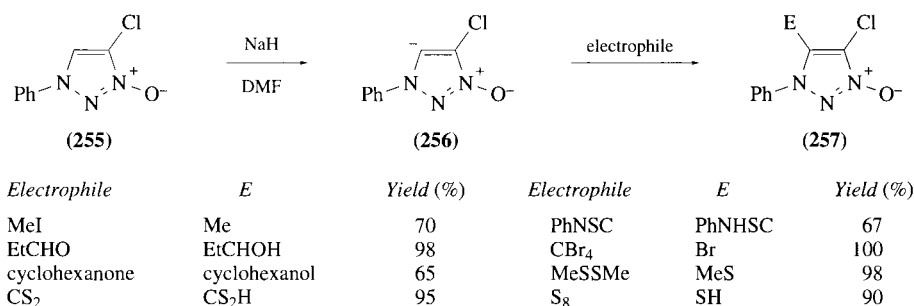
Protons of 1,2,3-triazole rings can also be activated by *N*-oxides. The H(4) and H(5) protons in 3-substituted 1,2,3-triazole-1-oxides (254) are more reactive but exchange with deuterium at a similar

Relative H/D exchange rate: 1.7×10^5

54

1

rate. The exchange rate ratio is 1.8, 2.4, and 6.1 in the methyl, benzyl, and phenyl derivatives, respectively. As a consequence, both regio- and mono-selectivity between the 4- and 5-positions of compound (254) is low in deprotonations followed by reaction with an electrophile. 3-Phenyl-5-chlorotriazole 1-oxides (255) are deprotonated with NaH in DMF. The resulting anions (256) react with carbon, silicon, and sulfur electrophiles to give substituted products (257) in good yield. The results are summarized in Scheme 47 <87ACS(B)724>.



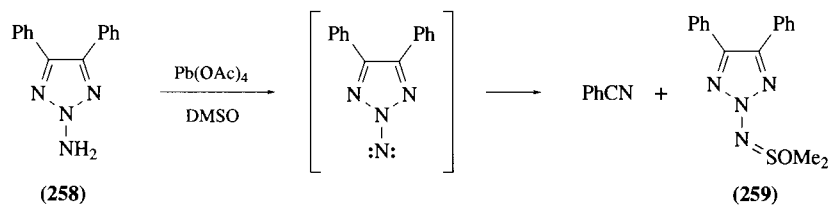
Scheme 47

4.01.4.11 Reactions with Radical and Electron-deficient Species

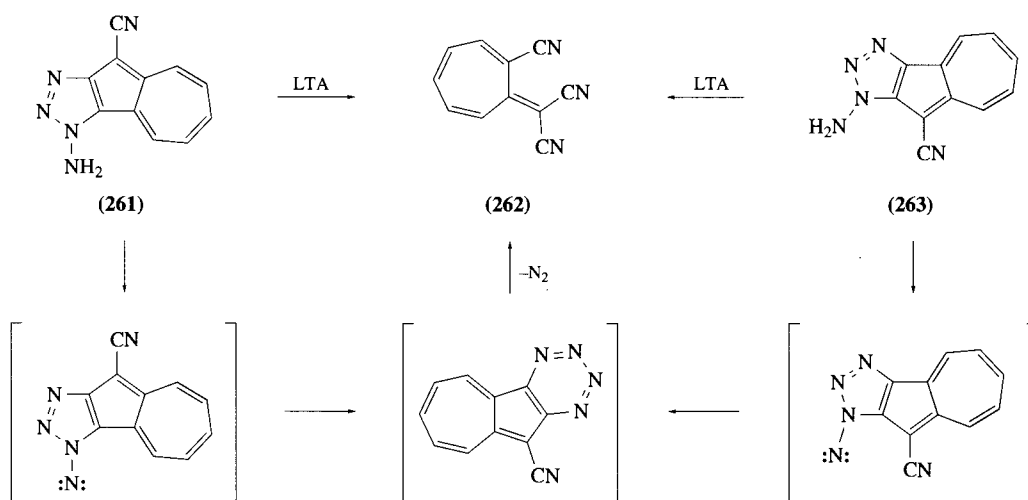
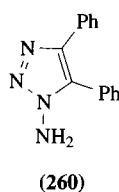
The reaction between *N*-chlorobenzotriazole and 1-methyl-2-phenylindole involves formation of the indole radical cation and benzotriazole radical via an initial electron transfer <82JOC4895, 91JCS(P2)1779>. Chemical reactions of benzotriazole on a freshly etched surface of metallic copper are studied by surface-enhanced Raman scattering, x-ray photoelectron spectroscopy, and cyclic voltammetry. The surface product is (benzotriazolato)copper(+), which covers the surface in the shape of polymeric material and shows good anticorrosion effects for copper <91JPC7380>.

Lead tetraacetate (LTA) oxidation of 2-amino-1,2,3-triazole (258) in DMSO gives benzonitrile (63%) and dimethylsulfoximine (259) via the intermediate nitrene (Scheme 48). However, 1-amino-1,2,3-triazole (260) undergoes LTA oxidation in the presence of styrene or DMSO to form only diphenylacetylene (62%) by elimination of two equivalents of nitrogen. No aziridine, sulfoximine, or nitriles are detected <88M1041>. 1-Amino-4-cyanazuleno[2,1-*d*]triazole (261) and 3-amino-4-cyanazuleno[1,2-*d*]triazole (263) react with LTA in dichloromethane to afford the ring cleavage product 1,8,8-tricyanoheptafulvene (262) via a nitrene and a tetrazine intermediate as shown in Scheme 49 <85TL335>. The LTA oxidation of 1-amino-5-phenylbistriazole (264) leads to the ring-expansion product, triazolotetrazine (265) in 81% yield <88CC1608>. Similar oxidation of the 2-amino derivative (266) results in the formation of 1,3-dicyano-2-phenyltriazenimide <91JCS(P1)2045>. Of synthetic importance is the oxidation of 1-aminobenzotriazole with LTA and other oxidants; the resulting benzyne, formed by the elimination of two nitrogen molecules from the nitrene intermediate, undergoes cycloaddition reactions with various dienes (Equations (21) and (22); Scheme 50). Without a trap, diphenylene is formed in 83% yield <69JCS(C)742>. Diaminobenzo[1,2-*d*:4,5-*d'*]bistriazole (267) has been used as a synthetic equivalent of the 1,4-benzodiyne (268) (Scheme 51). Thus, the oxidation of bistriazole (267) by LTA followed by cycloaddition with dienes or 1,3-dipoles gives the bisannulation products (269) and (270) <86JOC979>. A similar oxidation of 2-aminobenzotriazole

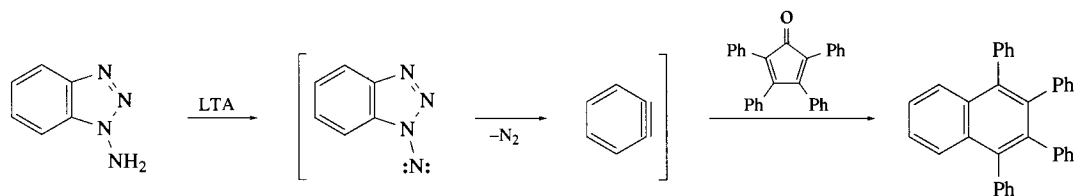
with LTA or iodobenzene diacetate, however, gives *cis,cis*-mucononitrile (**271**) (Scheme 52) <69JCS(C)742>. 7-Substituted 1-aminobenzotriazoles are converted into benzynes upon exposure to either NBS or LTA. Intramolecular trapping by the 7-hydroxyethyl group leads to dihydrobenzofurans <93TL6939>.



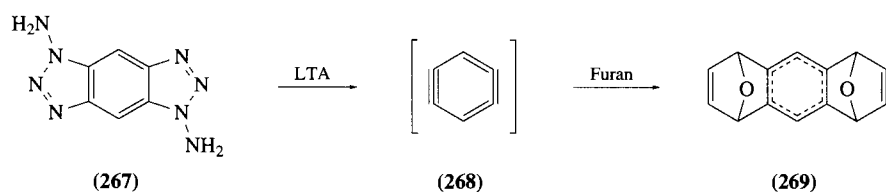
Scheme 48



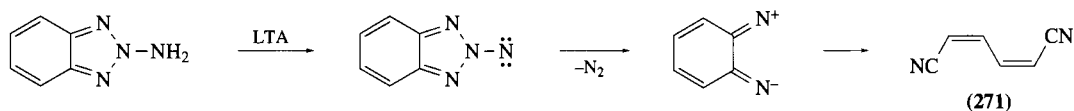
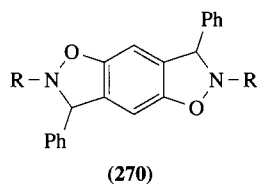
Scheme 49



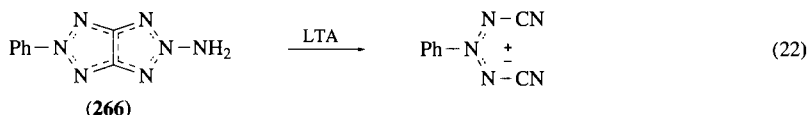
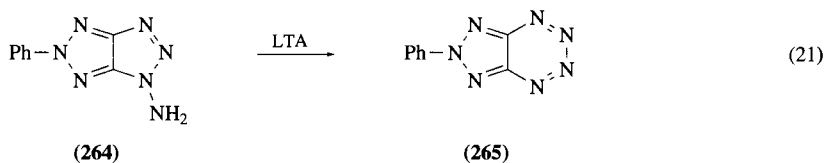
Scheme 50



Scheme 51

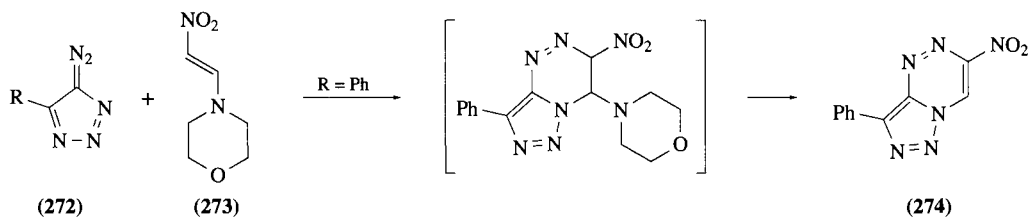


Scheme 52

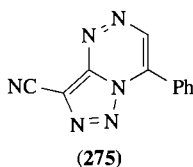


4.01.4.12 Cyclic Transition-State Reactions

Diazo-substituted 1,2,3-triazoles undergo regiospecific dipolar cycloaddition reactions with electron-rich unsaturated compounds. Thus, 4-diazo-5-phenyl-4*H*-1,2,3-triazole (**272**, R = Ph) reacts with 1-morpholinyl-2-nitroethene (**273**) in CH₂Cl₂ at 20°C by a net 1,7-cycloaddition and elimination of morpholine to give the product (**274**) (Scheme 53). 4-Diazo-5-cyano-4*H*-1,2,3-triazole (**272**, R = CN) similarly adds to phenylacetylene to form compound (**275**) <87JOC5538>.

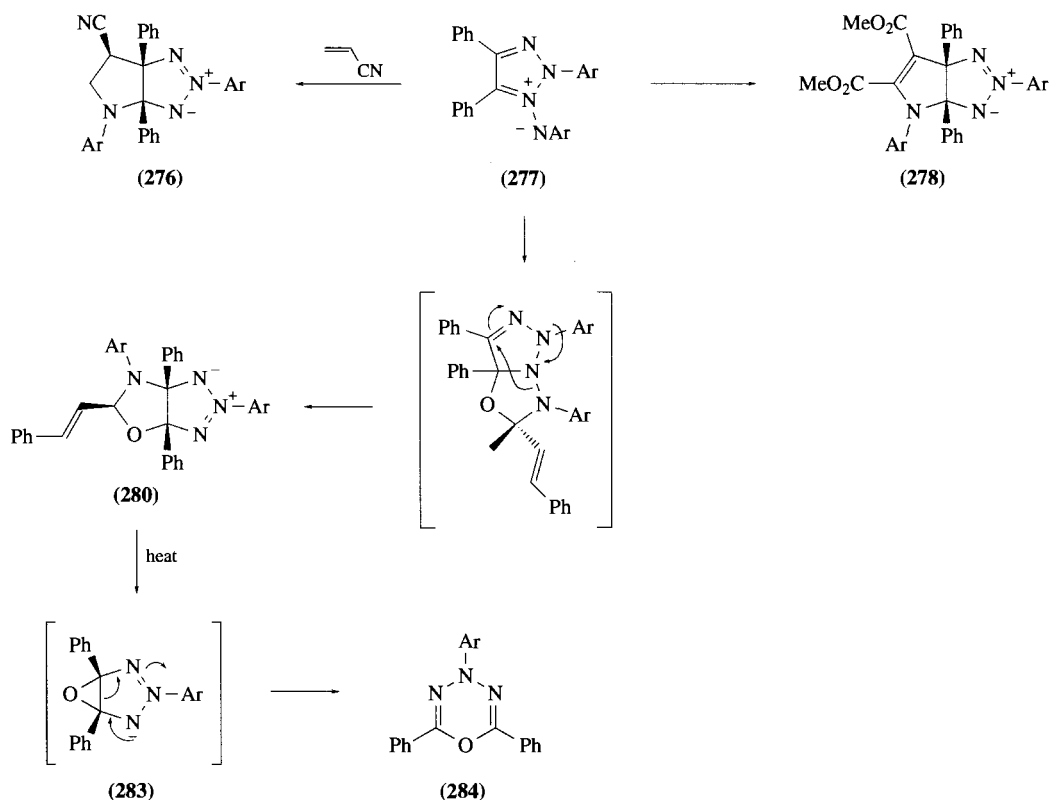


Scheme 53

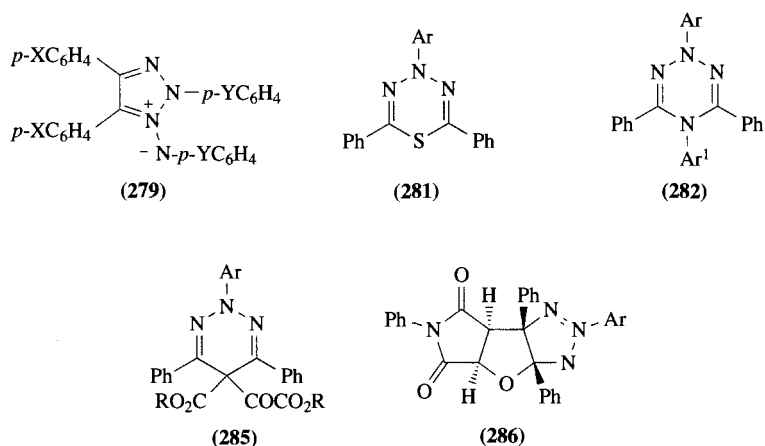


The reactions of 1,2,3-triazolium 1-imide (**277**) with a range of alkene and alkyne dipolarophiles give rise to a variety of new ring systems (Scheme 54). Compounds (**276**) and (**278**) are obtained from (**277**) by reaction with acrylonitrile and DMAD, respectively. These reactions are tandem 1,3-dipolar (*endo*) cycloadditions and sigmatropic rearrangements which are regio- and stereospecific <90JCS(P1)2537>. Kinetic and mechanistic studies show that these reactions are dipole-HOMO controlled. The second-order rate constants are insensitive to solvent polarity, the reaction indicates

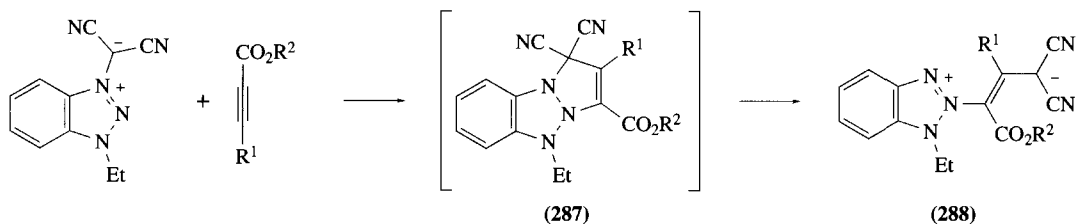
a high negative entropy of activation. Substituent effects at the triazole carbon terminus of the dipole (X in **279**) show a linear Hammett correlation with $\rho = 1.51$. Substituents at the *N*-terminus of the dipole (Y in **279**) show a rare inverted *V*-type Hammett correlation with the reaction being inhibited by both MeO and NO₂ groups. The regioselectivity of the reactions agrees with *ab initio* calculated orbital coefficients and HOMO and LUMO energies <92JCS(P2)1103>. Triazolium (**277**) reacts with (*E*)-cinnamaldehyde to afford the tetrahydrooxazolo[4,5-*d*]-1,2,3-triazole (**280**), which is stable at ambient temperature. In refluxing ethanol, however, compound (**280**) is converted to 1,3,4,5-oxatriazine (**284**) via the intermediate (**283**). Reaction of (**277**) with methyl cyano-dithioformate and aryl-*N*-sulfinylamines gives 1,3,4,5-thiatriazines (**281**) and 1,2,3,5-tetrazines (**282**), respectively <89JCS(P1)371, 90JCS(P1)2527>. 1,2,3-Triazole 1-oxides undergo a similar multistep sequence of 1,3-dipolar cycloadditions, sigmatropic rearrangements and ring expansions with dialkyl acetylenedicarboxylate and *N*-phenylmaleimide to give (**285**) and (**286**) as products <90JCS(P1)3321>.



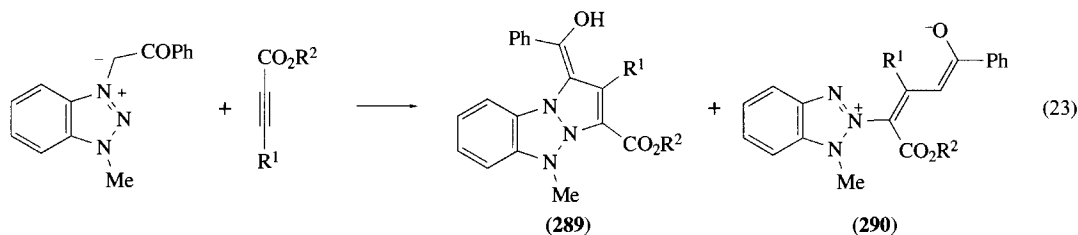
Scheme 54



Benzotriazolium ylides undergo 1,3-dipolar cycloadditions. Stable 3-dicyanomethylethyl-benzotriazolium ylide gives products (**288**) by 1,3-dipolar cycloadditions with a variety of acetylenic esters followed by ring opening (Scheme 55). None of the expected intermediate 1,3-dipolar cycloadduct (**287**) is obtained <84H(22)1335>. Intramolecular [3 + 2] cycloaddition of 1-(4-pentynyl)-benzotriazolium 3-dicyanomethylide leads to an unstable cycloadduct which readily undergoes ring opening <91CZ256>. The reaction of benzotriazolium ylides with DMAD yields nonidentifiable products <90H(31)1801>. Very recently, in the mid-1990s, 3-methyl-1-phenacylbenzotriazolium ylide was treated with acetylenic esters in THF and compounds of the type (**289**) and (**290**) were obtained (Equation (23)). The reaction is regioselective <94H(41)765>.



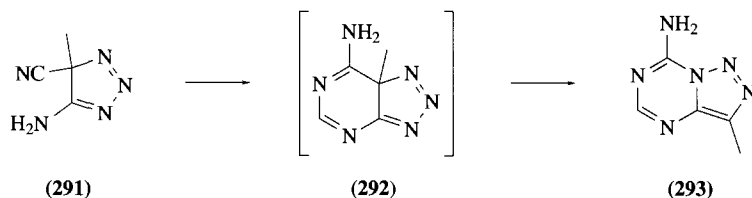
Scheme 55



4.01.5 REACTIVITY OF NONCONJUGATED RINGS

4.01.5.1 Isomers of Aromatic Compounds

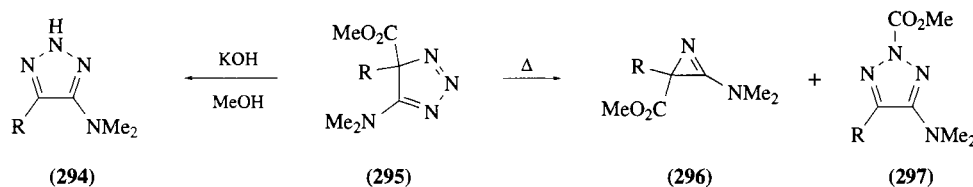
5-Amino-4-cyano-4-methyl-4*H*-1,2,3-triazole (**291**) reacts with formamidine at room temperature to give the substituted 1,2,3-triazolo[1,5-*a*]-1,3,5-triazine (**293**) via a translocative rearrangement of the presumed intermediate (**292**) (Scheme 56) <85JOC4986>.



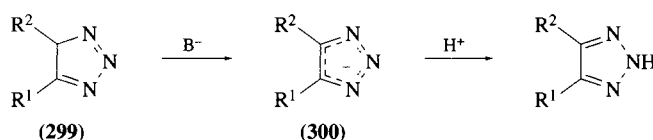
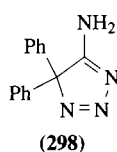
Scheme 56

The 4*H*-triazoles (**295**), formed from sodium azide and α -chloroenamines, undergo saponification and decarboxylation to give the aromatic triazoles (**294**) (Scheme 57). On heating neat at 80 °C, compounds (**295**) are converted into a mixture of azirines (**296**) and 2*H*-1,2,3-triazoles (**297**). The photolysis of (**295**) in benzene gives only 3-amino-2*H*-azirines <80CC940>. 4*H*-1,2,3-Triazoles are the intermediates in the transformation of vinyl azides to 2*H*-azirines <86JOC3176, 87CB2003>, a reaction which has been studied using *ab initio* calculations <84T2095>. 5-Amino-4*H*-1,2,3-triazole (**298**) exhibits restricted rotation of the amino group in solution (Scheme 58); in the crystal state, it exists

as shown. Methylation of (298) affords *N*-monomethyl and *N,N*-dimethyl derivatives <93CB103>. The 1,3-dipolar cycloadducts (299) of nitriles and aryl diazomethanes are converted by butoxide into stable anions (300), which afford 1,2,3-triazoles on acidification (Scheme 58) <88JCS(P1)2917>.



Scheme 57



Scheme 58

4.01.5.2 Reactivity of Dihydro Derivatives

Since the publication of CHEC-I in 1984, dihydro-1,2,3-triazoles have attracted considerable attention because of their importance as intermediates in organic syntheses and because they are a new class of anticonvulsant drugs <84JPS850>. There are two excellent reviews on the chemistry of Δ²-1,2,3-triazolines <84AHC(37)217> and Δ³- and Δ⁴-1,2,3-triazolines <84AHC(37)351>.

4.01.5.3 Δ²-1,2,3-Triazolines

4.01.5.3.1 Aromatization reactions

The aromatization of Δ²-triazolines to triazoles can be achieved by oxidation, by rearrangement, or by elimination of a small molecule. All of these methods are discussed in detail in a review <84AHC(37)217>. The oxidative dehydrogenation of Δ²-1,2,3-triazolines using potassium permanganate in a phase-transfer catalyzed system affords a convenient route for the synthesis of various 1,2,3-triazoles <84CHEC-I(5)7027, 82JPR857>. Heterocyclic substituted 1,2,3-triazolines undergo oxidation to the corresponding triazoles with potassium permanganate in a benzene–water two-phase system in the presence of tetrabutylammonium chloride <88JMC196>. However, the reaction has limited scope when electron-withdrawing and/or sterically crowded groups are present on the triazoline rings. Nickel peroxide (NiO₂) has been used as an effective oxidant for the triazoline ring system <90S191>. The oxidation occurs selectively and no side products are observed. Yields are usually better than those obtained using the potassium permanganate method (Equation (24) and Table 16). Steric crowding prevents the bulky permanganate ion from closely approaching the reaction site, whereas the effectiveness of the NiO₂ oxidation, possibly via an hydroxyl radical, is unaltered <90JOC5891>.

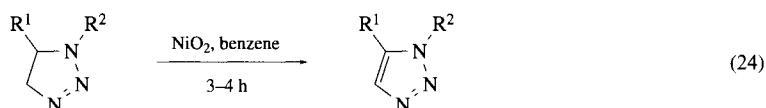
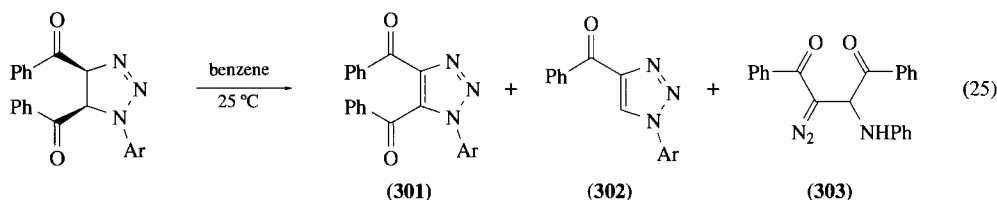


Table 16 Comparison of NiO_2 and $KMnO_4$ oxidation of 1,5-disubstituted 1,2,3-triazolines <90JOC5891>.

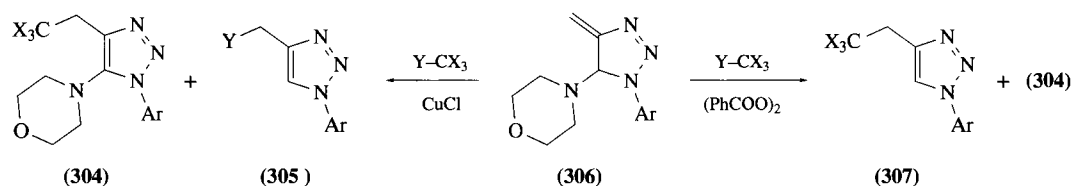
R^1	R^2	Yield (%)	
		NiO_2	$KMnO_4$
4-pyridyl	4- $NO_2C_6H_4$	66	45
4- $NO_2C_6H_4$	C_6H_5	60	36
2- ClC_6H_4	3,4- $Cl_2C_6H_3$	63	17
C_6H_5	4- BrC_6H_4	79	63
2-pyridyl	4- BrC_6H_4	71	45
2,6- $Cl_2C_6H_3$	4- BrC_6H_4	74	<1

Treatment of 1-aryl-4,5-dihydro-5-hydroxy-1,2,3-triazolines with alkoxides gives 1-aryl-1,2,3-triazoles by dehydration <86T3913>. 1-Aryl-5-amido-1,2,3-triazolines are readily converted to the corresponding 1-aryltriazoles when refluxed in methanolic potassium hydroxide by the loss of an amide molecule <92JOC3075>. This transformation is similar to the base-induced elimination of an amine from 5-aminotriazolines <64JA2213>. Deamination can also be readily achieved by refluxing 5-aminotriazolines with hydrochloric acid in ethanol <84JHC1121>. In many cases, 5-aminotriazolines, the cycloaddition products of azides and enamines, undergo spontaneous deamination to give triazoles at elevated temperature <84JHC1121, 86S1010, 90JCS(P1)2971>. Oxygen oxidation of *trans*-dibenzoyltriazolines gives two aromatized products, dibenzoyltriazole (**301**) and 4-benzoyltriazole (**302**), along with the ring-opened product (**303**) (Equation (25)) <89JCS(P1)2235>.

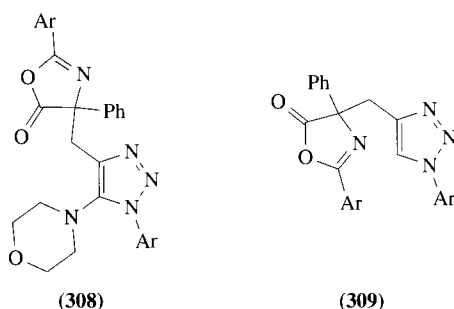


4.01.5.3.2 Reactions of Δ^2 -1,2,3-triazolines with radicals

1-Aryl-4-methylene-5-morpholino- Δ^2 -triazolines (**306**) react with halomethyl radicals generated by the reaction of halomethanes with $CuCl$ to give triazoles (**304**) and (**305**) (Scheme 59). By contrast, compounds (**304**) and (**307**) are formed when the halomethyl radicals are generated from halomethanes and benzoyl peroxide <87T625>. Triazolines (**306**) react with oxazolonyl radicals, generated from the thermolysis of bioxazolines, to yield products (**308**) and (**309**) by transfer of a hydrogen or morpholinyl radical, respectively <90CB217>.



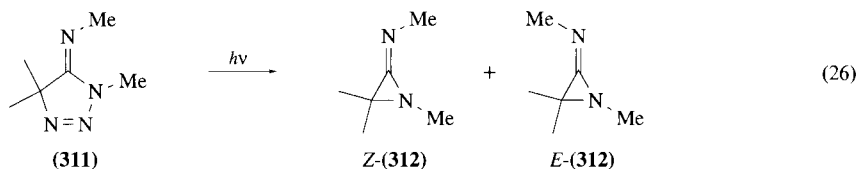
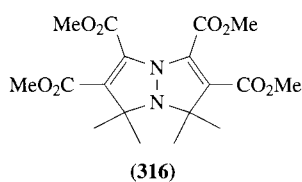
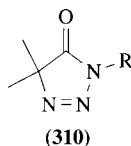
Scheme 59



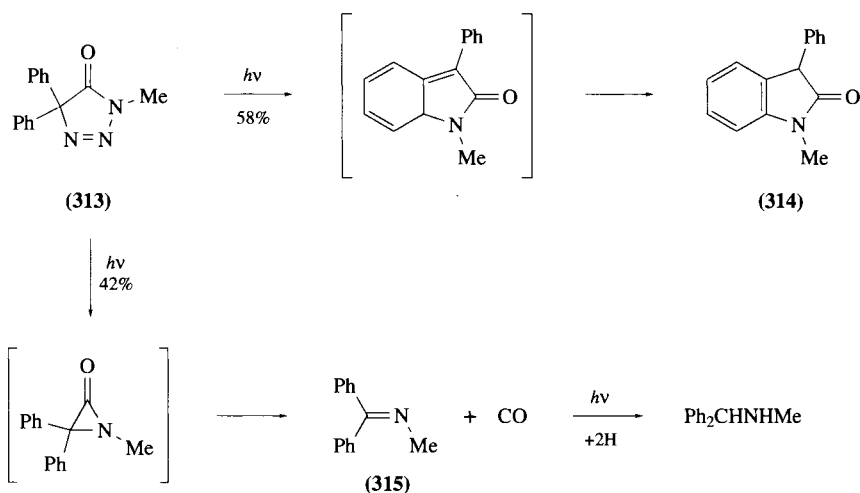
4.01.5.3.3 Ring fission of Δ^2 -1,2,3-triazolines

Most Δ^2 -1,2,3-triazolines are thermally unstable, and often undergo decomposition to aziridines, anils, and other products. In some cases, Δ^2 -1,2,3-triazolines initially formed by cycloaddition cannot be isolated due to spontaneous decomposition $\langle 82\text{JOC}5042, 89\text{JCS}(\text{P}1)2235, 90\text{JCS}(\text{P}1)2971, 91\text{TL}2457 \rangle$.

The photolysis and thermolysis of Δ^2 -1,2,3-triazolines are of considerable interest from a mechanistic point of view; for further details see review by Kadaba *et al.* $\langle 84\text{AHC}(37)217 \rangle$. Photochemical elimination of molecular nitrogen from 3,5,5-trialkyl-3,5-dihydro-4*H*-1,2,3-triazole-4-ones (e.g., **310**) gives aziridinones and iminooxiranes, the latter in turn decomposes to a ketone and a nitrile $\langle 82\text{TL}4681, 87\text{CB}225 \rangle$. The mechanism and solvent effects have been studied and a diradical intermediate is proposed $\langle 87\text{CB}217 \rangle$. The electron-impact-induced decomposition of compounds (**310**) has been described $\langle 86\text{LA}1891 \rangle$. Photolysis of 1,4,4-trialkyl-4,5-dihydro-5-imino-1*H*-1,2,3-triazoles (**311**) affords a quantitative yield of the (*E*)- and (*Z*)-aziridinimines (**312**) (11 : 89) in addition to molecular nitrogen (Equation (26)) $\langle 90\text{CB}2195 \rangle$. Irradiation ($\lambda > 280 \text{ nm}$) of 3-methyl-5,5-diphenyl-4,5-dihydro-1,2,3-triazolone (**313**) in deuterated benzene yields the dihydroindolone (**314**), the imine (**315**) and its photoreduction product, *N*-methylbenzylamine (Scheme 60) $\langle 92\text{CB}2625 \rangle$. 3,5-Dihydro-4*H*-1,2,3-triazole-4-one (**310**, $\text{R} = \text{CH}_2\text{Bu}^t$) and DMAD react slowly at 50°C in a 1 : 1 ratio to give (**316**, 40%) $\langle 90\text{LA}465 \rangle$.

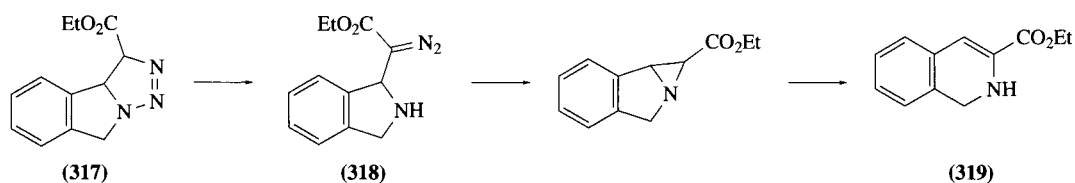


Triazoline (**317**), available from an intramolecular 1,3-dipolar cycloaddition, rearranges on silica gel to give diazo compound (**318**) (Scheme 61). Treatment of (**318**) with rhodium acetate afford dihydroisoquinoline (**319**) $\langle 86\text{JOC}1120 \rangle$. Triazoline (**320**) undergoes photochemical elimination of nitrogen (Equation (27)) followed by a rearrangement to afford 2-azatricyclo[4.4.0.0.^{2,8}]decenone (**321**) $\langle 83\text{JA}3273 \rangle$. However, a different photorearrangement occurs with triazoline (**322**) giving diene (**323**) as the major product. Apparently the diradical intermediate generated by photochemical elimination of nitrogen from (**322**) undergoes preferential *H*-atom transfer from the C(4) methyl group to give (**323**). The photochemistry of triazoline (**324**) is dominated by reactions characteristic

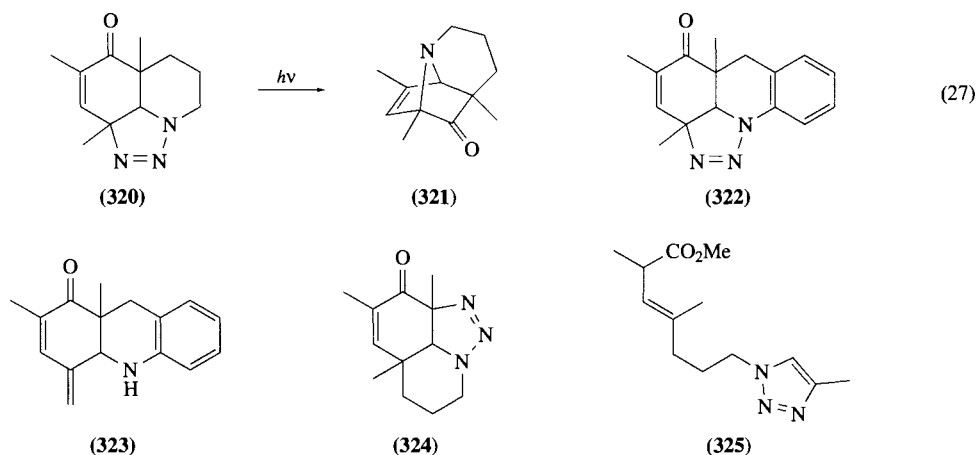


Scheme 60

of the cyclohexenone chromophore rather than those of triazolines; irradiation in methanol gives triazole methyl ester (325) in 80% yield <83JOC2432>.

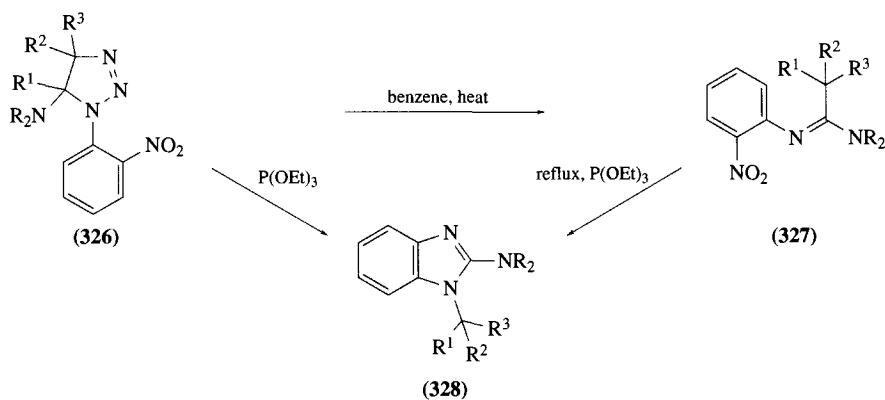


Scheme 61



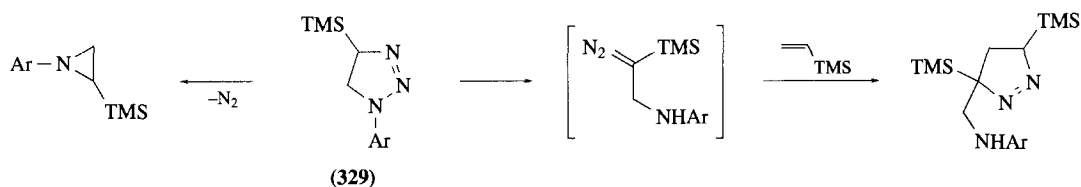
5-Amino-1-aryl-1,2,3-triazolines (326), readily available from the [3 + 2] cycloaddition of azides to enamines (Scheme 62), undergo thermal rearrangement in benzene with the elimination of nitrogen to give the corresponding amidines (327). In refluxing triethyl phosphite, triazolines (326) are converted into 1-alkyl-2-aminobenzimidazoles (328) in good yield. Monitoring of the reaction suggests that triazolines (326) are first rapidly transformed into amidines (327), during which time the triethyl phosphite acts simply as high-boiling solvent. Compounds (327) are then slowly converted into (328) through reduction of the nitro group, cyclization, and rearrangement <92JCS(P1)2709>. Thermolysis of 5-amino-4-methyl-4-methoxycarbonyl- Δ^2 -1,2,3-triazolines leads to amidines and 1-methoxycarbonyl-diazoethane <84JHC513>. 5-(4-Pyridyl)substituted 1,2,3-triazolines undergo permanganate-catalyzed thermolysis in refluxing benzene to give imines in 30–52% yields.

A mechanism which involves initial coordination of the pyridyl nitrogen with the manganese atom is proposed <93JHC1191>.

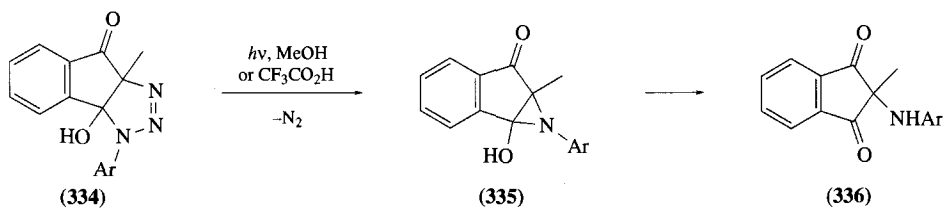


Scheme 62

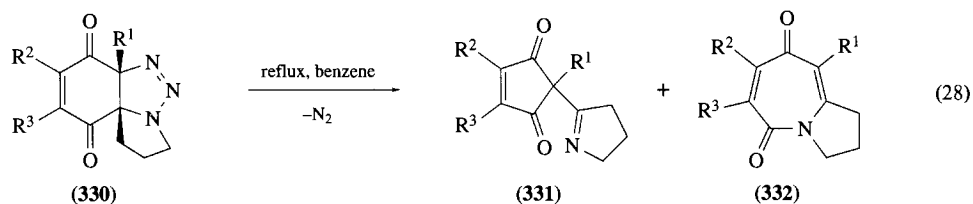
4-Silylated-1,2,3-triazolines (329) decompose thermally in trimethyl(vinyl)silane/chloroform to give aziridines and Δ^1 -pyrazolines (Scheme 63). The thermal stability of (329) is strongly dependent on the activating or deactivating effects exerted by the N(1) substituent; only compounds with strongly electron-withdrawing groups can be isolated <91JCS(P1)2789>. The intramolecular azide-alkene cycloadducts (330) of 2-(azidopropyl)-1,4-benzoquinones undergo thermolytic rearrangement to products of ring contraction (331) and expansion (332) (Equation (28)). For R¹ = R² = H and R³ = OMe, compound (330) is rapidly converted into the diazo enedione (333) in the presence of a trace of acid <84JOC1676>. Upon photolysis or treatment with CF₃CO₂H the hydroxytriazolines (334) undergo decomposition to (336) through aziridine intermediates (335) (Scheme 64). Thermolysis of (334) at 95 °C gives the ring-expanded 2-arylisquinoline-1,3-dione (337) <92JCS(P1)2845>.

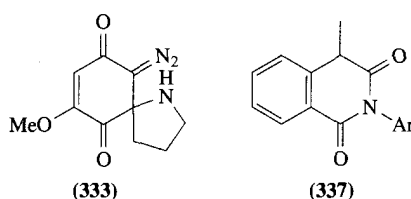


Scheme 63

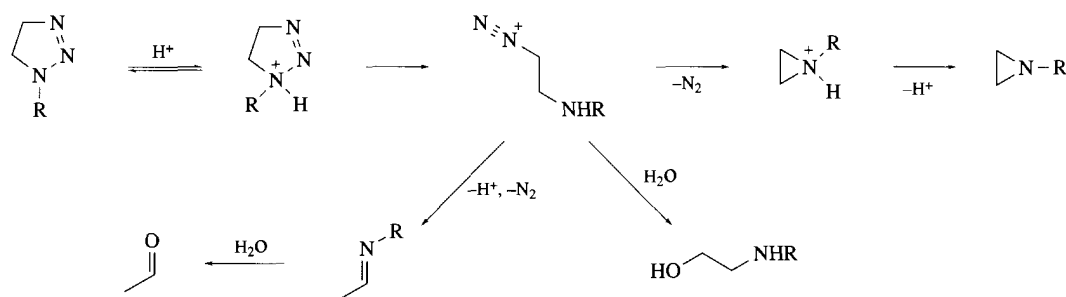


Scheme 64





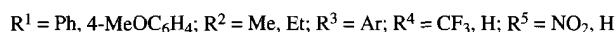
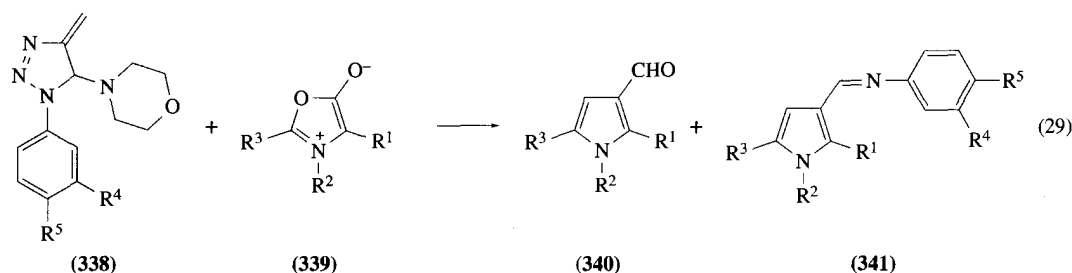
The mechanism of the acid-catalyzed decomposition of 1-alkyltriazolines has been studied $\langle 93\text{JOC}2097 \rangle$. The hydrolytic decomposition of these triazolines in aqueous buffers leads predominantly to 1-alkylaziridines with lesser amounts of 2-(alkylamino)ethanol, alkylamines, and acetaldehyde. The rate of hydrolysis of 1-alkyltriazolines is about twice as fast as that of the analogous acyclic 1,3,3-trialkyltriazenes and varies in the order *t*-butyl > isopropyl > ethyl > butyl > methyl > propyl > benzyl $\langle 92\text{JOC}6448 \rangle$. The proposed mechanism, involving rate-limiting formation of a 2-(alkylamino)ethyldiazonium ion, is shown in Scheme 65. A theoretical study (*ab initio* calculation) of the acid-induced decomposition of 4,5-dihydro-1,2,3-triazolines has also been reported $\langle 91\text{JA}7893 \rangle$.

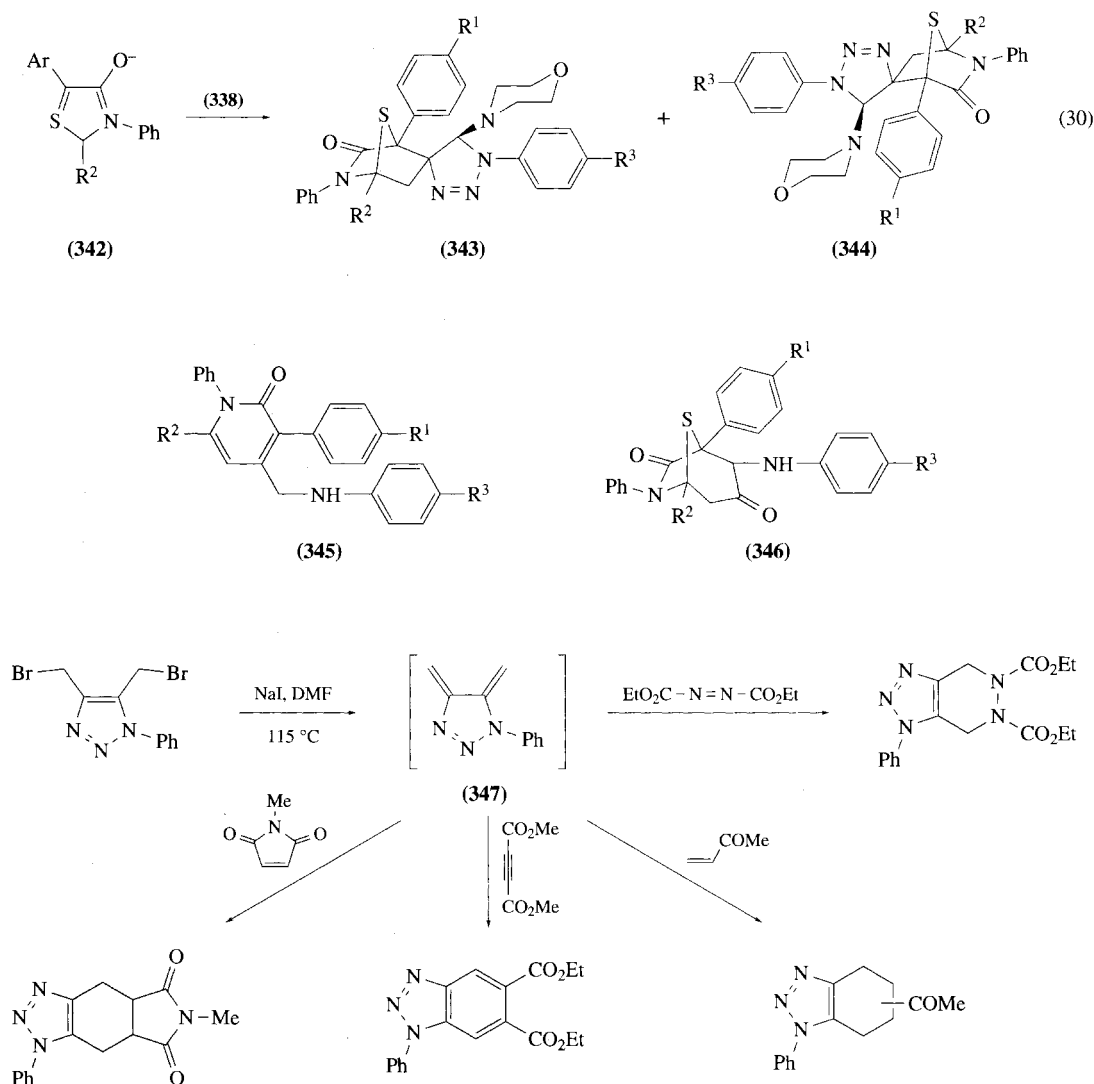


Scheme 65

4.01.5.3.4 Cycloaddition reactions of Δ^2 -1,2,3-triazolines

5-Amino-4-methylene- Δ^2 -1,2,3-triazolines (**338**) react rapidly with oxazolium-5-olates (**339**) in a 1 : 2 molar ratio at room temperature to form 1,2,5-trisubstituted pyrrole-3-aldehydes (**340**) and the corresponding anils (**341**) (Equation (29)). The formation of (**340**) is explained by the cycloaddition product of (**338**) and (**339**) undergoing rearrangement accompanied by carbon dioxide and nitrogen elimination $\langle 86\text{CB}1083 \rangle$. Similar reactions of (**338**) with sydnone are also reported $\langle 85\text{LA}1377 \rangle$. The cycloaddition reactions of (**338**) with thiazolium-4-olates (**342**) give two isomeric cycloadducts (**343**) and (**344**) (Equation (30)), which are catalytically transformed by Raney nickel into pyridinones (**345**). The acid-catalyzed rearrangements of (**343**) and (**344**) afford δ -thia-6-azabicyclo[3.2.1]octane derivatives (**346**) $\langle 92\text{CB}883 \rangle$. 4,5-Dihydro-4,5-dimethylene-1-phenyl-1,2,3-triazole (**347**), generated *in situ* from 4,5-bis(bromomethyl)-1,2,3-triazole by sodium iodide-induced 1,4-elimination, reacts with symmetrically and unsymmetrically substituted dienophiles to form Diels–Alder cycloadducts as shown in Scheme 66 $\langle 92\text{TL}4499 \rangle$.





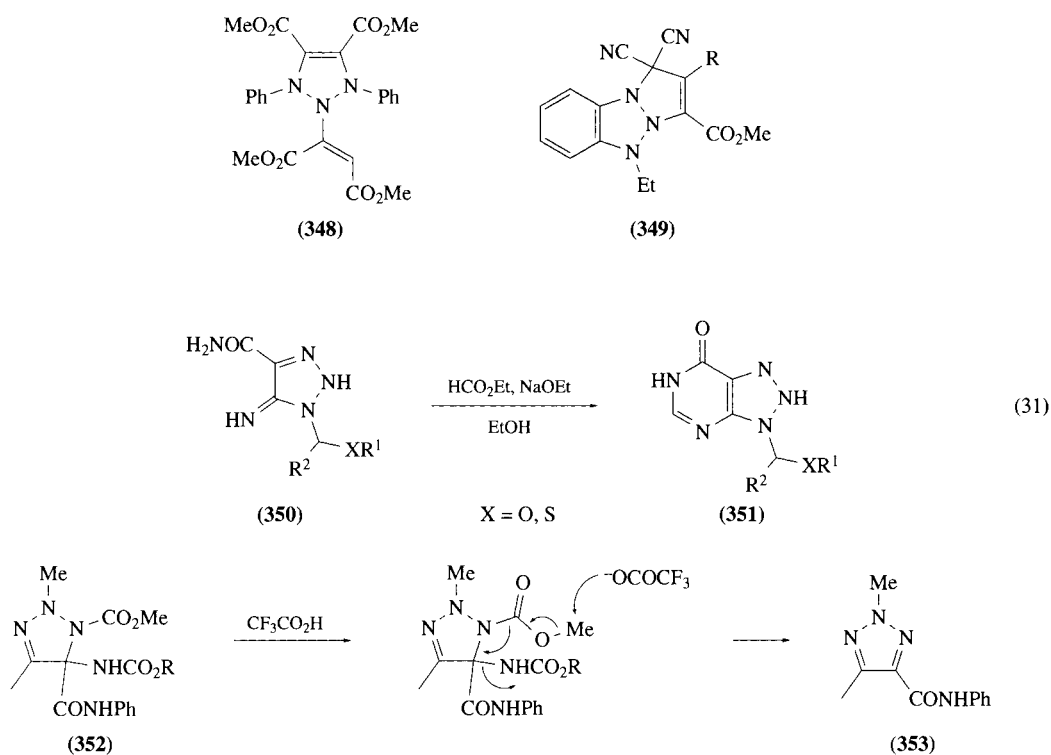
Scheme 66

4.01.5.3.5 Δ^3 - and Δ^4 -1,2,3-Triazolines

The chemistry of Δ^3 - and Δ^4 -1,2,3-triazolines is far less known than that of Δ^2 -1,2,3-triazolines and it is not discussed at all in CHEC-I. A short review $\langle 84\text{AHC}(37)351 \rangle$ describes the synthesis, structure, physical properties and reactions of the few examples of these classes of compound.

In 1959, Mohr and Hertel first reported several Δ^4 -1,2,3-triazoline intermediates $\langle 59\text{GEP}1061789 \rangle$. Δ^4 -1,2,3-Triazolines, unlike Δ^2 -1,2,3-triazolines, are stable towards acids, for example, Δ^4 -1,2,3-triazoline (348) is unchanged in refluxing acetic anhydride $\langle 68\text{JCS}(C)389 \rangle$. It was reported that the cycloaddition of 1-ethylbenzotriazolium 3-dicyanomethylide with DMAD and methyl propiolate afforded the 2,3-dihydrobenzotriazoles (349, R = H, CO₂Me) $\langle 83\text{JCS}(P2)1317 \rangle$. However, the structure of the products was established later as the 1-ethyl-2-substituted benzotriazolium ylides originating from the opening of the unstable cycloadducts (349) $\langle 84\text{H}(22)1335 \rangle$. 2,3-Dihydrobenzotriazoles have been obtained by the cycloaddition of 3-methyl-1-phenacylbenzotriazolium ylide, and were characterized by NMR and by x-ray analysis $\langle 95\text{H}(41)765 \rangle$ (see also Section 4.01.4.12).

Δ^3 -Triazolines (350) are easily converted into the corresponding 8-azapurines (351) on treatment with ethyl formate and sodium ethoxide (Equation (31)) $\langle 88\text{S}879 \rangle$. When 5-amido- Δ^3 -1,2,3-triazoline (352) is treated with trifluoroacetic acid, the 2-methyl-1,2,3-triazole (353) is afforded (Scheme 67) $\langle 91\text{JCS}(P1)3361 \rangle$.

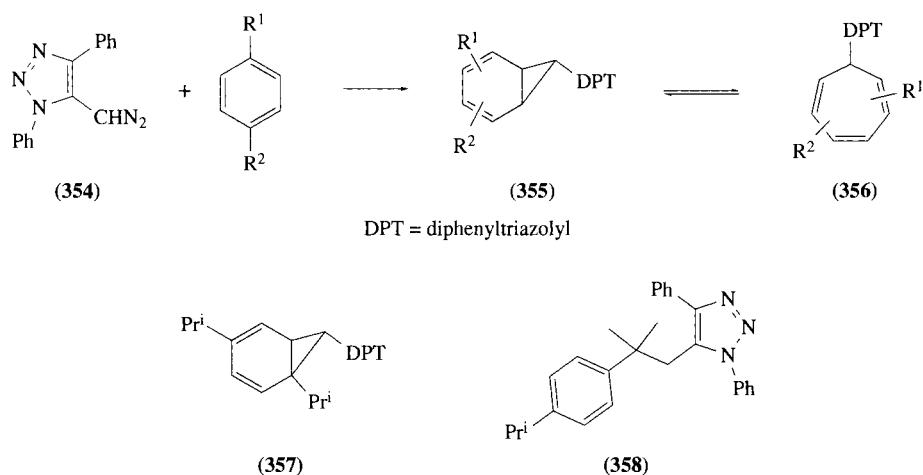


Scheme 67

4.01.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Substituents at the C(4) and C(5) positions of 1,2,3-triazole and at the benzene ring of benzo-triazole can undergo normal functional transformations which are independent of the triazole ring. In addition, these substituents can undergo some specialized reactions, particularly the formation of triazolo fused bi- and tricyclic systems.

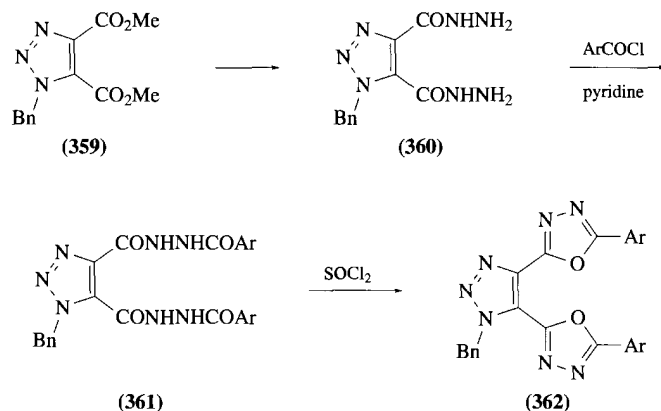
5-(Diazomethyl)-1,4-diphenyl-1,2,3-triazole (**354**) reacts with 1,4-disubstituted benzenes or naphthalenes to give a mixture of carbene derived norcaradiene/cycloheptatriene products (**355**) and (**356**) (Scheme 68). Attack is favored adjacent to the more highly branched substituent. When $R^1 = R^2 = \text{Pr}^i$, a mixture of triazole derivatives (**357**) and (**358**), formed by addition to benzene and insertion into the C—H bond respectively, is obtained <83JOC4002>.



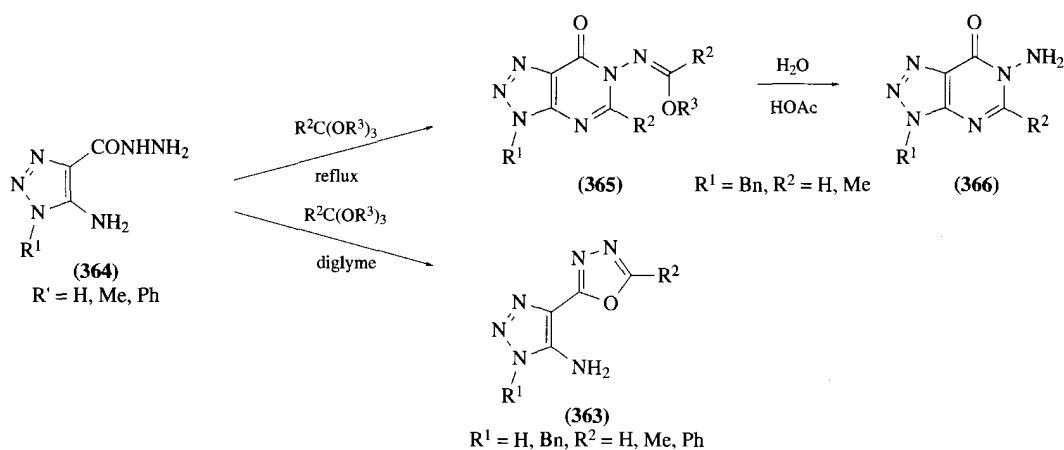
Scheme 68

The 4-aminotriazoles are of special interest because they are intermediates for the synthesis of purines and other annulated ring systems. 4-Amino-1,2,3-triazoles undergo *N*-alkylations, *N*-acylations and deacylations. An amino group in the C(4) or C(5) position of 1,2,3-triazole is readily converted to an azido group <83BSB913, 85T4621>. The corresponding imino derivatives are obtained with aldehydes and orthoformates. For the reactivity of *C*-amino derivatives of 1,2,3-triazole; see review <86AHC(40)129>.

Reactions of 4- and 5-substituents with suitable substrates are valuable methods for the preparation of 4- and 5-heteroaryl-substituted 1,2,3-triazoles. For instance, 1-benzyl-4,5-bis-hydrazinocarbonyl-1,2,3-triazole (**359**), obtained from hydrazine and 4,5-dimethoxycarbonyl-triazole (**359**), is aroylated with the appropriate aroyl chloride in the presence of pyridine to give triazoles (**361**) (Scheme 69). Cyclization of (**361**) using thionyl chloride gives the 4,5-bis(1,3,4-oxadiazol-2-yl)-1,2,3-triazoles (**362**) <90JHC1685>. 4-Hydrazido-5-amino-1,2,3-triazoles (**364**) react with orthoesters in refluxing diglyme to give 5-amino-4-(1,3,4-oxadiazol-2-yl)-1,2,3-triazoles (**363**) (Scheme 70). Conversely, the cyclized products (**365**) are obtained if an excess of orthoesters is used. Compounds (**365**), in turn, are hydrolyzed to the 1-aminohypoxanthine derivatives (**366**) <85JHC1435>. 2-Aryl-4-(5-tetrazolyl)-1,2,3-triazoles (**367**) have been prepared from 4-cyano-2-aryl-1,2,3-triazoles and ammonium azide in DMF <83JHC1561>.



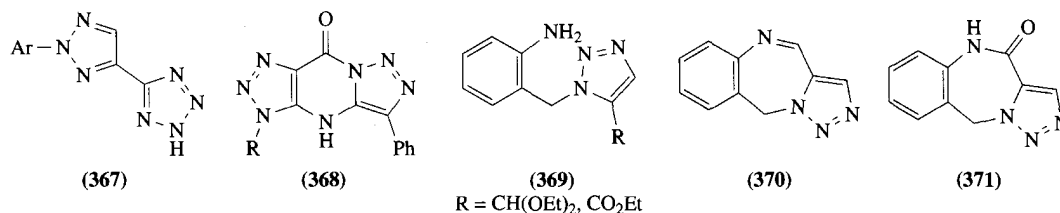
Scheme 69



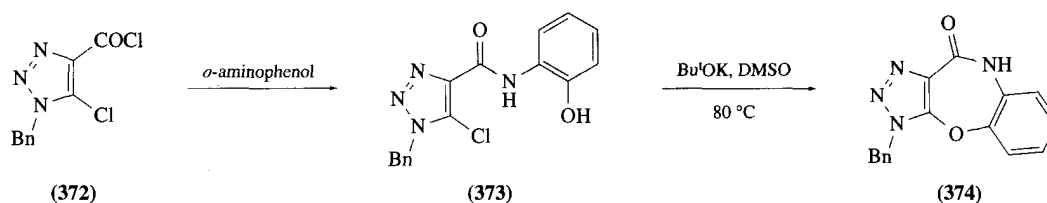
Scheme 70

Reactions of 4,5-disubstituted triazoles with appropriate substrates provide very useful methods for building triazolo fused bicyclic or tricyclic systems. 5-Azido-1,2,3-triazoles bearing an appropriate substituent (e.g., CHO, CN, CO₂R) at the 4-position can be transformed with active methylene nitriles into tricyclic heterocycles (e.g., (**368**)) <86BSB679, 87BSB587>. A new tricyclic system, 5*H*-1,2,3-triazolo[5,1-*c*][1,4]benzodiazepine (e.g., (**370**) and (**371**)), is prepared by the intramolecular ring closure of triazoles (**369**) <89JHC1605>.

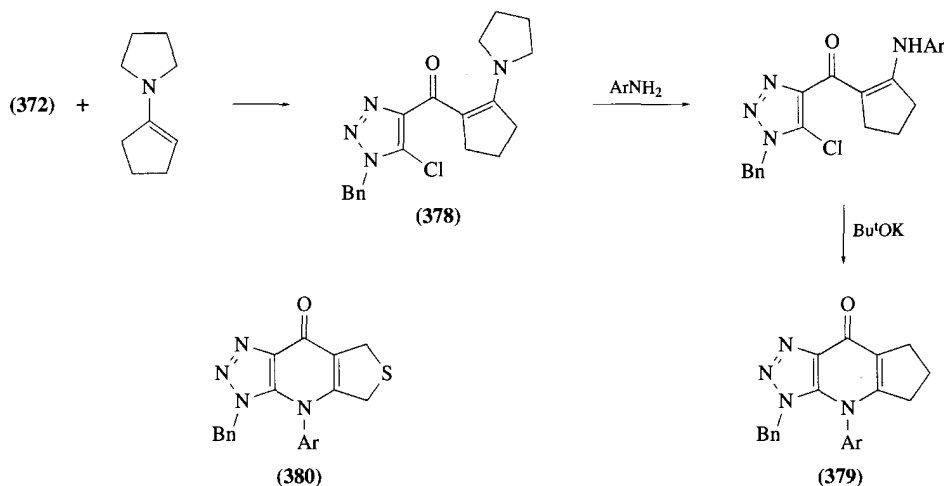
5-Chloro-1,2,3-triazole-4-carbonyl chloride (**372**) condenses with *o*-aminophenol in ethyl acetate



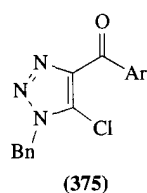
to afford the amide (**373**) which undergoes ring closure to the annulated triazole (**374**) upon treatment with Bu^tOK in DMSO <85JHC1693>. The acylation of simple arenes such as benzene and alkylated benzenes with *N*-alkyl-5-chloro-1,2,3-triazole-4-carboxylic acid chloride (**372**) under Friedel-Crafts conditions results in good yields of the corresponding ketones (**375**). Resorcinol dimethyl ethers undergo similar acylation reactions with concomitant monodemethylation, and these derivatives (**376**) (Equation (32)) undergo a facile base mediated cyclization to 9-oxo-3*H*,9*H*-benzopyrano[2,3-*d*]-1,2,3-triazoles (**377**) (Scheme 72) <85JHC77>. The acid chloride (**372**) can also acylate the pyrrolidine enamine to give compound (**378**), which undergoes transaminations with aryl amines followed by cyclization on treatment with Bu^tOK to afford the 1,2,3-triazole-fused pyridones (**379**). Similar reaction sequences have also been used to prepare the tricyclic pyridones (**380**) <90JHC1135>.



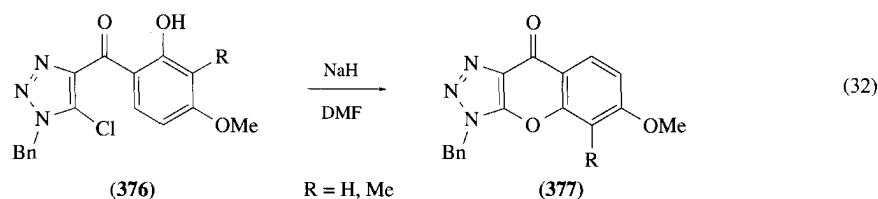
Scheme 71



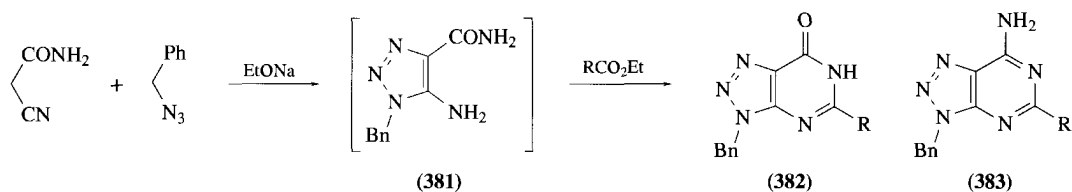
Scheme 72



Ar = Ph, 4-MeC₆H₄, 3,4-Me₂C₆H₃



1,2,3-Triazolo[4,5-*d*]pyrimidines (8-azapurines), a class of biheterocycles with anti-cancer and anti-allergic properties, have been synthesized from 4-amino-1,2,3-triazole-5-carboxamide with carboxylic acid amides and with amidines <79JCS(P1)922>. A one-pot synthetic sequence involves the addition of benzyl azide to an ethanolic suspension of the sodium salt of cyanoacetamide to obtain 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide (Scheme 73) (381). The intermediate (381) subsequently reacts with an excess of an ethyl carboxylate to give 8-azapurine-6-one (382) <85JHC1607>. 3,5-Disubstituted 7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (383) have been similarly prepared from nitriles and 5-amino-1-benzyl-4-cyano-1,2,3-triazole <87JHC997>. 5-Amino-4-cyano-1,2,3-triazoles react with diamines in the presence of P_2S_5 to yield 1,2,3-triazolo derivatives (384) (Scheme 74), which on treatment with orthoesters give annulated azapurines (385) and with aldehydes yield compounds (386) <89S739>. The 1,2,3-triazoles (384) react with biselectrophiles to form pyrimido-annulated 8-azapurines (387)–(389) <90LA207>. 8-Azapurines are also prepared from the reaction of ethyl 5-amino-1*H*-1,2,3-triazole-4-carboxylates with orthoformate and hydrazine or substituted phenethylamine <90LA819>. The synthesis of 8-azapurines from 4,5-disubstituted 1,2,3-triazoles has also been reviewed <86AHC(39)117>.

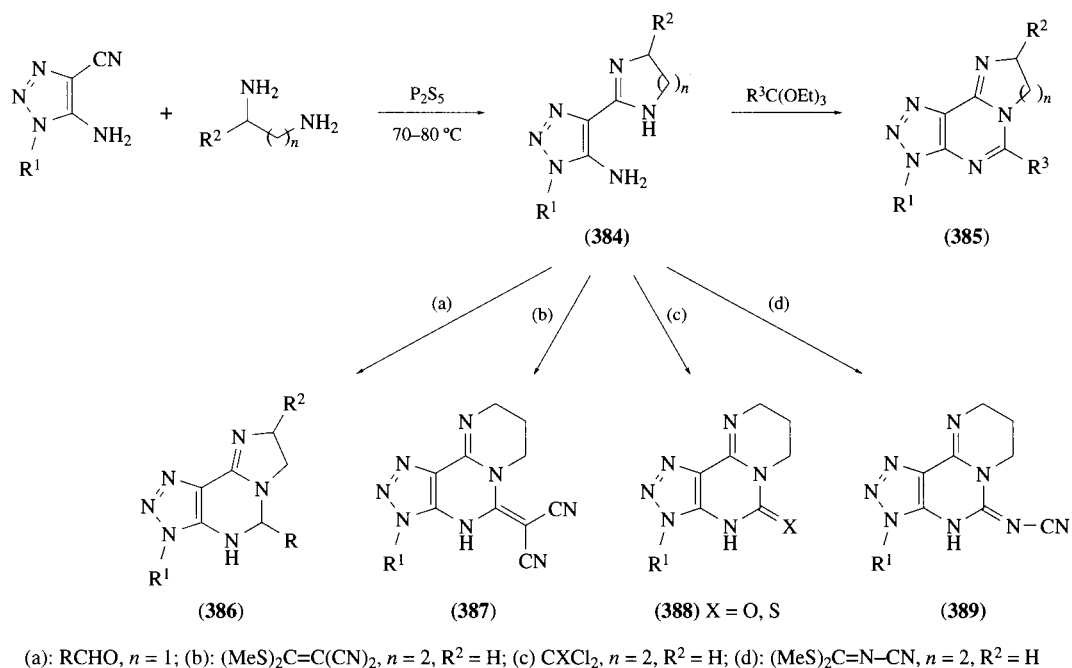


Scheme 73

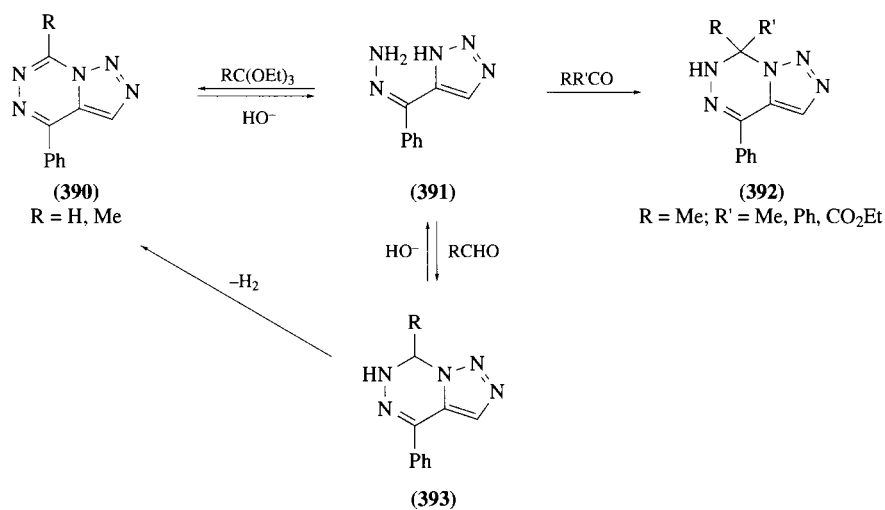
The hydrazone derivatives of 4-benzoyl-1,2,3-triazole (391) can be cyclized by reaction with orthoesters, ketones and aldehydes to form triazolo[1,5-*d*]-1,2,4-triazines (390), (392), or (393), respectively (Scheme 75). Compounds (390) and (393) are sensitive to base, and the starting hydrazone is recovered upon treatment with NaOH <88JHC743>. Oxidation of 5-methyl-1,2,3-triazoles (394) with potassium permanganate under alkaline conditions gives the corresponding carboxylic acids (395) (30–70%) (Scheme 76). Acids (395) lose carbon dioxide when heated above their melting points to give triazoles (396). Compounds (395) are converted to 1,2,3-triazolo[1,5-*d*]-1,3,4-oxadiazin-4-ones (397) either by reaction with dicyclohexylcarbodiimide (DCC) or with thionyl chloride in the presence of pyridine <87JHC1275>.

N-Oxidation of triazoles followed by *O*-alkylation or *O*-acylation activates the exocyclic α -position. Removal of the exocyclic α -protons provides anions which may react with electrophiles or nucleophiles. Thus, deprotonation of the methyl group of 5-methyl-2-phenyl-*N*-methoxytriazolium salt (398) leads to a neutral species (399) (Scheme 77), which is susceptible to nucleophilic attack with loss of a methoxide ion to form the α -substituted 4-methyltriazoles (400). The nucleophiles can be fluoride, cyanide, or methoxide ions <82JCS(P1)2749>. When 5-methyl-2-phenyl-1,2,3-triazole 1-oxide (402) is treated with iodotrimethylsilane and pentamethylpiperidine, 4-iodomethyl-2-phenyl-1,2,3-triazole (401) is formed. This iodomethyltriazole is an excellent starting material for the preparation of side chain-substituted derivatives through classical nucleophilic substitution reactions. Thus, (401) reacts with potassium acetate to give (400, Nu = OAc), hydrolysis and methanolysis give (400, Nu = OH and OMe) in good yield <92JCS(P1)2555>.

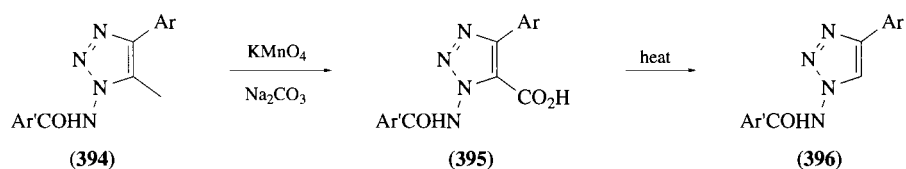
Few reports describe reactions of substituents at the benzene ring of benzotriazoles. The facile deprotonation of the methyl group in *N*-Boc-7-methyl-1-aminobenzotriazole (403) with butyllithium followed by reactions with electrophiles gives substituted products (404) (Scheme 78). The electrophile can be an alkyl halide, an aldehyde or a ketone, and the Boc group is removed by brief exposure to CF_3CO_2H in CH_2Cl_2 <93TL6935>. 1-Acetylbenzotriazole (405) is hydrolyzed to form 3-(1*H*-5-hydroxybenzotriazol-6-yl)propionic acid (406), which is then converted (Scheme 79) to



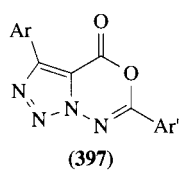
Scheme 74



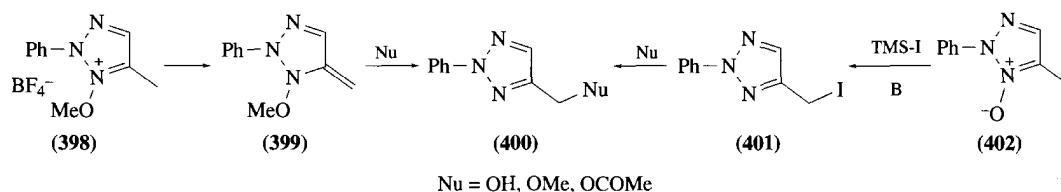
Scheme 75



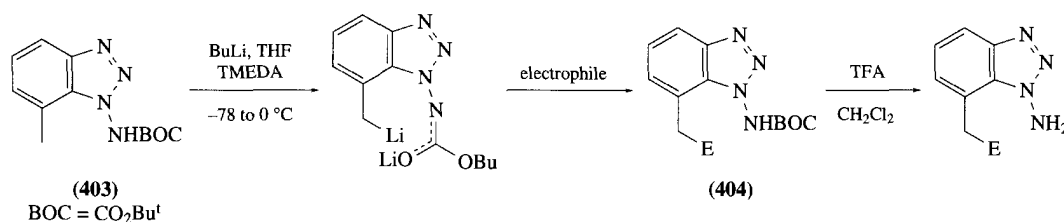
Scheme 76



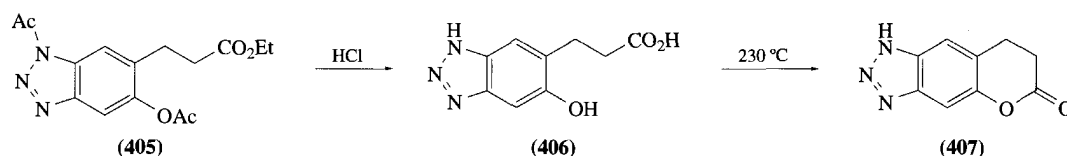
triazolo[6,7-*d*]dihydrocoumarin (**407**) in 95% yield simply by heating at 230°C <92JHC1519>. 5-(Benzotriazol-5-ylmethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione is synthesized in four steps, starting from benzotriazole-5-carboxylic acid. Bisbenzotriazolyl-substituted Meldrum's acid is similarly prepared <93SC2019>.



Scheme 77



Scheme 78



Scheme 79

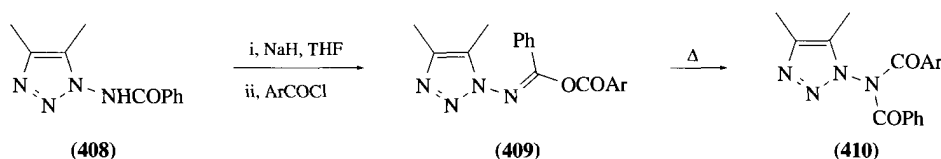
4.01.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Numerous publications have been devoted to the reactions of substituents attached to the nitrogen atoms of 1,2,3-triazoles, and particularly of benzotriazoles. Several comprehensive reviews have appeared <91T2683, 94MI 401-01, 94S445>.

4.01.7.1 Reactivity of *N*-amino, *N*-hydroxy, *N*-nitro and *N*-cyano Substituents

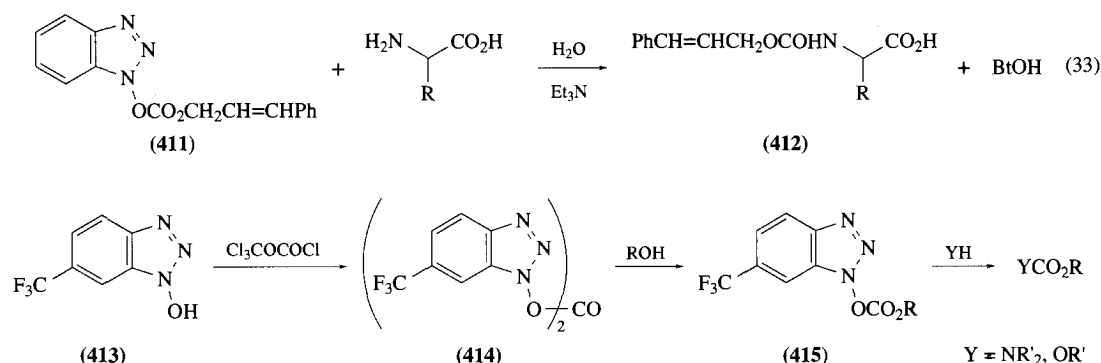
For a review of *N*-amino-1,2,3-triazoles, see Kuzmenko and Pozharskii <92AHC(53)85>. For the oxidation of *N*-aminotriazoles and benzotriazoles, also see Section 4.01.4.11.

The *N*-amino group of 1,2,3-triazoles reacts with aromatic aldehydes in toluene in the presence of Al₂O₃ to give 1-arylideneamino-1,2,3-triazoles in 61–95% yield. However, these Schiff's bases do not undergo cycloaddition with ketenes <87JHC1461>. *N*-Benzoylamino-1,2,3-triazoles (**408**), upon treatment with NaH in THF and subsequent reaction with an acid chloride, afford 1-(α -aroyloxybenzylideneamino)-1,2,3-triazoles (isoimides) (**409**) (Scheme 80). Intermediates (**409**) rearrange upon heating to imides (**410**) through a [1,3] *O*–*N* aroyl transfer. The reaction is slightly accelerated by electron-withdrawing substituents in the migrating moiety <83JHC1469, 84JHC1653>. Hydrolysis of *N*-acylaminotriazoles under acidic conditions is one of the common routes to *N*-amino-1,2,3-triazoles <92AHC(53)85> (also see Section 4.01.8.1).



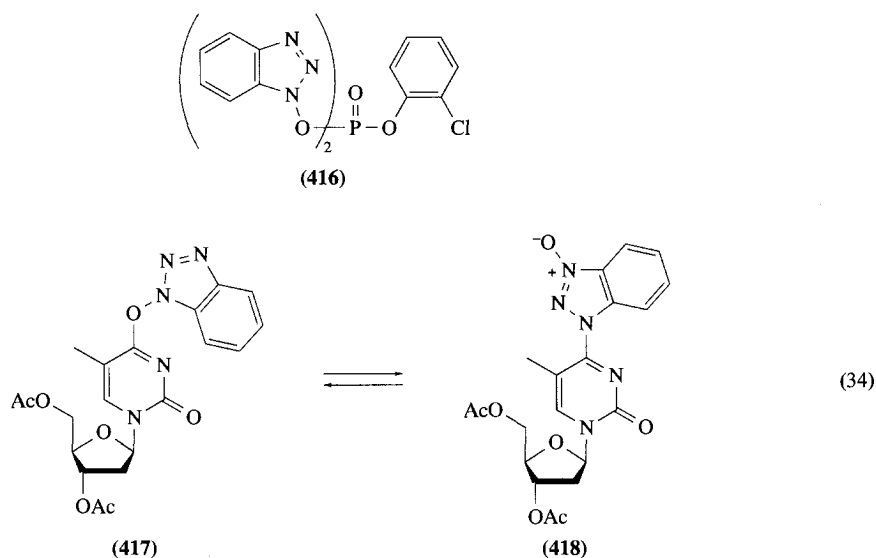
Scheme 80

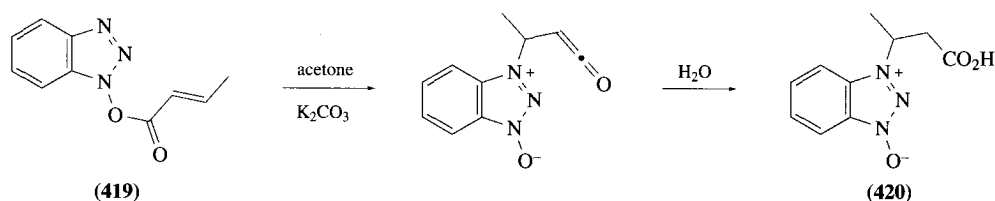
1-Hydroxybenzotriazole and its esters have been widely used as coupling agents for the construction of amide bonds in peptide synthesis $\langle 86\text{ACS(B)}242 \rangle$. 1-(Cinnamyl-oxy-carbonyloxy)benzotriazole (**411**) reacts with amino acids in water in the presence of Et_3N to form the *N*-protected amino acids (**412**) $\langle 85\text{CL}515 \rangle$ (Equation (33)). 1,1'-Bis[6-(trifluoromethyl)benzotriazolyl]carbonate (**414**), prepared from compound (**413**) and trichloromethyl chloroformate (Scheme 81), reacts with alcohols to afford carbonates (**415**) which can convert amines and alcohols into the corresponding carbamates and carbonates $\langle 87\text{S}557, 87\text{S}346 \rangle$. *t*-Butyl and benzyl benzotriazol-1-yl carbonates, available from the reaction of benzotriazol-1-yl chloroformate with an equimolar amount of *t*-butyl alcohol, are effective in the *t*-butoxycarbonylation of amino acids $\langle 83\text{CC}1357 \rangle$, and in the preparation of protected amine $\langle 86\text{TL}5375 \rangle$ and hydroxy functions $\langle 85\text{JOC}1751 \rangle$. 1-Acyloxybenzotriazoles have been used in the acylation of monobactams $\langle 84\text{H(21)}191, 84\text{TL}3293 \rangle$, and for the regioselective acylation of carbohydrates $\langle 91\text{SI}015 \rangle$.



Scheme 81

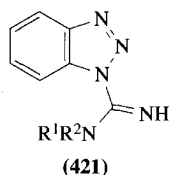
The benzotriazolyl phosphorochloridate (**416**), derived from 2-chlorophenyl phosphorodichloridate and 1-hydroxybenzotriazole, is a very efficient phosphorylating reagent which has been successfully used in the phosphorylation of nucleoside base residues. It has been determined that the benzotriazolyl nucleoside (**417**) is in equilibrium with its *N*-oxide isomer (**418**) in a ratio of 1 : 3 (Equation (34)) $\langle 85\text{TL}2245 \rangle$. 1-(Crotonyloxy)benzotriazole (**419**) undergoes rearrangement (Scheme 82), upon refluxing in acetone containing a catalytic amount of K_2CO_3 and water, to β -(3-benzotriazolyl)butyric acid 1-oxide (**420**) through the intermediate ketene $\langle 85\text{JOC}2174 \rangle$. The same rearrangement has been found in many other esters of 1-hydroxybenzotriazole $\langle 84\text{LA}1308, 85\text{JOC}696, 88\text{JOC}205 \rangle$. Crossover experiments demonstrate that the rearrangement is intermolecular $\langle 91\text{JCS(P2)}1545 \rangle$. 1-Alkoxy-6-nitrobenzotriazoles have been prepared by the reaction of 1-hydroxy-6-nitrobenzotriazole with an alkyl halide $\langle 82\text{JHC}1029 \rangle$.





Scheme 82

1-Nitrobenzotriazole reacts with cyclic amines in acetonitrile to give triazenes via azo coupling of the ring-opened intermediate, 2-(nitroimino)diazobenzene <84JOC2197>. 1-Cyanobenzotriazole reacts with amines in CH_2Cl_2 to give amidines (**421**), which slowly eliminate benzotriazole at room temperature to form the corresponding cyanamides <91RRC573>.



4.01.7.2 Reaction of Alkyl Substituents with an α -Functional group

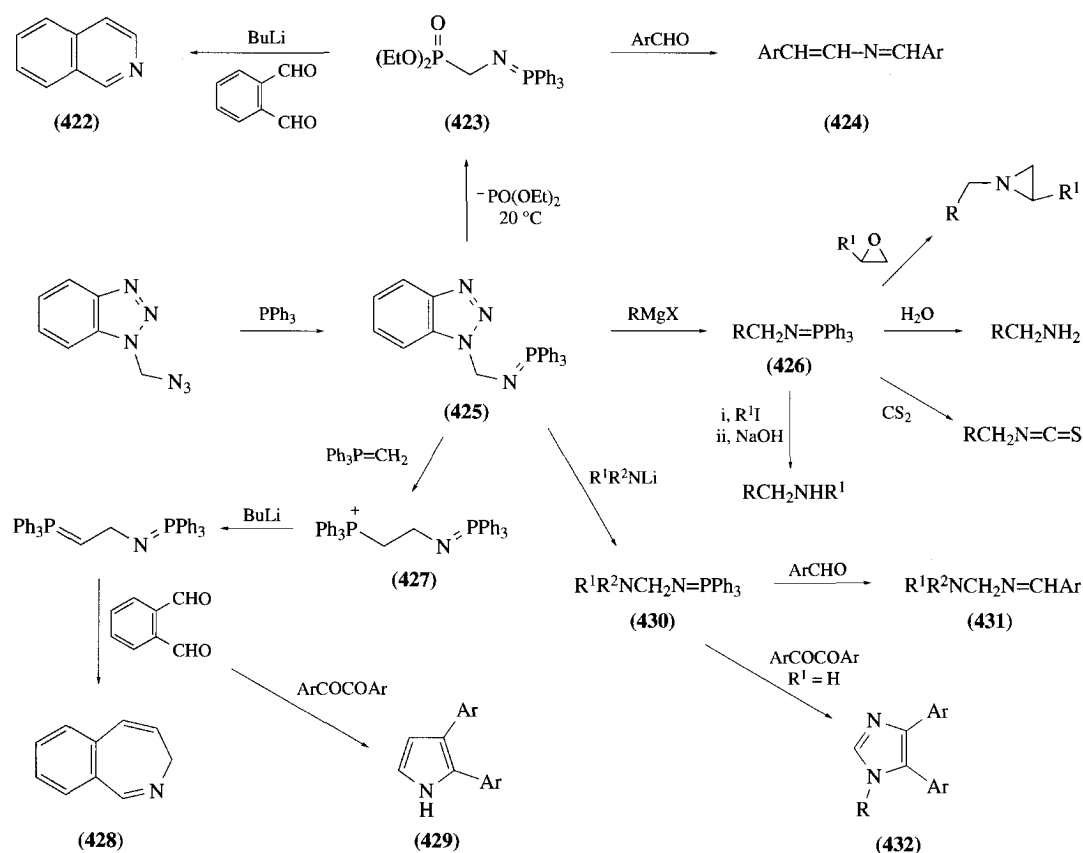
The benzotriazolate anion is a good leaving group and it can be used in place of a halogen substituent in many reactions. Benzotriazole derivatives are frequently more stable than their chloro or bromo analogs and are easy to prepare. The benzotriazole ring is extremely stable and opens only under severe conditions, offering advantages over 1,2,3-triazole. Therefore, benzotriazole has become one of the most useful synthetic auxiliary groups. Generally, N(1) and N(2) substituted benzotriazoles with an α -electron-donating substituent are in equilibrium and cannot be separated (see Section 4.01.3.6). Therefore, all reactions discussed in this section are based on mixtures of the N(1) and N(2) isomers unless otherwise mentioned.

4.01.7.2.1 Reactions of substituents with an α -amino or α -imino group

The benzotriazole moiety of *N*-(α -aminoalkyl)benzotriazoles is readily replaced by hydride upon reduction with sodium borohydride, or with a carbanion by reaction with Grignard or lithium reagents. These are two most important reactions of benzotriazole derivatives from which versatile routes have been developed for the synthesis of primary, secondary, and tertiary amines.

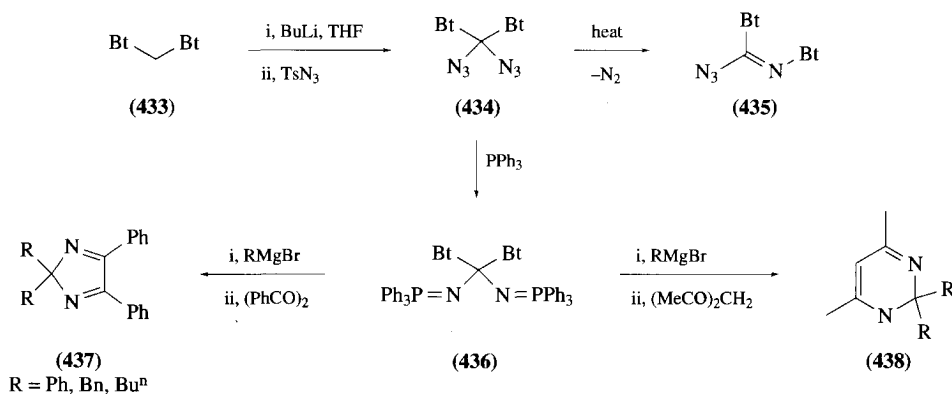
1-(Benzotriazol-1-yl)-*N*-triphenylphosphoranylidene-methylamine (**425**), readily available from *N*-(azidomethyl)benzotriazole and PPh_3 , reacts with Grignard reagents followed by hydrolysis of the intermediates (**426**) to give primary amines <89TL3303>. The initial products (**426**) also react with isocyanates, carbon disulfide, aldehydes, epoxides, and alkyl halides to afford a wide variety of carbodiimides, imines, isothiocyanates, aziridines, and secondary amines (Scheme 83) <90S565>. The benzotriazole group in (**425**) can be displaced by a phosphorus anion to give the intermediate (**423**). Compound (**423**) undergoes Wittig reactions with aldehydes to form 2-azabutadienes (**424**), and with phthalic dicarboxaldehyde to give isoquinoline (**422**) <93JOC1987>. Similarly, benzotriazole derivative (**425**) and methylenetriphenylphosphorane give intermediate (**427**) which affords 2(3*H*)-benzazepine (**428**) and 2,3-diarylpyrroles (**429**) when treated with BuLi followed by phthalic dicarboxaldehyde or diaryl 1,2-diones, respectively <93JOC1987>. Compound (**425**) also reacts with lithium amides to give intermediates (**430**). Subsequent treatment of (**430**) with aryl aldehydes affords α -(arylideneamino)alkylamines (**431**) <91CJC1153>. When $\text{R}^1 = \text{H}$, the intermediates (**430**) react with α -diaryl ketones to give 1-substituted 4,5-diarylimidazoles (**432**) in high yields <90H(31)2187>. Reactions

of thiolates with (425) followed by treatment with an aldehyde, an isocyanate or an acyl chloride yield functionalized *N,S*-acetals <94S107>.



Scheme 83

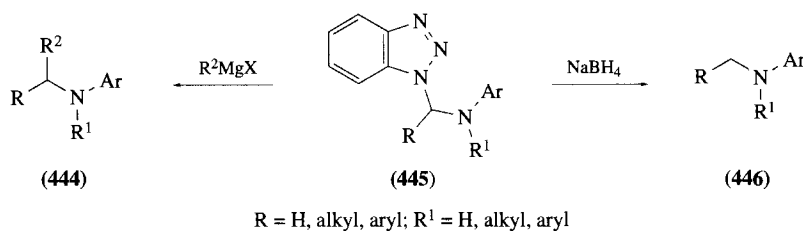
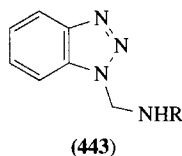
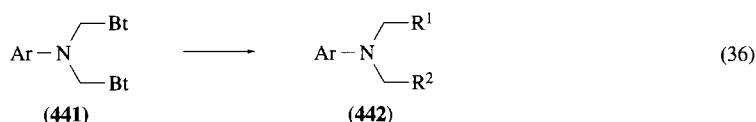
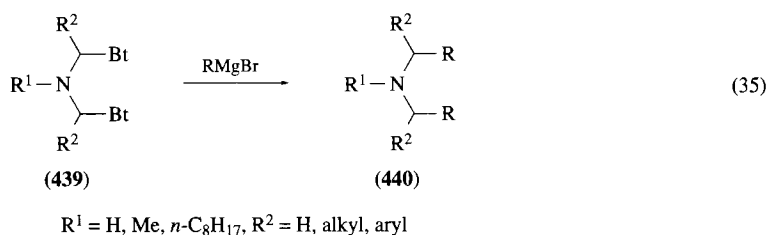
Dibenzotriazole methane (433) undergoes lithiation with BuⁿLi and subsequent reaction with tosyl azide to give the *gem*-diazido derivative (434) (Scheme 84), which then reacts with PPh₃ to afford the intermediate (436). The geminal diamino compounds generated from the reaction of (436) with Grignard reagents can be trapped by 1,2- or 1,3-diketones to give isoimidazoles (437) and 1,2-dihydro-4,6-dimethyl-2,2-diphenylpyrimidines (438), respectively. Thermolysis of (434) gives (435) with elimination of one molecule of nitrogen <90JCR(S)330>.



Scheme 84

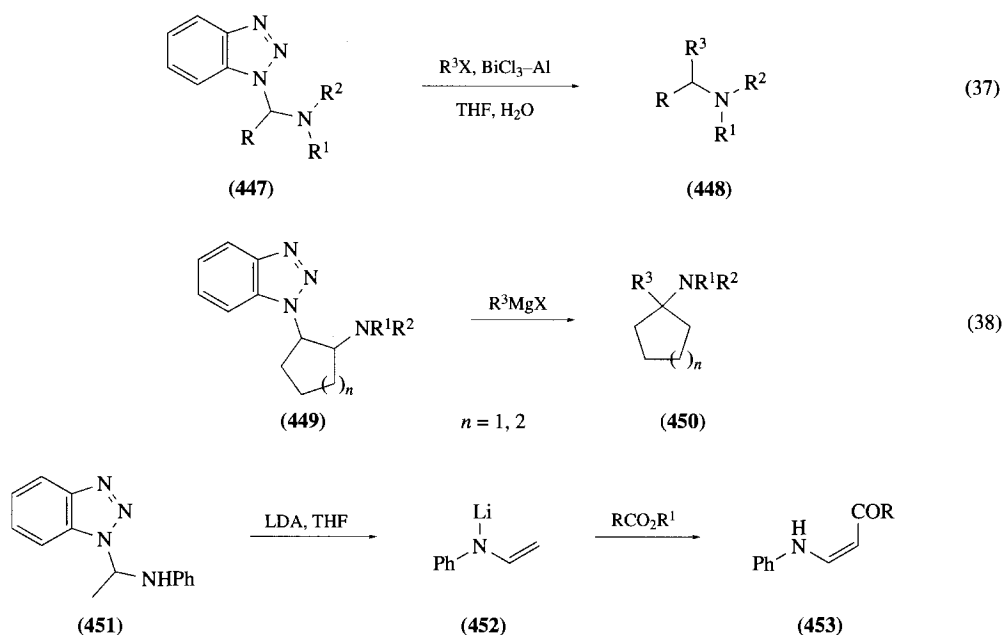
When bis(benzotriazolylmethyl)amines (439, R¹ = R² = H) are treated with three equivalents of Grignard reagents, symmetrical secondary amines (440) are obtained in high yield (Equation (35)) <89JCS(P1)225, 91S703>. Benzotriazole reacts with formaldehyde and ammonia under forcing con-

ditions to give $(\text{BtCH}_2)_3\text{N}$, which affords symmetrical tertiary amines $(\text{RCH}_2)_3\text{N}$ on treatment with Grignard reagents. Primary aliphatic amines are similarly converted to tertiary amines (**440**) by the reaction of benzotriazole derivatives (**439**, $\text{R}^1 = \text{R}^2 = \text{alkyl}$) with Grignard reagents. Secondary aliphatic amines condense with benzotriazole and an aldehyde (1:1:1 ratio). Further reaction with Grignard reagents gives tertiary amines $\langle 89\text{JCS(P1)225, 90RTC337} \rangle$. Grignard reactions of *N,N*-bis(benzotriazolylmethyl)arylamines (**441**) afford the *N,N*-dialkyarylamines (**442**) (Equation (36)). Two different alkyl groups can be introduced by a stepwise procedure to give unsymmetrical *N,N*-dialkylamines (**442**, $\text{R}^1 \neq \text{R}^2$) $\langle 90\text{CJC456} \rangle$. Grignard reactions of 1-[(alkylamino)methyl]-benzotriazoles (**443**) afford unsymmetrical secondary amines $\langle 90\text{CB1443} \rangle$. The condensation products of benzotriazole, an aldehyde, and an aromatic primary amine (e.g. **445**, $\text{R}^1 = \text{H}$) react with Grignard reagents to afford secondary amines (**444**, $\text{R}^1 = \text{H}$) (Scheme 85) $\langle 89\text{OPP340} \rangle$. The secondary aromatic amines are similarly converted to the tertiary amines (**444** and **446**, $\text{R}^1 = \text{alkyl}$) $\langle 90\text{CJC456} \rangle$. Heteroaromatic amines also give good yields of the mono-*N*-alkylation product $\langle 87\text{JCS(P1)805} \rangle$.



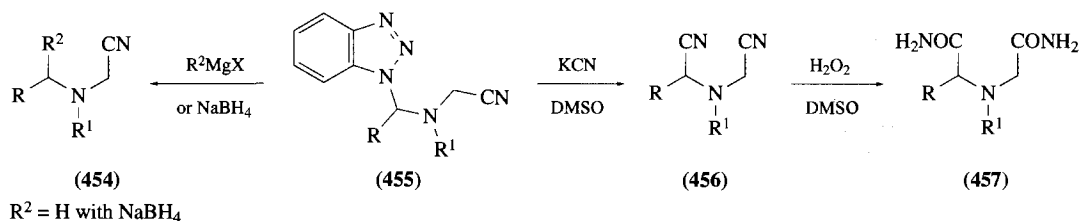
Scheme 85

In the presence of bismuth(III) chloride-metallic aluminum, active alkyl halides react with benzotriazoles (**447**) at room temperature in THF-water to give the corresponding homoalkylated amines (**448**) (Equation (37)) $\langle 91\text{TL4247, 92OM1381} \rangle$. Benzotriazole derivatives (**449**) (Equation (38)), obtained from benzotriazole, a cyclic ketone, and a secondary amine, undergo reaction with Grignard reagents to yield highly branched tertiary amines (**450**) $\langle 89\text{S66} \rangle$. Treatment of *N*-(1-anilinoethyl)benzotriazole (**451**) (Scheme 86) with LDA (2.5 equivalents) in THF gives *N*-lithio-*N*-vinylaniline (**452**), which reacts with an ester to furnish the mesomerically stabilized enaminones (**453**) $\langle 93\text{S233} \rangle$. The lithio intermediate (**452**) also undergoes regioselective reactions with various arenedicarboxylates and esters of α,β -unsaturated acids $\langle 94\text{JCS(P1)113} \rangle$.



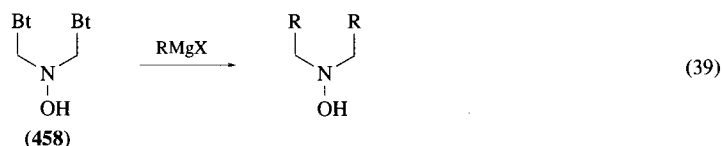
Scheme 86

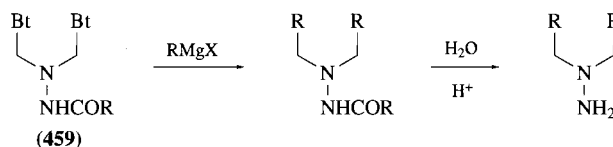
N-Alkyl-*N*-(1-benzotriazolylalkyl)aminoacetonitriles (455), Mannich-type condensation products of benzotriazole with an aldehyde and an α -aminoacetonitrile, undergo reactions with sodium borohydride or a Grignard reagent to give unsymmetrical *N,N*-dialkylaminoacetonitriles (454) (Scheme 87). Upon decyanomethylation, derivatives (454) afford unsymmetrical secondary amines (90JCS(P1)667). The benzotriazolyl group of compounds (455) is also displaced by KCN in DMSO to yield *N*-alkyliminodiacetonitriles (456). Further treatment of (456) with H_2O_2 in DMSO gives unsymmetrical iminodiacetoamides (457) (90S999).



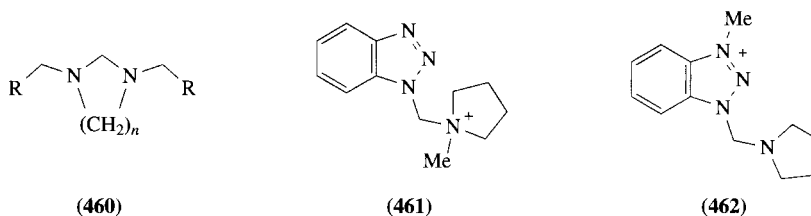
Scheme 87

The reaction of α -(aminoalkyl)benzotriazoles with Grignard reagents can be extended to other amino-containing compounds. Thus, hydroxylamine and hydrazines are alkylated using benzotriazole methodology via benzotriazole derivatives (458) and (459) as shown in Equation (39) and Scheme 88 (89JCS(P1)225, 89JCS(P1)2297). The reaction of diamines with benzotriazole and formaldehyde followed by nucleophilic displacement of the benzotriazole groups from the intermediates results in imidazolidines (460, $n = 2$) (90JCS(P1)541). (Benzotriazol-1-ylmethyl)amines on treatment with alkylating agents, afford benzotriazol-1-ylmethylammonium salts (e.g., 461). At elevated temperature, an alkyl substituent migrates from the ammonium center to the benzotriazolyl N(3) to form a thermodynamically more stable salt (462), which can further decompose to 1-methylbenzotriazole (89JHC1579).



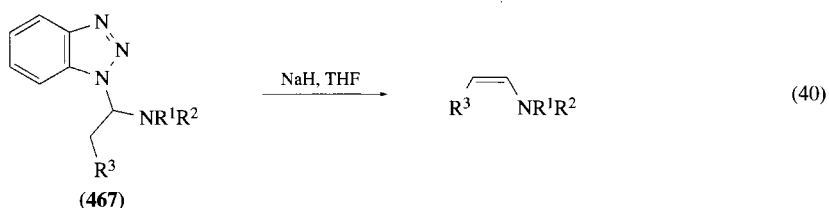


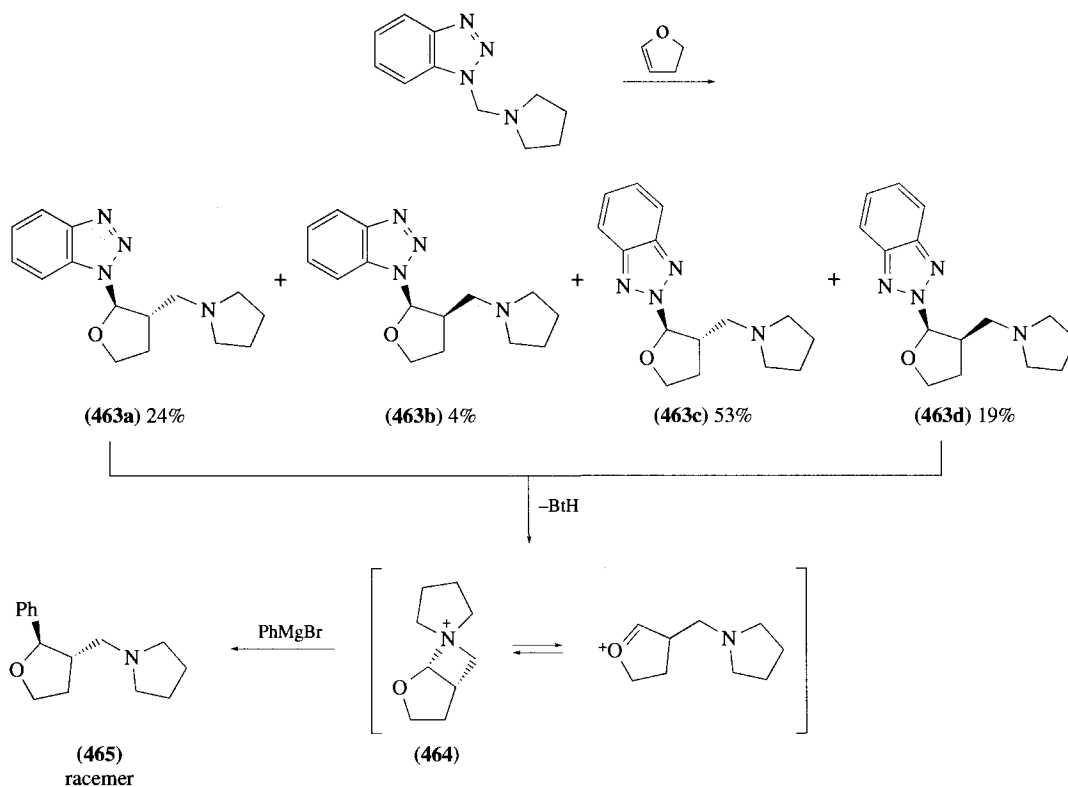
Scheme 88



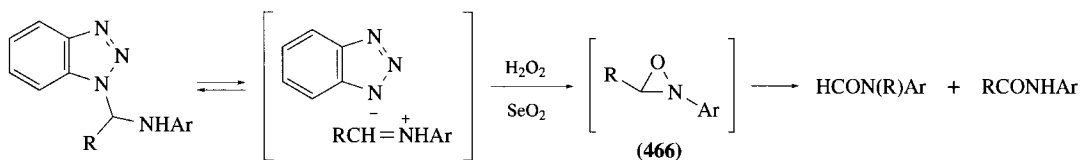
N-(α -Aminoalkyl)benzotriazoles add readily to enol ethers to give the corresponding 1-benzotriazolyl-3-aminoalkyl ethers. Subsequent replacement of the benzotriazole moiety by an alkyl or aryl group (with a Grignard reagent) or by a hydrogen (with LiAlH_4) affords 1,3-amino-ethers. The addition of *N*-(α -aminoalkyl)benzotriazoles to enol ethers is not stereospecific, thus all four isomeric adducts (463a–d) are formed when *N*-(pyrrolidin-1-ylmethyl)benzotriazole adds to 2,3-dihydrofuran. The three most abundant isomers can be separated by column chromatography. Reaction of the unseparated mixture (463a–d) with PhMgBr gives only one diastereomer of the amino-ether (465) with a *trans* configuration, indicating participation of the same cation intermediate (464) with anchimeric assistance from the amino groups in each of the substitutions to yield the final product (465, Scheme 89) (92JOC4932). *N*-(α -Aminoalkyl)benzotriazoles also easily add to enamines and enamides, such as 9-vinylcarbazole and 1-vinyl-2-pyrrolidinone (93JOC812). *N*-(α -Arylaminoalkyl)benzotriazoles are converted by H_2O_2 – SeO_2 into mixtures of formamides and amides in proportions which depend rationally on the nature of the R group. For $\text{R} = \text{Bu}^t$, the formamide $\text{HCON}(\text{Bu}^t)\text{Ar}$ is formed in satisfactory yields. Hydrolysis of this formamide results in the *N*-*t*-butylated amine. The mechanism probably involves reversible ionic dissociation followed by oxidation to an oxaziridine (466) (Scheme 90) (89JCS(P1)639).

The elimination of benzotriazole from *N*-(α -aminoalkyl)benzotriazoles containing a β -hydrogen (e.g., 467) by NaH in THF (Equation (40)) results in the formation of enamines (90T8153). Readily prepared 1,3-bisbenzotriazolyl tertiary amines (468) can be similarly converted into dienamines (469) (Equation (41)) (91TL3597). In the case of 1,3-bisbenzotriazolyl *N,N*-disubstituted propylamines (e.g., 471) from which dienamines can not be formed (Scheme 91), only one benzotriazole is eliminated on treatment with NaH to give benzotriazole substituted enamines (470). Reduction of (471) with NaBH_4 gives saturated amines (472) (92PIC1653). When 1,3-bisbenzotriazolyl aromatic secondary amines (473) are treated with LDA followed by subsequent reaction with esters, the dienaminones (474) are afforded (Scheme 92) (93S233). The reaction of glyoxal with 2 equivalents of both benzotriazole and a primary or secondary amine results in the formation of dibenzotriazolyl-1,2-diaminoethanes (475). Subsequent reaction of (475) with sodium borohydride or Grignard reagents (Equation (42)) gives high yields of vicinal diamines (476) (90JOC3209). Tertiary vicinal diamines (476) have also been prepared by SmI_2 -promoted reduction of *N*-(*N*', *N*'-dialkylaminoalkyl)benzotriazoles (92TL4763). 1-Substituted 2,6-dibenzotriazolylpiperidine (477) affords 1,2,6-trisubstituted piperidine with Grignard reagents (90JOC3205). Alkylzinc halides react with α -benzotriazolylaminoesters (478) to give α -alkylated α -aminoesters (479) (89S323). Replacing the glyoxalate ester in the condensation reaction with the diethoxy monoacetal of glyoxal followed by Grignard reaction and hydrolysis results in a simple route to α -aminoaldehydes (90S1173).

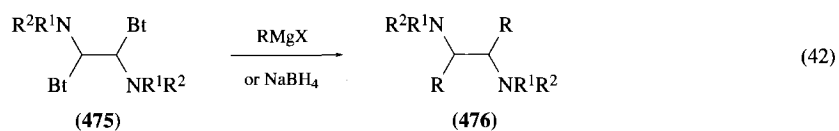
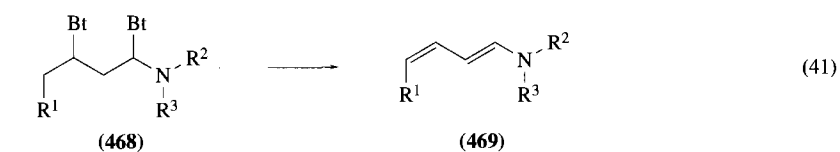




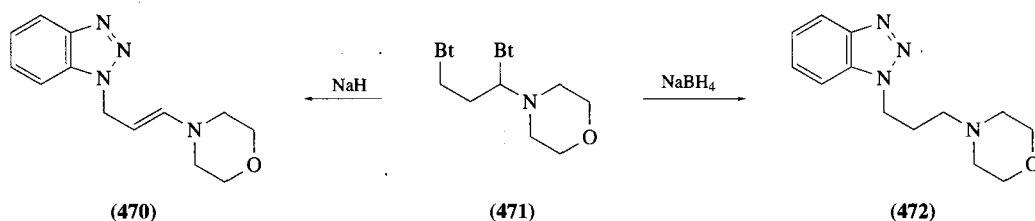
Scheme 89



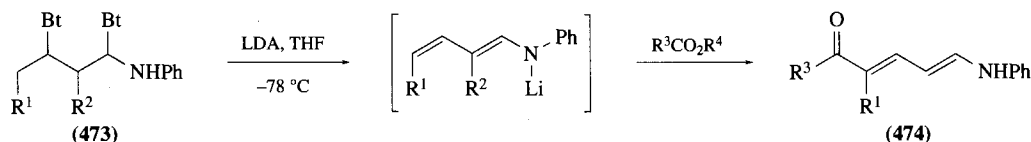
Scheme 90

R = H when NaBH_4 is used

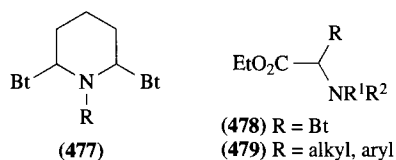
β -Aminoesters (480) are prepared from α -(aminoalkyl)benzotriazoles (447) and Reformatsky reagents [89S747]. The preparation of propargylamines (481) by the reaction of (447) with lithiated terminal alkynes is experimentally convenient, general and high yielding [89S31]. The benzotriazole methodology is also successfully applied to the aminoalkylation of aliphatic nitro compounds to form β -nitroalkylamines (482) [90G375]. The benzotriazole derivatives (447) react readily as methyleneamine synthetic equivalents with 2-methylfuran under mild conditions in the presence of Lewis acids to afford aminoalkylated heterocycles (483). Similarly, secondary and tertiary aminoalkylbenzotriazoles (447) react with pyrrole, indole, and their *N*-methyl analogs to give 2-aminoalkylpyrroles and 3-aminoalkylindoles [92T4971]. *N*-(α -Aminoalkyl)benzotriazoles (447) react with



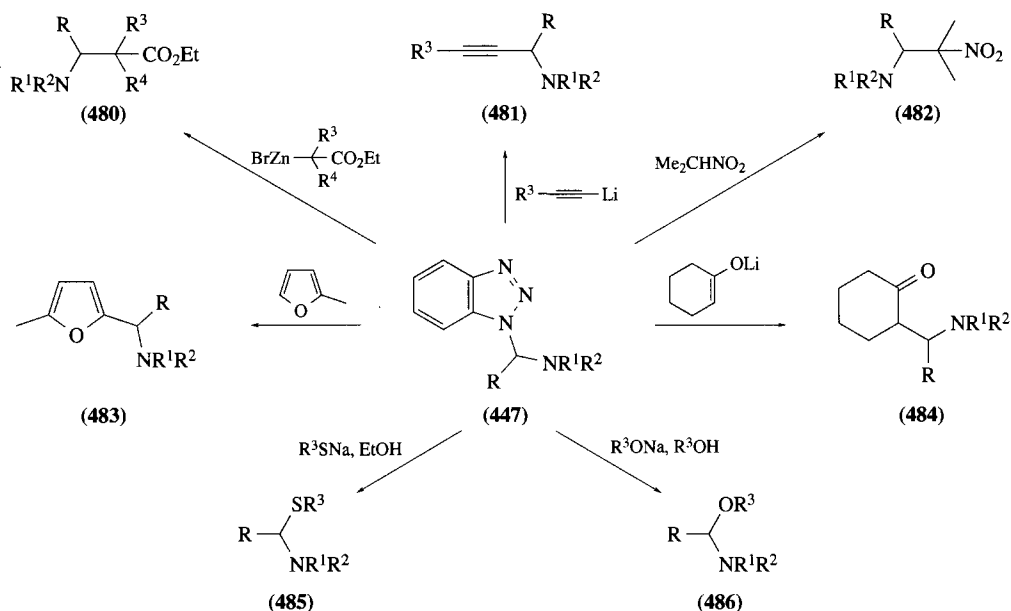
Scheme 91



Scheme 92



lithium enolates to give aminoalkylated ketones (484). Secondary or primary amines ($R^1 = H$), amides ($R^1 = COR$) or sulfonamides ($R^1 = SO_2R$) may also be used (90T987). *N*-(α -Benzotriazolylalkyl)amines (447) react with a variety of sodium thiolates and alkoxides to give the *N,S*-acetals (485) and *N,O*-acetals (486) in good yield (93S229) (see Scheme 93).

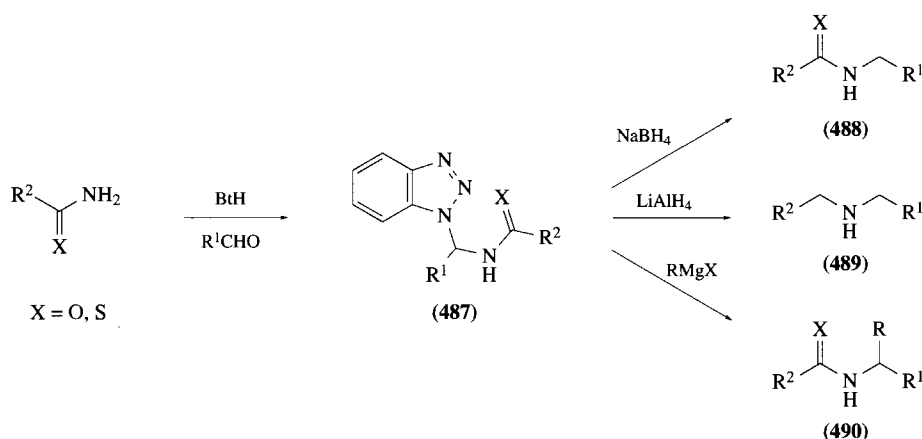


Scheme 93

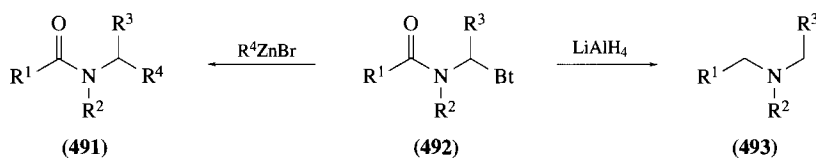
4.01.7.2.2 Reactions of substituents with an α -amido group

N-(α -Benzotriazolylalkyl)amides (487, $X = O$), readily available from the condensation of a primary amide (Scheme 94), an aldehyde and benzotriazole in toluene, react with Grignard reagents

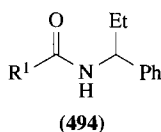
to give the α -alkylated amides (**490**, X = O). This procedure provides an efficient method for the *N*-alkylation of amides. Reduction of benzotriazolyl amides with NaBH₄ gives amides (**488**, X = O). However, LiAlH₄ reduction yields unsymmetrical secondary amines (**489**) <88JCS(P1)2339, 88JOC5854>. Thioamides can also be alkylated at the *N*-atom to give secondary thioamides (**488** and **490**, X = S) using the same method avoiding any *S*-alkylation <88JOC5854, 88TL1755>. A similar reaction has also been used for the *N*-alkylation of sulfonamides <89CS27>. *N*-Alkyl-*N*-[1-benzotriazol-1-yl]alkyl]amides (**492**), prepared from a secondary amide, an aldehyde, and benzotriazole, react with organozinc reagents to give tertiary amides (**491**) (Scheme 95). Reduction of (**492**) by LiAlH₄ affords tertiary amines (**493**). Secondary thioamides and sulfonamides undergo *N*-alkylation reactions in a similar way <93JOC2086>. In the presence of the chiral amino-alcohol (–)-*N,N*-dibutylnorephedrine, *N*-(amidobenzyl)benzotriazoles react enantioselectively with diethylzinc to give the corresponding *N*-(α -ethylbenzyl)amides (**494**) with up to 76% ee <92TA437>.



Scheme 94

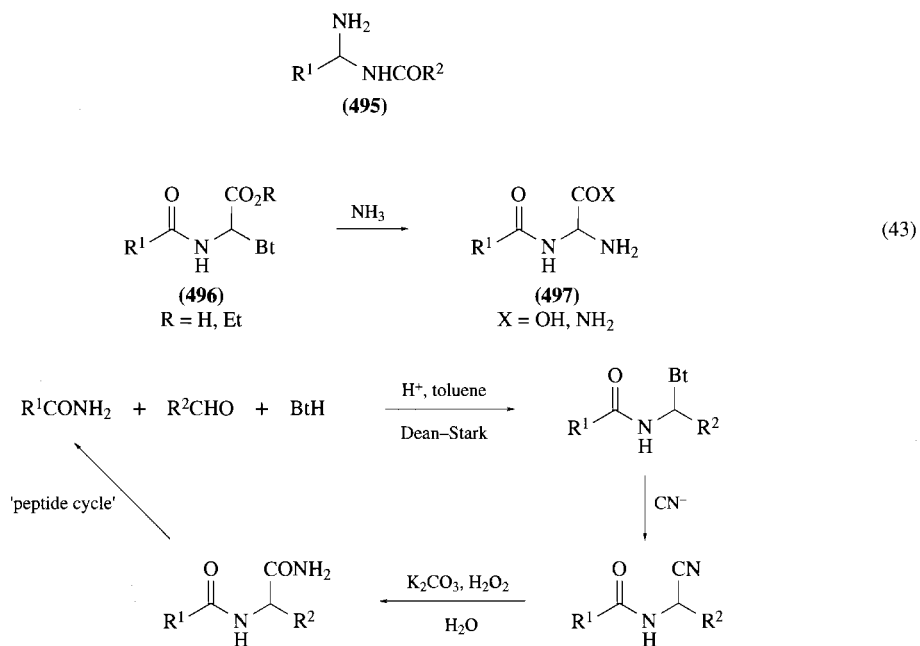


Scheme 95

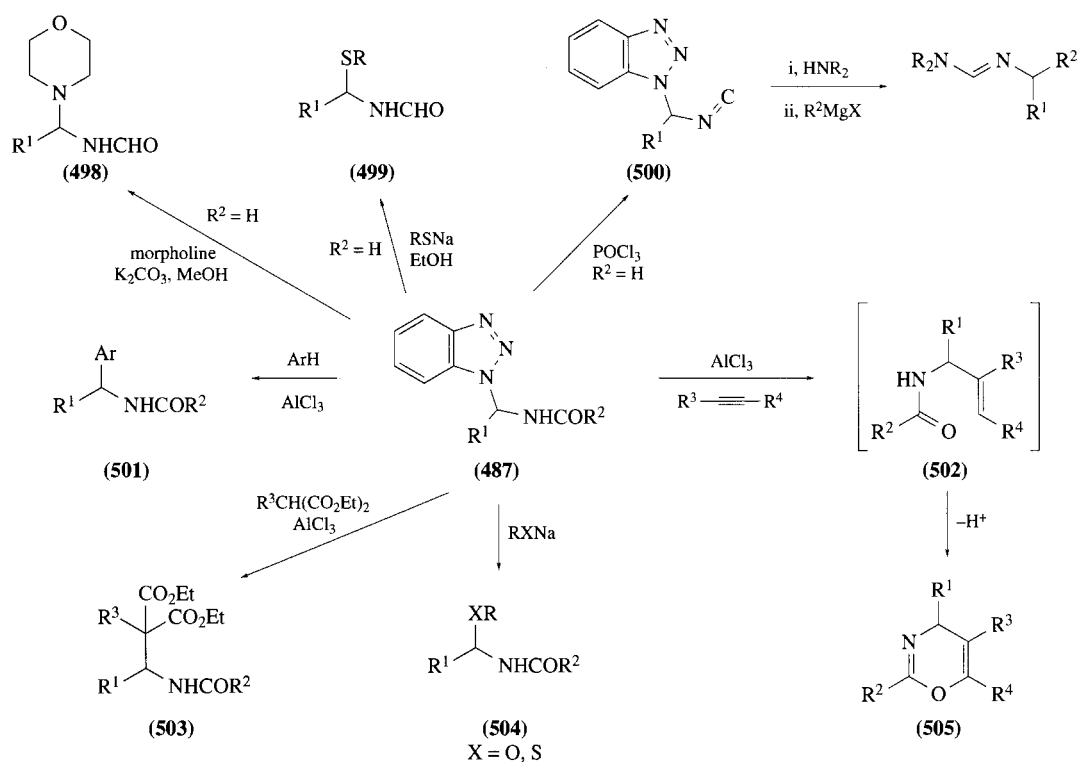


The benzotriazole group of the α -amido benzotriazole derivative (**487**) is readily replaced by ammonia. Thus, treatment of (benzotriazolylalkyl)amides with ammonia results in the formation of monoacyl amins (**495**, R^2 = alkyl, aryl) (Equation (43)). Using protected amino acid amides as the amide component leads to 'gem-dipeptides' (**495**, R^2CO = Bz-Gly, Z-L-Val, Z-Gly and Z-Phg etc.) <90JOC2206>. A similar method has been used for the efficient synthesis of mono-acyl- α -aminoglycines (**497**) and the corresponding peptide analogs by the reaction of benzotriazole derivatives (**496**) generated from glyoxylic ester or acid and ammonia <89CC337>. Substitution of the benzotriazolyl group in (**487**) by cyanide followed by mild hydrolysis allows the elongation of peptides (Scheme 96) <90JCS(P1)1853, 92OPP121>. The benzotriazole moiety of 1-[α -(formylamino)alkyl]benzotriazoles (**487**, R^2 = H) is displaced by morpholine and by thiols in basic conditions to give products (**498**) and (**499**) (Scheme 97), both of which undergo dehydration to form α -aminoalkyl or α -alkylthioalkyl isocyanides respectively <93S45>. Benzotriazole derivatives (**487**) are readily dehydrated by treatment with POCl₃ to α -(benzotriazolyl)alkyl isocyanides (**500**), which react with

secondary amines followed by Grignard reagents to yield unsymmetrical formamidines <90JCS(P1)1847>.



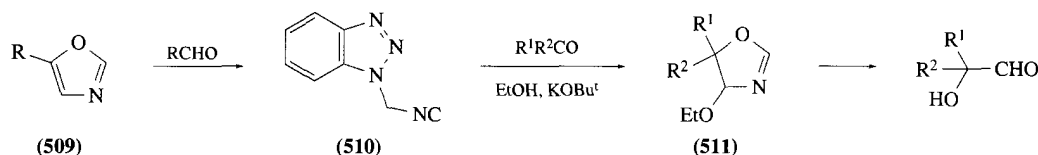
Scheme 96



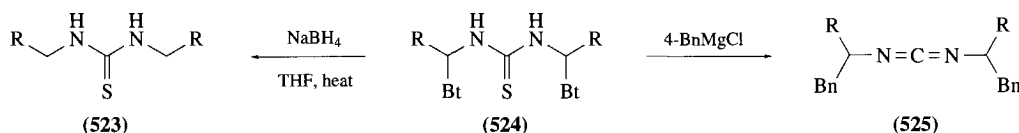
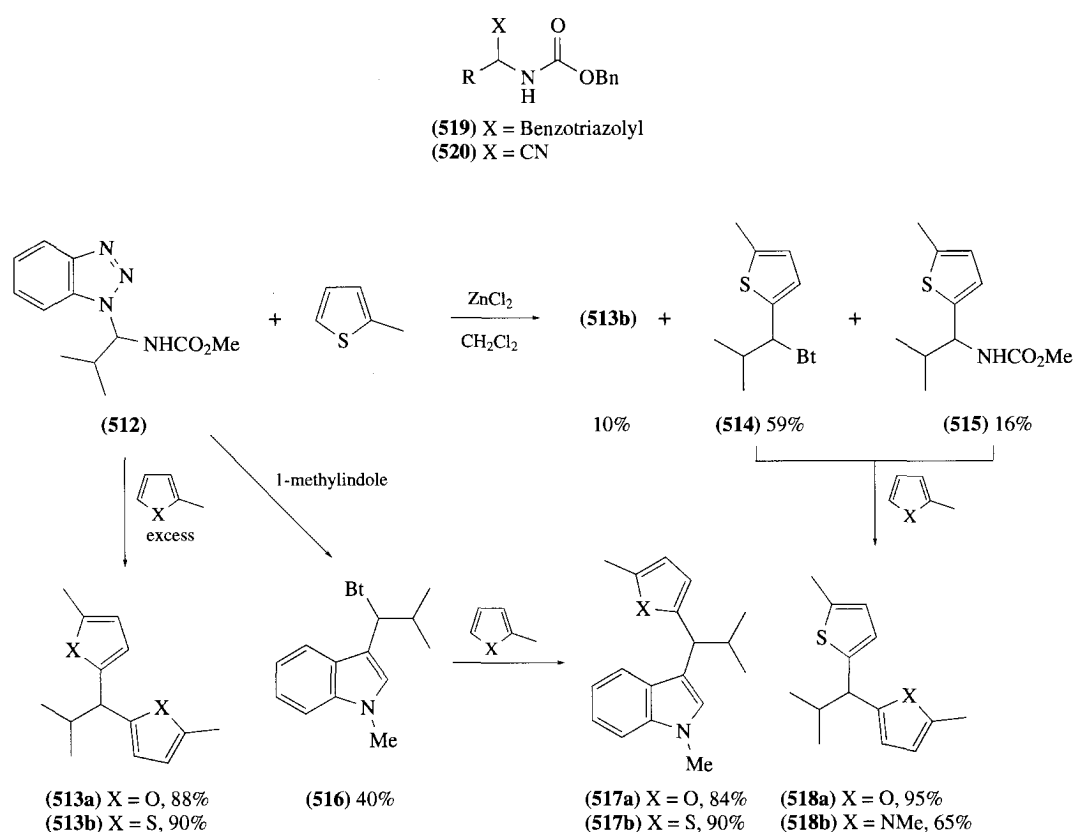
Scheme 97

N-(α -Benzotriazolylalkyl)amides (**487**, R^2 = alkyl, aryl, and H) are very efficient amidoalkylating reagents for a variety of nucleophiles. Mixtures of electron-rich aromatic or heteroaromatic com-

Scheme 98



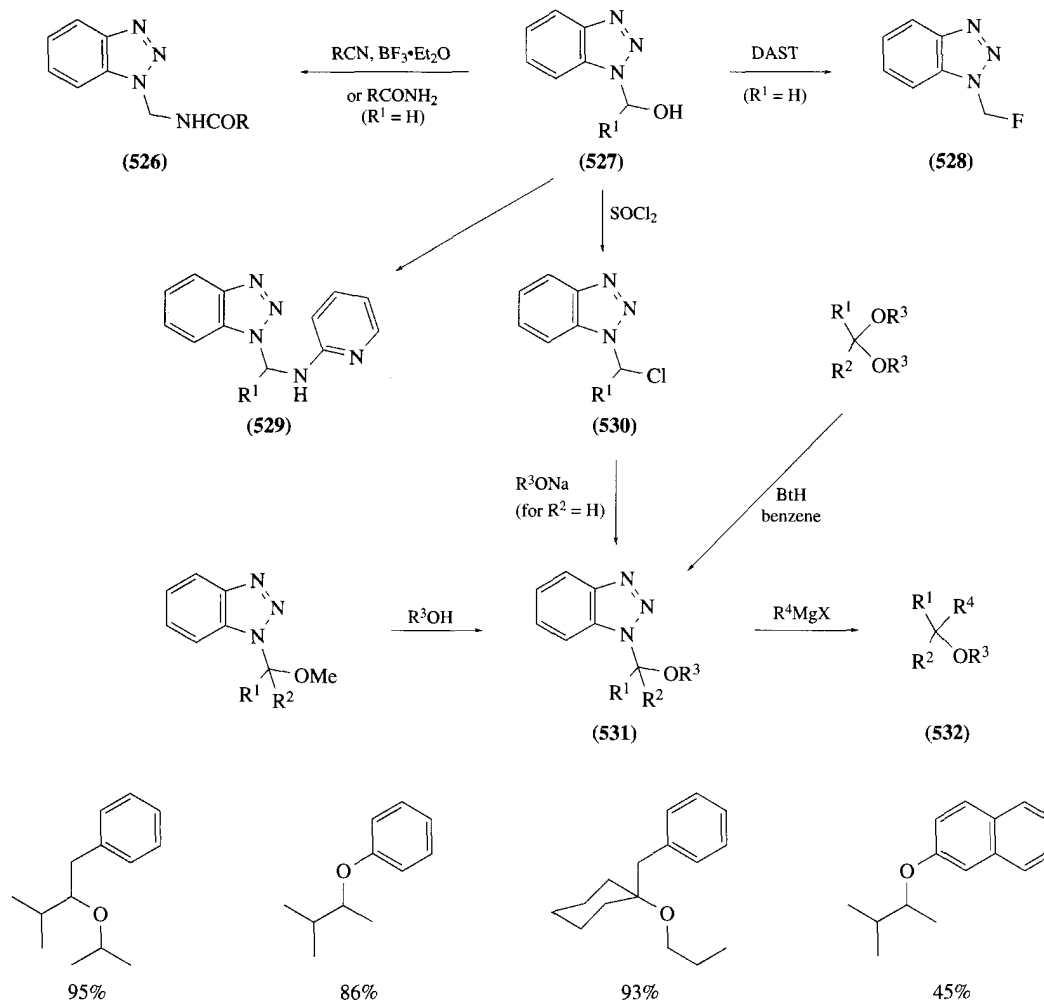
Scheme 99



4.01.7.2.3 Reactions of substituents with an α -OR or α -SR group

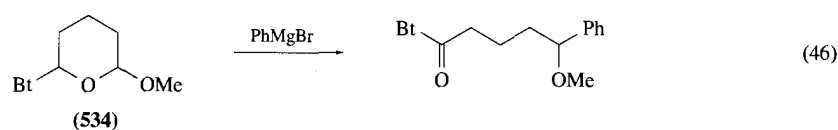
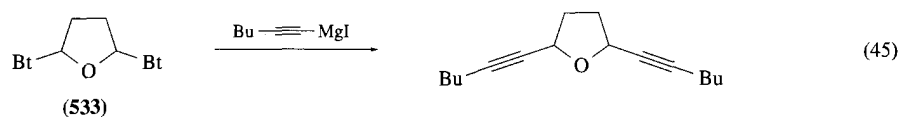
1-Hydroxymethylbenzotriazole (**527**, $\text{R}^1 = \text{H}$), formed *in situ* from benzotriazole and paraformaldehyde, reacts with aliphatic nitriles at 120°C in the presence of boron trifluoride etherate to give α -(amidomethyl)benzotriazoles (**526**) (Scheme 102) <92OPP475>. Compounds (**526**) are also prepared from (**527**) and *N*-unsubstituted amides <88JCS(P1)2339>. Treatment of (**527**) with thionyl chloride gives 1-(α -chloroalkyl)benzotriazole (**530**) <87JCS(P1)811>. 1-Hydroxymethylbenzotriazole reacts with diethylaminosulfur trifluoride (DAST) to give fluoro derivatives (**528**) <93PIC1243>, and with aromatic amines to yield an equilibrium mixture of *N*-mono- and *N,N*-bis(benzotriazolylmethyl)arylamines. Electron-releasing substituents on the arylamine ring shift the equilibrium towards the bisbenzotriazolylmethylated products, and removal of the water formed in the reaction results in quantitative yields of these bis-derivatives <90CJC446>. 1-[1-(Hydroxyalkyl)]benzotriazoles (**527**) convert a wide variety of aromatic and heteroaromatic primary amines into their mono *N*-[1-(benzotriazol-1-yl)alkyl] derivatives (e.g., **529**) in high yield. Aliphatic primary amines frequently give bis-derivatives <87JCS(P1)799>.

1-(α -Alkoxyalkyl)benzotriazoles (**531**) react with Grignard reagents in refluxing toluene to give α -substituted ethers (**532**) in high yields, and some examples are listed in Scheme 102. These ethers are otherwise difficult to make by the classical Williamson method due to the occurrence of facile elimination in such reactions <89JOC6022>. The starting materials, α -benzotriazolylalkyl ethers (**531**), can be obtained from several different routes as shown in Scheme 102; however, the use of 1-(α -chloroalkyl)benzotriazoles (from (**530**) to (**531**)) is particularly suitable <87JCS(P1)811>. Reaction of

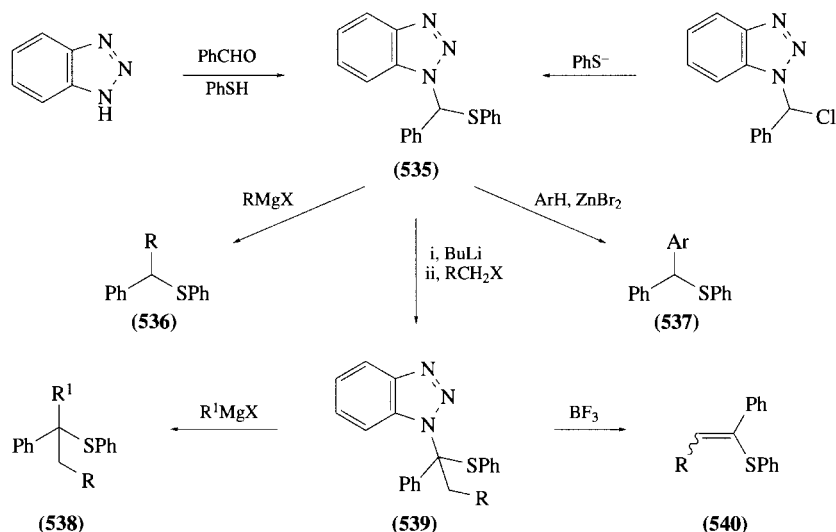


Scheme 102

2,5-dibenzotriazolyl tetrahydrofuran (**533**) with hex-1-ynylmagnesium iodide gives the disubstituted THF without ring opening (Equation (45)). With alkyl Grignard reagents, however, complex acyclic products are given. Treatment of the tetrahydropyran derivative (**534**) with organomagnesium reagents affords exclusively ring-opened products (Equation (46)) <90JCS(P1)1717>. Elimination of benzotriazole from *N*-(1-alkoxyalkyl)-benzotriazole by treatment with NaH at 140–160°C gives ketone enol ethers as a mixture of the (*E*)- and (*Z*)-isomers <91S279>. The acid-catalyzed hydrolysis of benzotriazolyl substituted ribo- and 2'-deoxyribonucleosides has been described and the mechanism is discussed <91JCS(P2)595>.



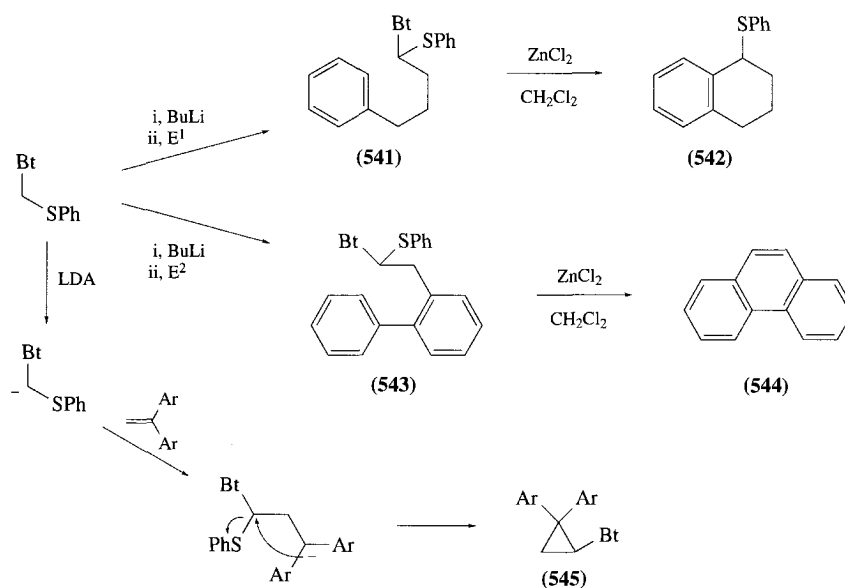
A similar reaction of 1-[α -(alkylthio)alkyl]benzotriazoles (**535**) and (**539**) with Grignard reagents gives *sec*- or *tert*-alkyl sulfides (**536**) or (**538**) (Scheme 103) <91HCA1924>. The benzotriazolyl alkyl sulfides are prepared by several routes: (i) displacement of the chloride from appropriate benzotriazolyl chlorides by sodium thiolates, (ii) condensation of benzotriazole and thiols with carbonyl compounds, and (iii) lithiation of *N*-substituted benzotriazoles (**535**) and subsequent treatment with electrophiles <91HCA1924>. Sulfides (**539**) can be converted by $\text{BF}_3 \cdot \text{OEt}_2$ into vinyl sulfides (**540**) <91HCA1931>. The α -(phenylthiobenzyl)benzotriazole (**535**) reacts with a variety of phenols, naphthols, and anisoles in the presence of zinc bromide to give thioalkylation products (**537**) <93S47>. A similar thioalkylation reaction occurs intramolecularly with unreactive aromatics. Thus, treatment of 1-(phenylthiomethyl)benzotriazole with butyllithium followed by reaction with appropriate bromides gives intermediates (e.g., (**541**) and (**543**)) (Scheme 104). These products undergo cyclization in the presence of zinc chloride with concomitant elimination of benzotriazole or both substituents to give the annulation products (**542** or **544**) <93H(36)1367>. The carbanion generated from 1-(phenylthiomethyl)-benzotriazole and LDA undergoes nucleophilic addition to 1,1-diarylethylene followed by elimination of phenylthioate to yield the benzotriazole substituted cyclopropanes (**545**) <93SL213>.



Scheme 103

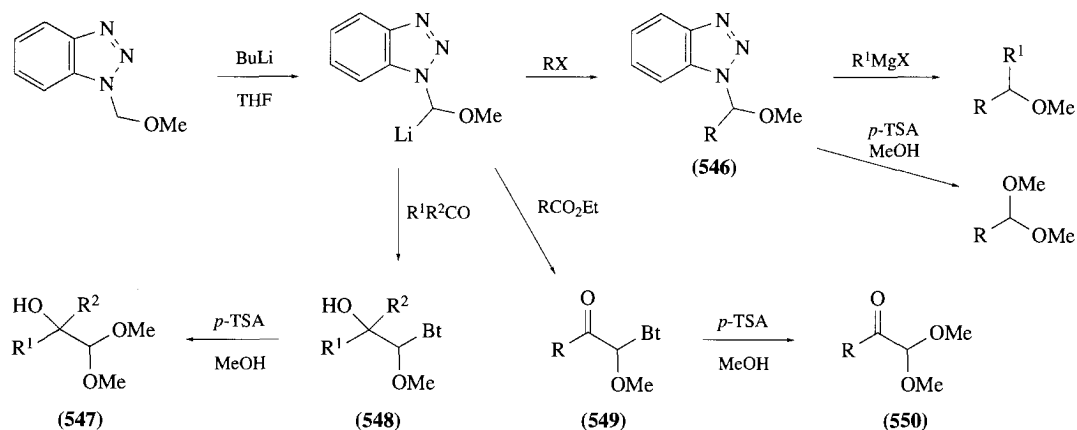
1-Methoxymethylbenzotriazole undergoes lithiation with butyllithium at the methylene group and the resulting carbanion affords substitution products (**546**), (**548**), and (**549**) upon treatment with various electrophiles (Scheme 105). Grignard reagents replace the benzotriazole residues of intermediates (**546**) to give methyl ethers <91JCS(P1)3295>. Benzotriazole is also substituted by the methoxy moiety on treatment with methanol in the presence of *p*-toluenesulfonic acid to afford the α -functionalized dimethyl acetals (**547**) and (**550**) <93SC3061>. 1-(α -Alkoxybenzyl)benzylbenzotriazoles undergo reversible ionization in solution to a benzotriazolyl anion and carboxonium cations $\text{PhCH}=\text{O}^+\text{R}$. These cations attack the β -carbon of enol ethers (e.g., ethyl vinyl ether, β -methoxystyrene and 2,3-dihydrofuran) whilst the benzotriazole anion adds to the α -position to form new α -(benzotriazol-1-yl)alkyl ethers (e.g., **551**) (Scheme 106). Reactions of (**552**) with Grignard reagents afford the 1,3-diethers as diastereomers (**553**) and (**554**). Reduction of (**552**) with LiAlH_4 gives diethers (**555**). The addition of 1-(α -alkoxybenzyl)benzylbenzotriazoles to cyclic enol ethers is nonstereospecific and all possible stereoisomers are formed <92JOC4925>.

The benzotriazole moiety in 1-(benzotriazol-1-yl)alkyl esters (**556**) is substituted by an alkyl, an aryl, or an alkynyl group upon treatment with an organozinc reagent to give α -substituted esters (**557**) (Equation (47)) <91S69>. The condensation products of an aldehyde, an oxime, and benzotriazole, *O*-(1-benzotriazolylalkyl)oximes (**558**) undergo an addition-rearrangement on treatment with an organolithium reagent to form amides as illustrated in Scheme 107. This provides a nonoxidative method for the transformation of aldehydes into amides <92JCS(P1)3055>.

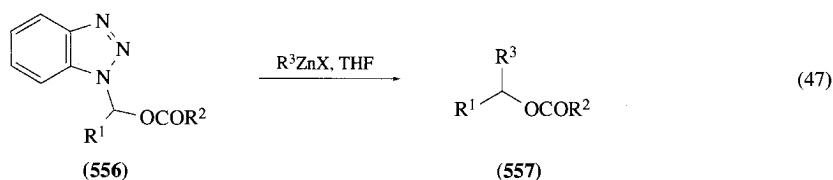


$\text{E}^1 = \text{PhCH}_2\text{CH}_2\text{CH}_2\text{Br}$, $\text{E}^2 = 2\text{-bromomethylbiphenyl}$

Scheme 104



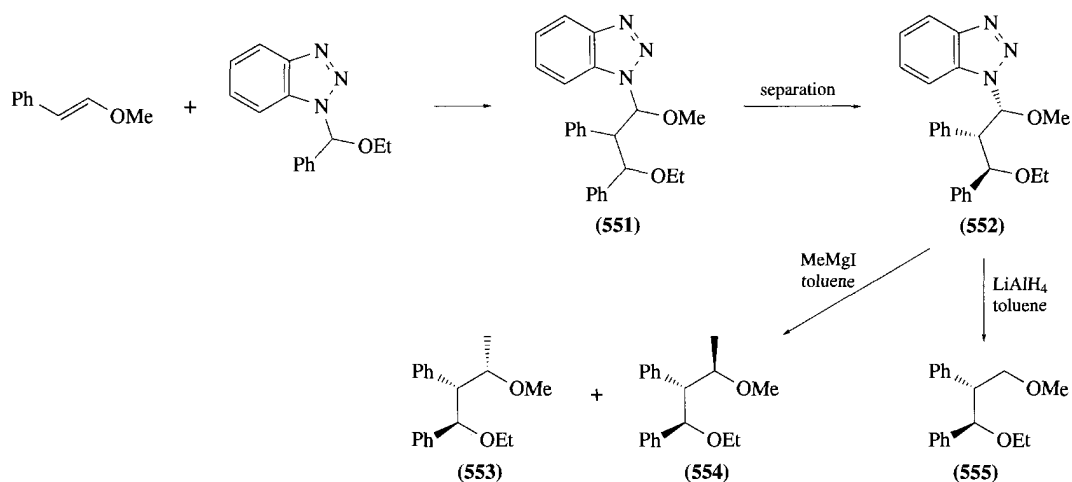
Scheme 105



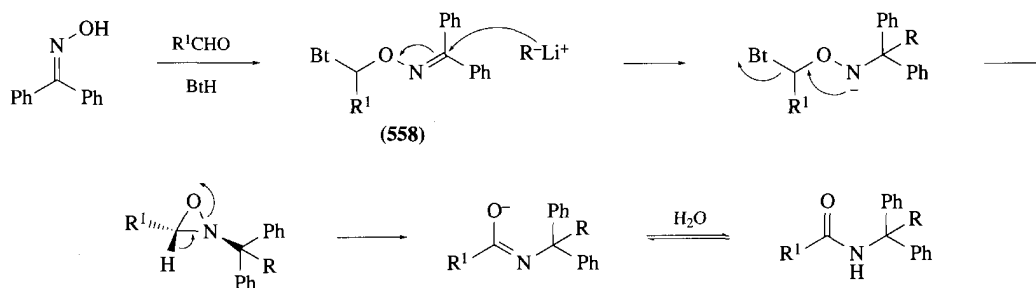
$\text{R}^1 = \text{H}$, alkyl and aryl; $\text{R}^2 = \text{alkyl and aryl}$; $\text{R}^3 = \text{Ph, Bn, BuC}\equiv\text{C and Bu}^n$

4.01.7.2.4 Reactions of substituents with an α -halogen

The chlorine atom in α -chloroalkylbenzotriazoles (**560**) undergoes exchange with other halogen atoms (Scheme 108). Thus, treatment of (**560**) with KF in the presence of 18-crown-6 gives the fluoro derivatives (**561**) [93PJC1243]. Sodium bromide or sodium iodide reacts with (**560**) to form (**559**, X = Br, I), whilst treatment of (**560**) with silver nitrate produces benzotriazol-1-ylmethyl

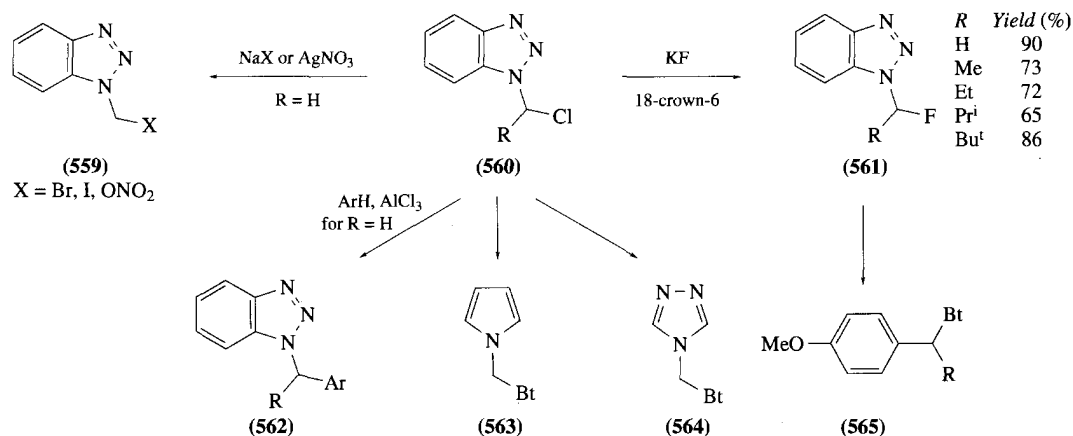


Scheme 106



Scheme 107

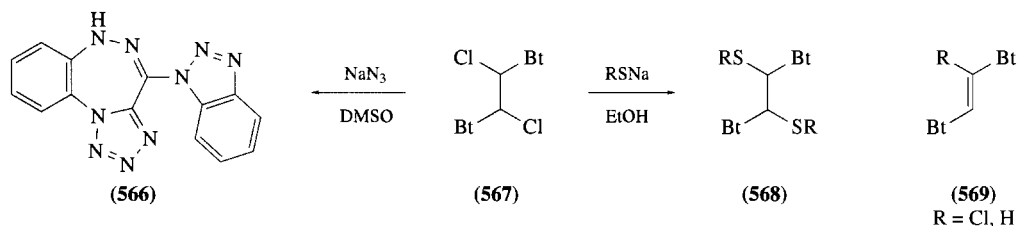
nitrate (**559**, X = ONO₂) in 72% yield (93ACS167). In the presence of a Lewis acid, 1-chloromethylbenzotriazoles (**560**) reacts with aromatic compounds to yield arylmethylbenzotriazoles (**562**) in high yields (92JCS(P1)1111). With *N*(*H*)-azoles, such as indole, pyrrole, carbazole, imidazole, and 1,2,4-triazole, the chlorine atom in (**560**) is replaced to afford *N*-(benzotriazol-1-ylmethyl)-heterocycles (e.g. **563** and **564**) (89JHC829). α -Fluoroalkylbenzotriazoles (**561**) similarly give the *para*-substituted derivatives (**565**) with anisole and 1-methoxynaphthalene (93PJC1243).



Scheme 108

The chlorine atom in 1-(α -chloroalkyl)benzotriazole is readily replaced by a wide range of carbon, nitrogen, phosphorus, oxygen, and sulfur nucleophiles, for example, 1-chloromethylbenzotriazole

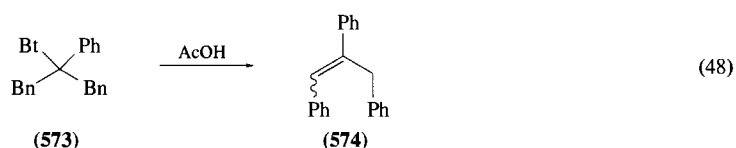
reacts with NaN_3 to give 1-azidomethylbenzotriazole <87JCS(P1)781>. Interestingly, however, 1,2-dibenzotriazolyl-1,2-dichloroethane (**567**) reacts with 2 equivalents of NaN_3 to give 4-(benzotriazol-1-yl)-6*H*-benzo[*c*]tetrazolo[1,5-*e*][1,2,5]triazepine (**566**) by a novel benzotriazole ring opening (Scheme 109) <91JOC1299>. Compound (**567**) undergoes nucleophilic substitutions with various sulfur nucleophiles resulting in disubstituted bisbenzotriazoles (**568**). Heterocycles are produced from the reactions with bisnucleophiles. However, elimination is the major pathway with sodium alkoxides and 1-chloro-1,2-di(benzotriazol-1-yl)ethylene (**569**, $\text{R} = \text{Cl}$) is produced as a mixture of the *Z*- and *E*-forms. The eliminative dechlorination of (**567**) upon treatment with zinc dust in ethanol gives *trans*-1,2-dibenzotriazol-1-ylethylene (**569**, $\text{R} = \text{H}$) <90JHC1543>. 1-Chloromethylbenzotriazole reacts with the sodium salts of alkanols, phenols, and thiols to give the corresponding ethers or sulfides in good yields <87JCS(P1)781, 90CB1185>.



Scheme 109

4.01.7.2.5 Reactions of Substituents with an $\alpha\text{-sp}^2$ or $\alpha\text{-sp}$ Carbon

The methylene or methine protons α to benzotriazole can be deprotonated by *n*-butyllithium or LDA. The lithiated intermediates (**571**) react with electrophiles at -78°C to give a variety of α -functionalized *N*-alkylbenzotriazoles (**570**) (Scheme 110). A similar procedure, using two equivalents of BuLi and two equivalents of electrophile allows the synthesis of tetrasubstituted methanes (**573**), from which the benzotriazole group can be removed by reduction with $\text{LiAlH}_4\text{-AlCl}_3$ to form 1,2,3-triphenylpropane (Equation (48)). Alternatively, (**573**) on heating with acetic acid gives the elimination product (**574**). Oxidative coupling of (**571**) with I_2 or 1,2-dibromoethane affords 1,2-dibenzotriazolyl-1,2-diarylethanes (**572**) <92JCS(P1)1111>. The methylene groups in *o*-(benzotriazolylmethyl)phenols (**575**) are lithiated following trimethylsilyl protection of the hydroxy group (Scheme 111). Subsequent substitution by various electrophiles such as alkyl halides, aldehydes, and ketones produces the alkylated derivatives (**576**). The benzotriazole moiety of intermediates (**576**) can be displaced by the alkyl anions of Grignard reagents or by the hydride ions of LiAlH_4 allowing the elaboration of many new types of substituted phenols (**577**) and naphthols <91CB1809>. *N*-[α -(*o*- and *p*-Methoxyaryl)alkyl]benzotriazoles <91CB1819> and 4-(benzotriazol-1-ylmethyl)-*N,N*-dialkylanilines <91JOC4397, 93T7445> undergo similar reactions. Michael addition of the benzotriazol-1-yl carbanion (**571**) to arylideneamines gives the corresponding 1-(benzotriazol-1-yl)-2-anilino-1,2-diarylethanes (**578**) which undergo a double elimination reaction under the action of Bu'OK in DMF to afford diarylalkynes <92JCS(P1)1295>. The benzotriazol-1-yl carbanions (**571**), resulting from lithiation of 1-(α -arylalkyl)benzotriazoles with butyllithium or LDA, undergo ring fragmentation with loss of nitrogen to give *ortho*-carbiminophenyl anions (**579**). Intermediates (**579**) can be protonated by an inter- or intra-molecular proton transfer or can react inter- or intra-molecularly with electrophiles to afford various products (e.g., **581**) <91CB1431, 92JCS(P1)1111>. The reaction proceeds slowly at temperatures below -20°C , but is rapid at $0\text{--}5^\circ\text{C}$. The anions (**579**) can also be trapped with tosyl azide to give 3-phenyl-1,2,4-benzotriazine (**582**). Benzil dianil (**580**) is also formed and the intermediate involved can be intercepted by quenching the reaction with methyl iodide to afford 1,2-bis(*N*-methylanilino)1,2-diarylethenes (**583**) (Scheme 112) <92JCS(P1)1111>. This ring-cleavage reaction also occurs when (**578**) is treated with Bu'OK in DMF at elevated temperature (85°C) <92JCS(P1)1295>.



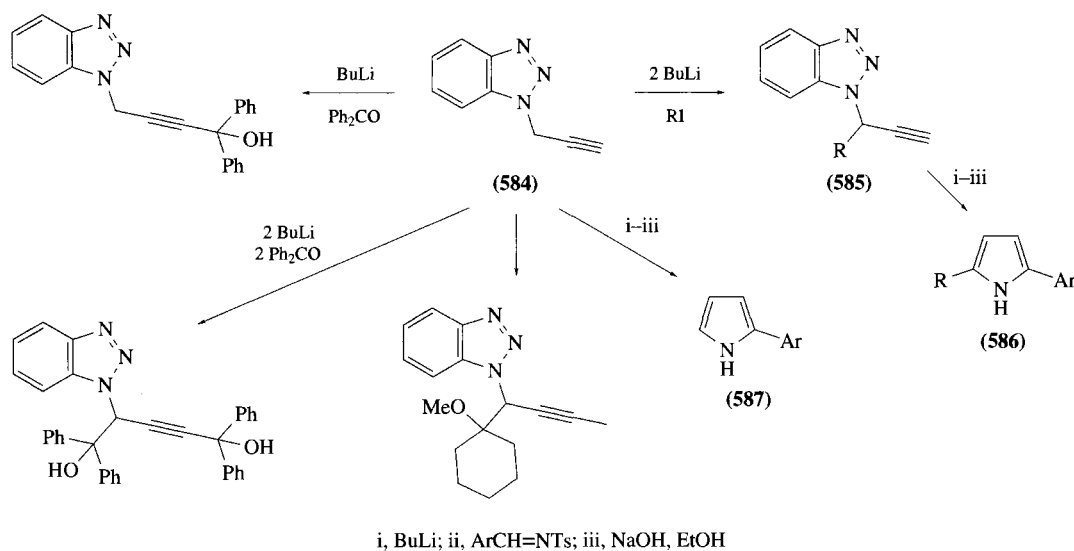
Scheme 110

Scheme 111

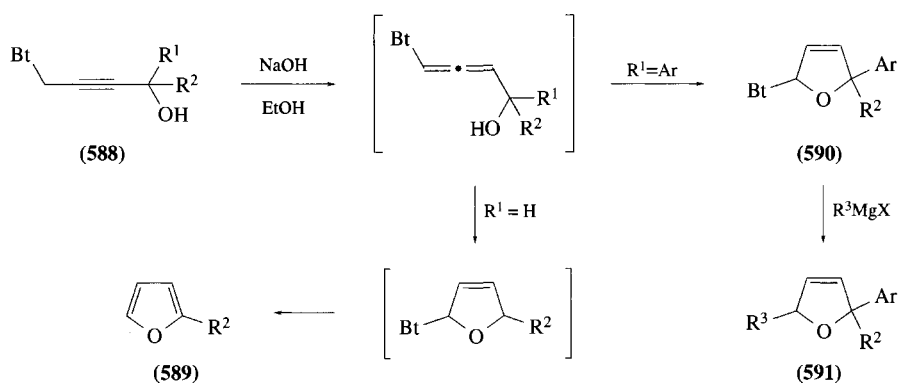
Scheme 112

1-Vinylbenzotriazole undergoes lithiation at the α -carbon and subsequent reactions with electrophiles to yield 1-(1-substituted vinyl)benzotriazoles. 1- and 2-Allylbenzotriazoles are also lithiated at the α -carbon. 1-Propargylbenzotriazole (**584**) can be deprotonated twice in a stepwise fashion (Scheme 113), first at the acetylenic CH and then at the CH₂ group. The dilithiated species reacts with an electrophile first at the carbon adjacent to the nitrogen atom and then at the terminal carbon. Thus, by controlling the quantities of BuLi and/or electrophiles and adding the electrophiles in a stepwise manner, a variety of substituted products can be obtained (Scheme 113) (92LA843). 1-(3-Lithiopropargyl)benzotriazole reacts with *N*-tosylarylimines to give adducts which undergo cycloelimination on treatment with ethanolic NaOH to afford 2-aryl- and 2-heteroaryl-pyrroles (**587**). Treatment of doubly lithiated 1-propargylbenzotriazole successively with 1 equivalent of alkyl halide followed by *N*-tosylarylimine, then ethanolic NaOH gives the 5-alkyl-2-arylpyrroles

(**586**) via intermediates (**585**) <94S93>. Monolithiation of 1-propargylbenzotriazole (**584**) followed by reaction with aromatic aldehydes or ketones (Scheme 114) gives the intermediates (**588**), which undergo base-assisted cyclization to 2-arylfurans (**589**) when $R^1 = H$, or to 1-(5,5-diaryl-2,5-dihydrofuran-2-yl)benzotriazoles (**590**) when $R^1 = \text{aryl}$. Compounds (**590**) react with Grignard reagents to give trisubstituted 2,5-dihydrofurans (**591**) <93JOC3038>.



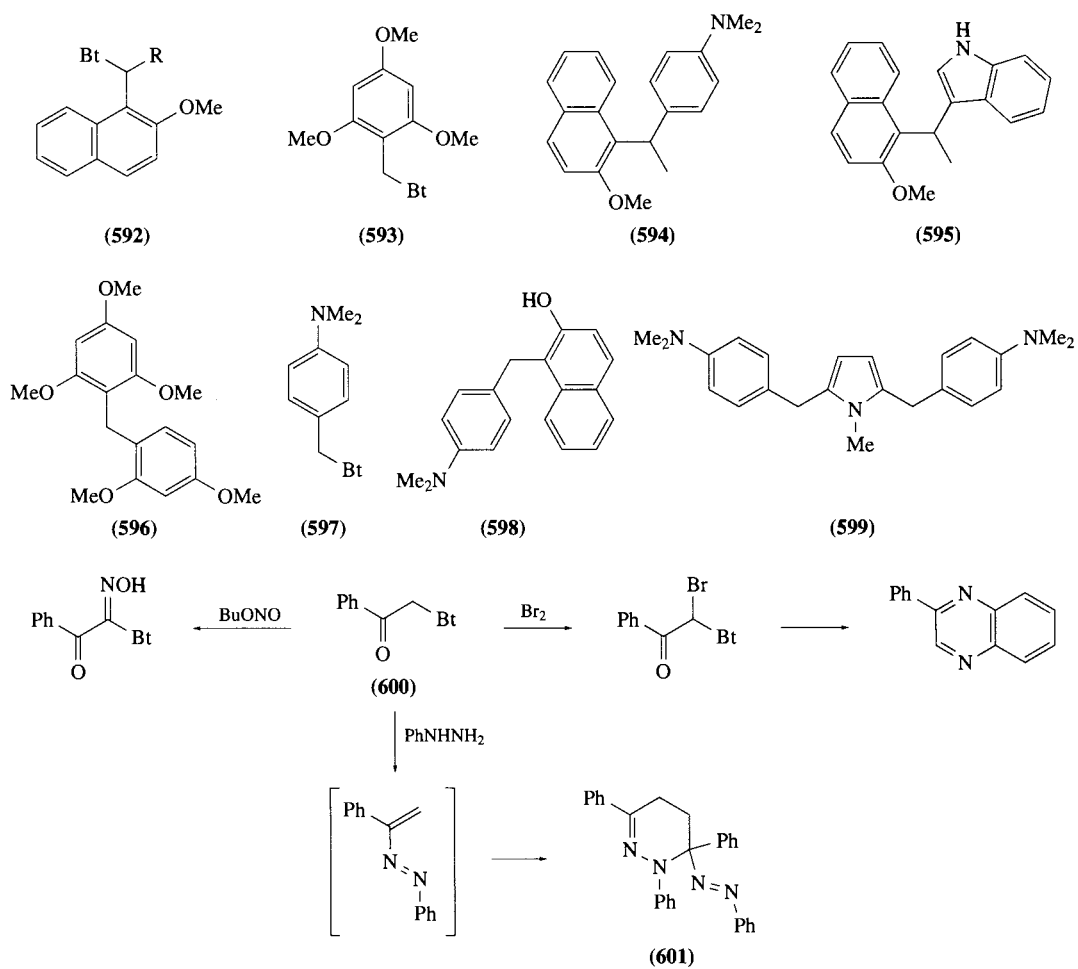
Scheme 113



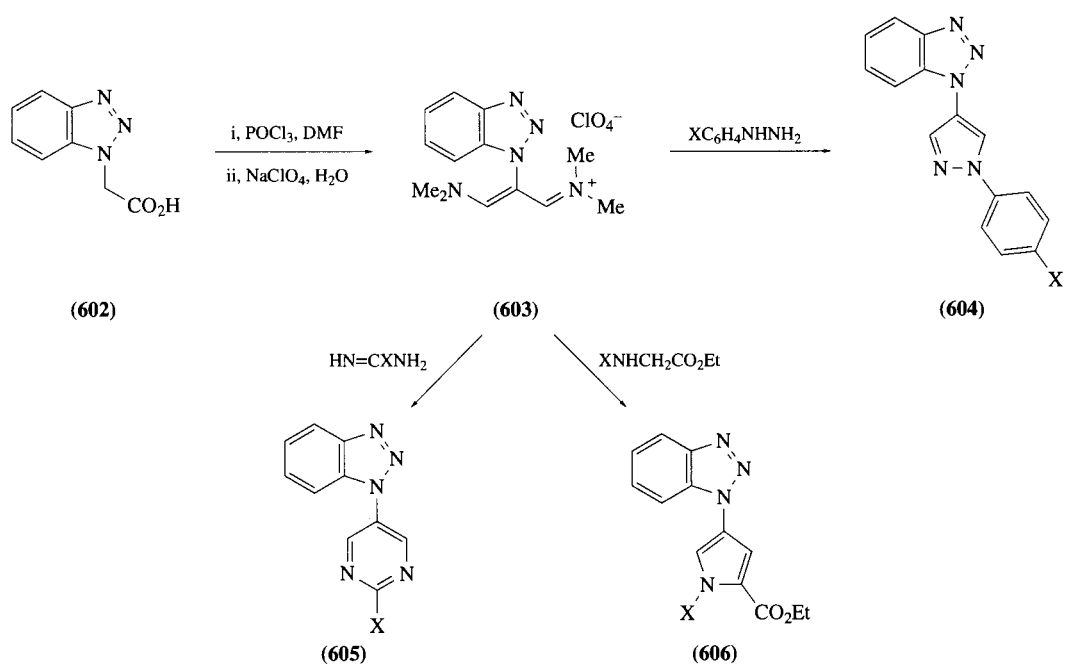
Scheme 114

1-[α -(Benzotriazol-1-yl)alkyl]-2-methoxynaphthalenes (**592**) and 2-[(benzotriazol-1-yl)methyl]-1,3,5-tri-methoxybenzene (**593**) react with electron-rich aromatics, such as *N,N*-dimethylaniline, indole, and di- or trimethoxybenzene to give substituted products (e.g., (**594**)–(**596**)) with the elimination of benzotriazole <91CB1819>. 4-(Benzotriazol-1-ylmethyl)-*N,N*-dimethylaniline (**597**) reacts similarly with a variety of electron-rich benzenoid and heteroaromatic compounds to afford leuco dyes such as (**598**) and (**599**) <91JOC4397>.

α -(Benzotriazol-1-yl)acetophenone (**600**) is transformed by butyl nitrite into the corresponding oxime (Scheme 115). Bromination of (**600**) gives the α -bromo derivative which forms 2-phenylquinoxaline on exposure to *o*-phenylenediamine. Stepwise treatment of (**600**) with phenylhydrazine and NaH affords α -(phenylazo)styrene dimer (**601**), evidently via a Diels–Alder dimerization following elimination of the benzotriazolyl group <93ACS167>. 1-(Benzotriazol-1-yl)acetic acid (**602**) reacts with POCl_3 and DMF with carbon dioxide evolution to give the vinamidinium salt (**603**)



Scheme 115

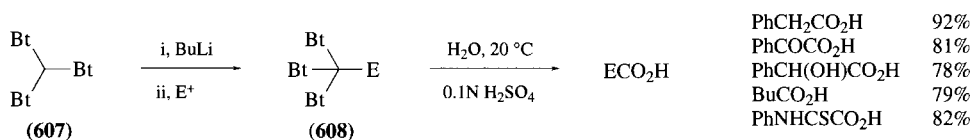


Scheme 116

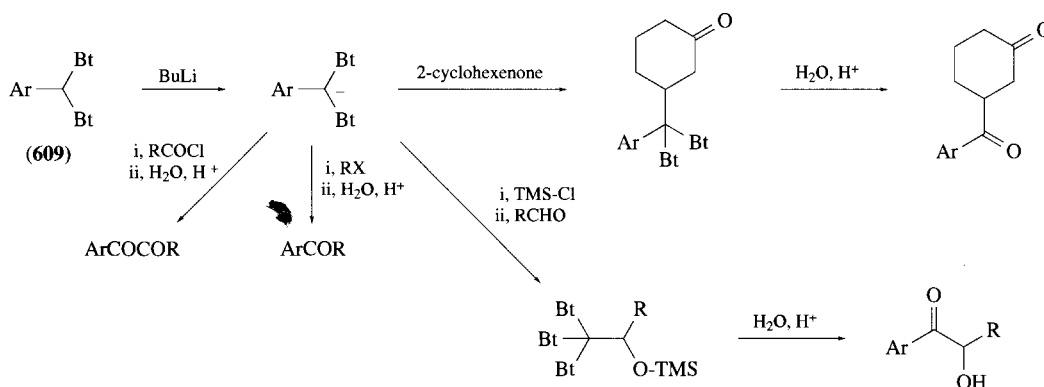
which precipitates as the perchlorate or hexafluorophosphate (Scheme 116). The vinamidinium salt (**603**) condenses with a wide variety of substituted amidines in EtOH/EtONa to produce pyrimidines (**605**), with substituted phenylhydrazines to give pyrazoles (**604**) and with glycine ethyl ester to form 2,4-disubstituted pyrroles (**606**) <93T10205>.

4.01.7.2.6 Reactions of substituents with an α -N-heterocyclic ring

Tribenzotriazolylmethane (**607**) undergoes lithiation with BuLi. The resulting carbanion reacts with electrophiles to give derivatives (**608**), which are hydrolyzed under very mild conditions (0.1 N H₂SO₄) to the corresponding acids in high yields <90S666>. When one benzotriazolyl moiety is replaced by a phenyl group, (e.g., **609**), hydrolysis to the ketone is very easy. Thus, a synthetic sequence from (**609**) to arylketones is achieved via lithiation and reaction with electrophiles followed by hydrolysis (Schemes 117 and 118). This method has been extended to preparations of ketones, α -hydroxy ketones, and 1,4-diketones as shown in Schemes 117 and 118 <87JCS(P1)819>.

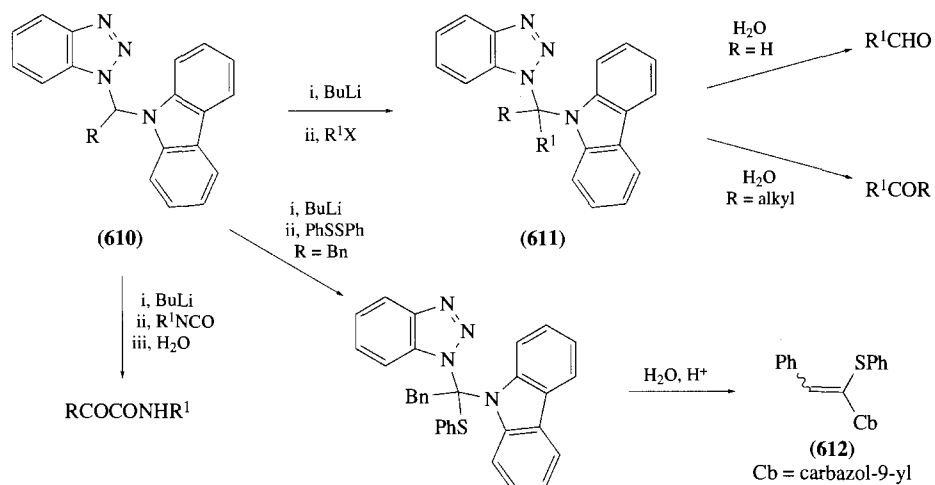


Scheme 117

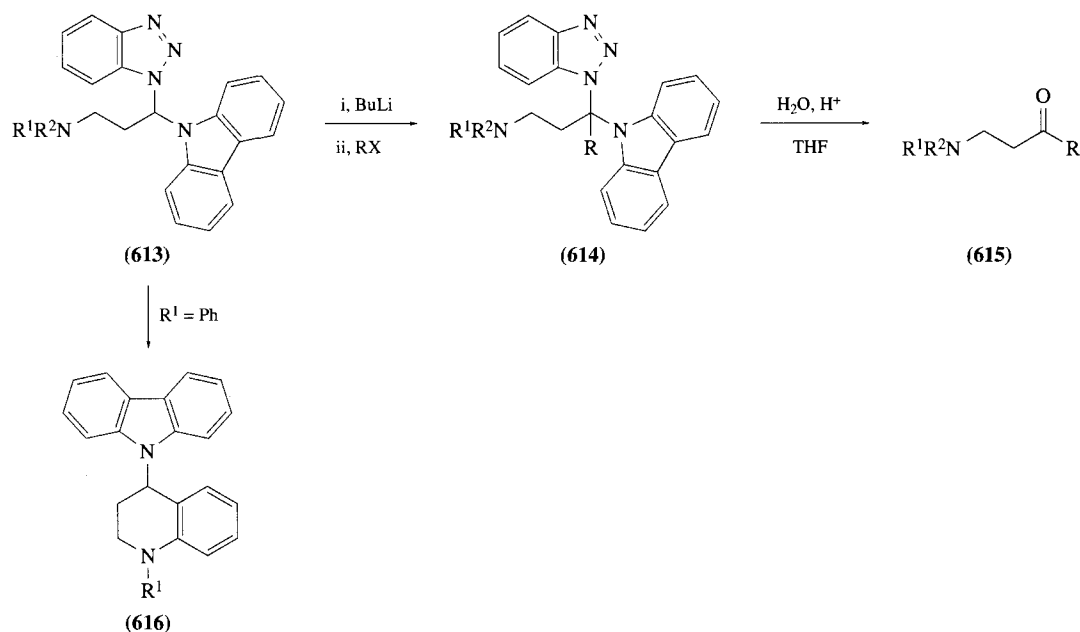


Scheme 118

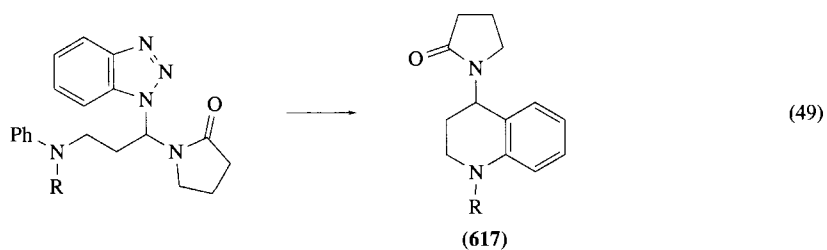
(Carbazol-9-yl)(benzotriazol-1-yl)methanes (**610**) are deprotonated by BuLi to form anions which react with alkyl halides to give substituted products (**611**) which are easily hydrolyzed to aldehydes and ketones (Scheme 119). The lithiated intermediates also react with acyl chlorides or α,β -unsaturated ketones to afford 1,2- and 1,5-diketones on hydrolysis. Isocyanates are employed to generate α -ketoamides. The products of the reaction between the lithiated intermediates and diphenyl disulfide undergo elimination on hydrolysis to give carbazole derivatives (**612**) <91JOC6917>. When 3-(dialkylamino)-1-(benzotriazol-1-yl)-1-(carbazol-9-yl)propanes (**613**), readily prepared by the addition of aminoalkylbenzotriazoles to *N*-vinylcarbazole, are treated with BuLi and alkyl halides (Scheme 120), hydrolysis of the intermediates (**614**) produces β -aminoketones (**615**) in good yields <93JOC1970>. When R¹ = Ph, heating (**613**) at 75°C in the presence of 1 mol% of TsOH produces 4-(carbazol-9-yl)-1,2,3,4-tetrahydroquinolines (**616**). A mechanism involving intramolecular electrophilic attack of the iminium cation on the electron rich *ortho* carbon atom of the aniline ring is proposed. Other 4-substituted tetrahydroquinolines such as (**617**) can be similarly prepared (Equation (49)) <93JOC812>.



Scheme 119

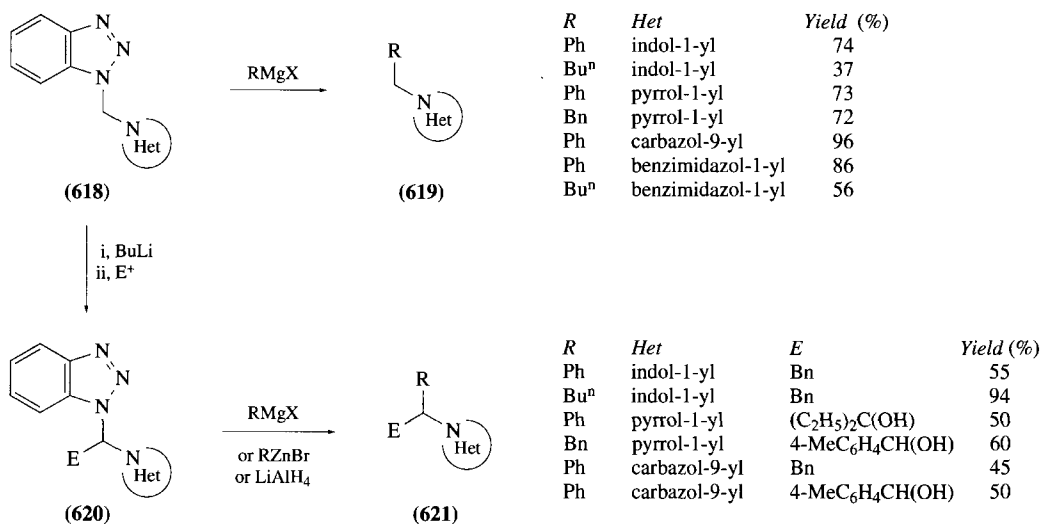


Scheme 120



The benzotriazolyl group in *N*-(benzotriazol-1-ylmethyl)-indole, -pyrrole, -pyrrolidin-2-one, -carbazole, and -benzimidazole (**618**) is readily displaced by Grignard reagents, organozinc reagents, LiAlH_4 , and thiophenol to give a variety of *N*-substituted heterocycles such as (**619**) (Scheme 121) <92S1295, 93T2829>. The pyrrole, indole, and carbazole adducts (**618**) undergo smooth deprotonation at the interring methylene group by BuLi. The resulting anions react with electrophiles to give intermediates (**620**) <89JHC829> which in turn react with Grignard reagents or organozinc reagents

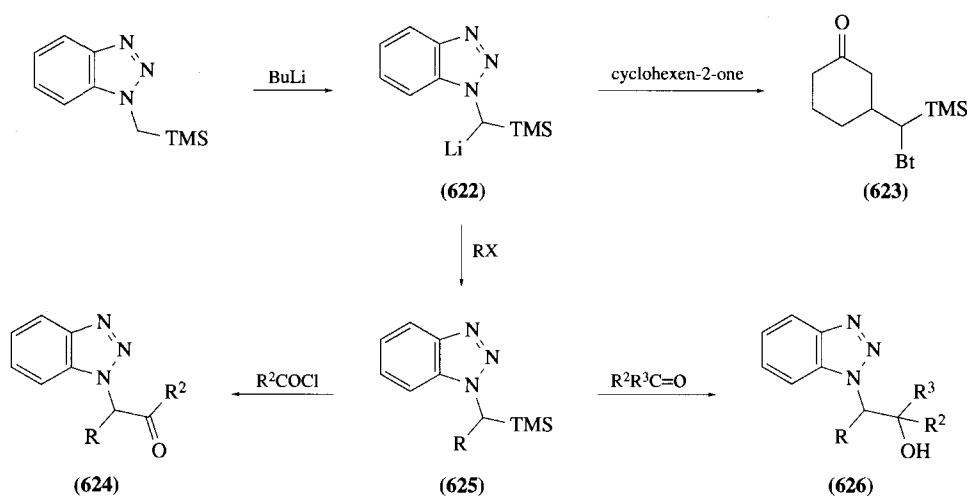
to give *N*-substituted heterocycles (**621**) <93T2829>. For the imidazole, benzimidazole, and 1,2,4-triazole systems (**618**, Het = imidazole etc.), competition for lithiations at other heterocyclic ring positions exists <89JHC829>.



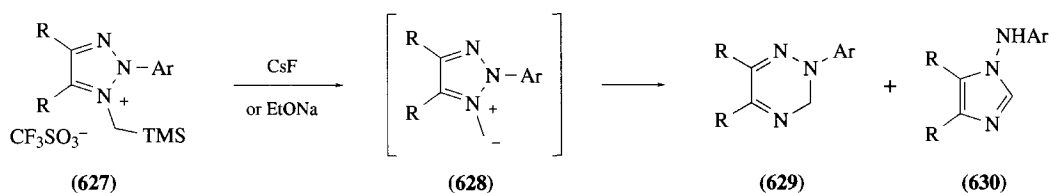
Scheme 121

4.01.7.2.7 Reactions of substituents with other α -heteroatoms

1-(Trimethylsilylmethyl)benzotriazole is readily deprotonated at the methylene group. The lithiated carbanion (**622**) reacts with alkyl halides to give benzotriazole derivatives (**625**), which undergo further reactions with acid chlorides or ketones to give (**624**) or (**626**), respectively (Scheme 122). The intermediate (**622**) can also add to α,β -unsaturated ketones to give compounds of the type (**623**) <90HAC21>. Deprotonation of [(1-benzotriazolyl)methyl]triphenylphosphonium chloride with butyllithium in DMSO gives benzotriazolyl Wittig reagent, which reacts with aldehydes to give 1-(alkenyl)benzotriazoles <88RTC641>. Desilylation of *N*-trimethylsilylmethyl-1,2,3-triazolium salt (**627**) by CsF or EtONa (Scheme 123) generates the triazolium methanide (**628**) which gives substituted 2,3-dihydro-1,2,4-triazines (**629**) and 1-aminoimidazoles (**630**) via 1,2,5-triazahexa-1,3,5-triene intermediates. Triazolium methides can also be generated by deprotonation of *N*-methyl-triazolium perchlorate salts <92JCS(P1)147>.



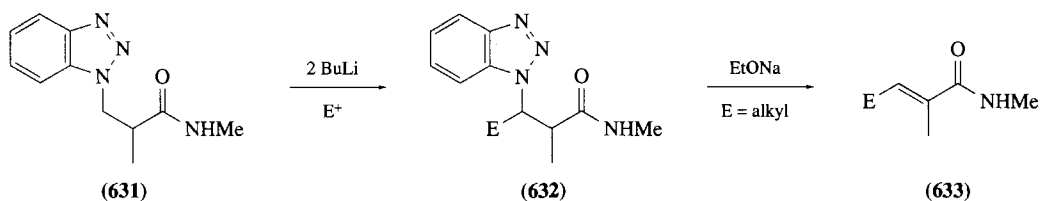
Scheme 122



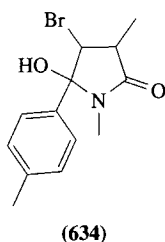
Scheme 123

4.01.7.3 Reactivity of Substituents Without an α -Functional Group

N-Methyl-2-methyl-3-(benzotriazol-1-yl)propanamide (631), on treatment with two equivalents of butyllithium, forms a dianion that reacts with alkyl and benzyl halides, aldehydes, and ketones to give monosubstituted products (632) (Scheme 124). With ethyl *p*-toluate, however, a lactam (634) is formed. The alkylated derivatives (632) eliminate benzotriazole upon treatment with NaOEt to afford trisubstituted α,β -unsaturated amides (633) <93JHC1261>.

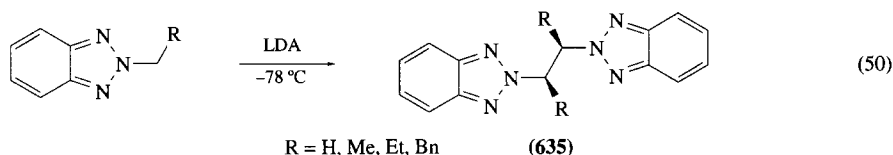


Scheme 124



(634)

1-Methylbenzotriazole is lithiated readily with BuLi or LDA at the methyl group and the subsequent reactions with various electrophiles provide 1-substituted benzotriazoles. Other 1-(*n*-alkyl)benzotriazoles also undergo lithiation with LDA <94LA1>. 2-Alkylbenzotriazoles behave differently on lithiation. Thus, treatment of 2-alkylbenzotriazole with LDA at -78°C produces a mixture of coupling products (635) and (636) (when R = Me) (Equation (50)). 2-Methylbenzotriazoles, when treated with LDA and benzophenone, gives the corresponding adduct in quantitative yield, whereas benzaldehyde does not react under the same conditions. A single electron-transfer mechanism involving intermediate carbanions, radicals and radical anions is proposed <94LA7>.



R = H, Me, Et, Bn

(635)

4.01.7.4 Cycloaddition Reactions of *N*-Substituents

Diels–Alder and hetero [4 + 2] cycloadditions of 1-(1,3-butadien-1-yl)benzotriazole (638) with *N*-phenylmaleimide, maleic anhydride, ethyl acrylate, Eschenmoser salt, and nitrosobenzene give a



Scheme 125



Scheme 126

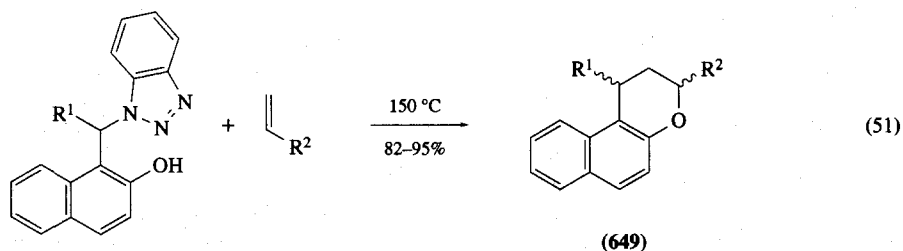
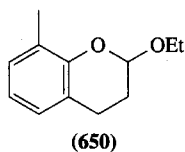


Scheme 127

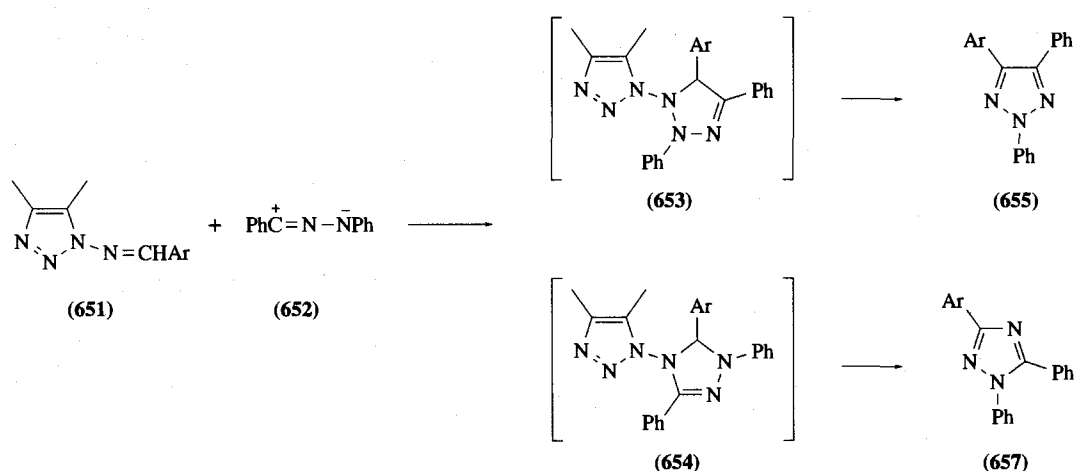


Scheme 128

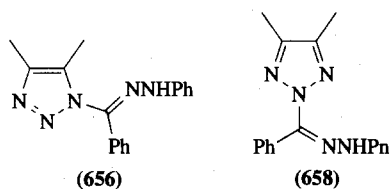
1,2,3-Triazoles



1-(*N*-Arylidene)amino-1,2,3-triazoles (**651**) react with diphenylnitrilimine (**652**) to give the 1,2,3- and 1,2,4-triazoles (**655**) and (**657**) as well as the 1- and 2-benzohydrazonyl-1,2,3-triazoles (**656**) and (**658**) (Scheme 129). Formation of the first two products can be rationalized by the elimination of triazoles from intermediates (**653**) and (**654**), the 1,3-dipolar cycloaddition products of (**651**), and (**652**). Further reaction of the triazoles (**651**) with (**652**) acting as electrophile gives (**656**) and (**658**) <88JCS(P1)3233>.



Scheme 129

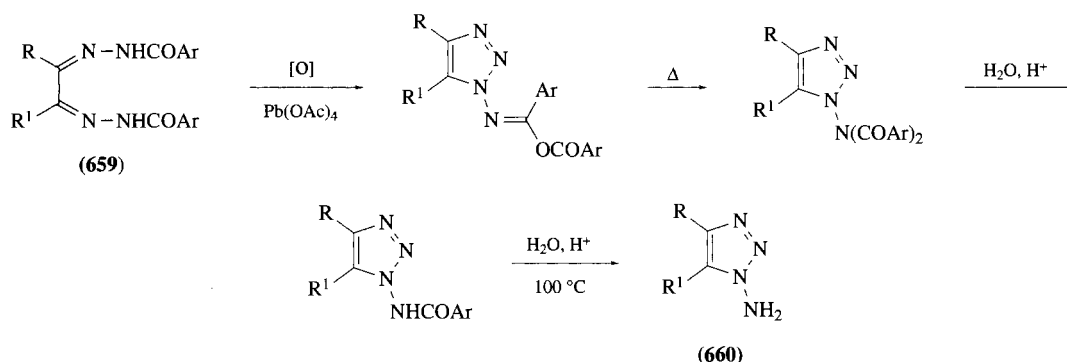


4.01.8 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

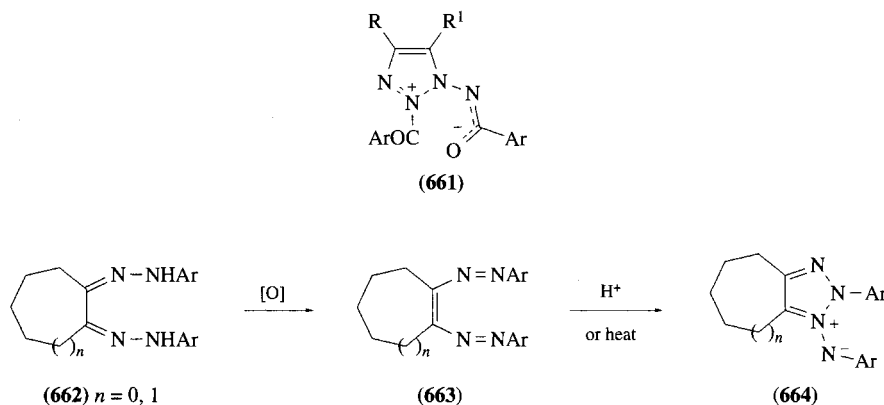
The synthesis of the 1,2,3-triazole ring has been the subject of many reviews, and is very well documented in CHEC-I. Developments since 1984 will be discussed using the same system as was employed in CHEC-I. For a general description and early work, see <84CHEC-I(5)705>.

4.01.8.1 Formation of One Bond

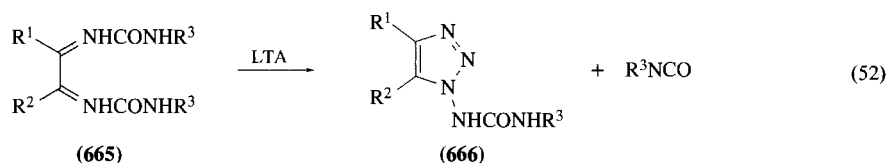
The intramolecular cyclization of suitable precursors is one of the most useful methods for the preparation of the 1,2,3-triazole ring, particularly of *N*-amino- and *N*-imino-triazoles and triazole *N*-oxides. The oxidations of bishydrazones (**659**) derived from α -dicarbonyl compounds, to 1-amino-1,2,3-triazoles (**660**) and their derivatives (Scheme 130) are well investigated $\langle 84CRV249, 84JHC1169, 84JHC1653, 92AHC(53)85 \rangle$. The mechanism of the oxidation and the product dichotomy has been studied. Zwitterionic intermediates (**661**) are proposed $\langle 93JHC913 \rangle$. The bishydrazones (**662**), obtained from cycloalkane-1,2-diones (six or more carbons), are oxidized at ambient temperature with nickel peroxide in dry benzene or lead dioxide in dichloromethane to give 1,2-bis(areneazo)cycloalkenes (**663**) (Scheme 131). These intermediates rearrange regioselectively to give fused 2,4-diarylcyclopolyeno[d]-1,2,3-triazoles (**664**) on heating or treatment with acid $\langle 83CC627, 89JCS(P1)159, 90JCS(P1)2537 \rangle$. The oxidation of bis-semicarbazones (**665**) by LTA in CH_2Cl_2 gives *N*-(1,2,3-triazol-1-yl)-*N'*-arylureas (**666**) (Equation (52)) $\langle 84JHC145 \rangle$.



Scheme 130

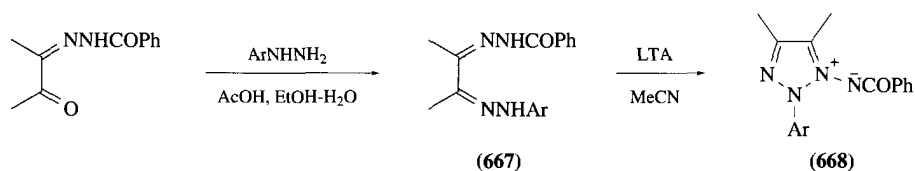


Scheme 131

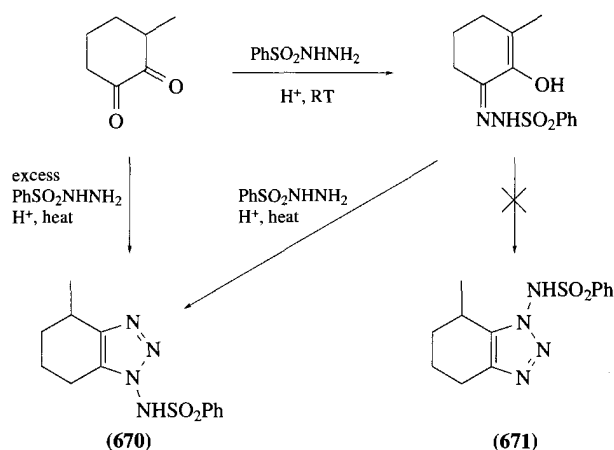


The mixed hydrazones (**667**), prepared from diacetyl monobenzoyl hydrazone and arylhydrazines, undergo oxidative cyclization to 2-aryl-*N*-benzoyl-4,5-dimethyl-1,2,3-triazol-1-ylimines (**668**) in 32–76% yield upon treatment with lead tetraacetate in acetonitrile (Scheme 132) $\langle 92JOC2252 \rangle$. The cyclization of bishydrazones to 1,2,3-triazoles can also occur in acidic or basic media. For instance, the tetrahydrobenzo[d]triazol-4-one (**669**) is prepared by the base-catalyzed cyclization of the corresponding α -hydrazono oxime (Equation (53)) $\langle 85HCA1748 \rangle$. 3-Methyl-1,2-cyclohexanedione reacts

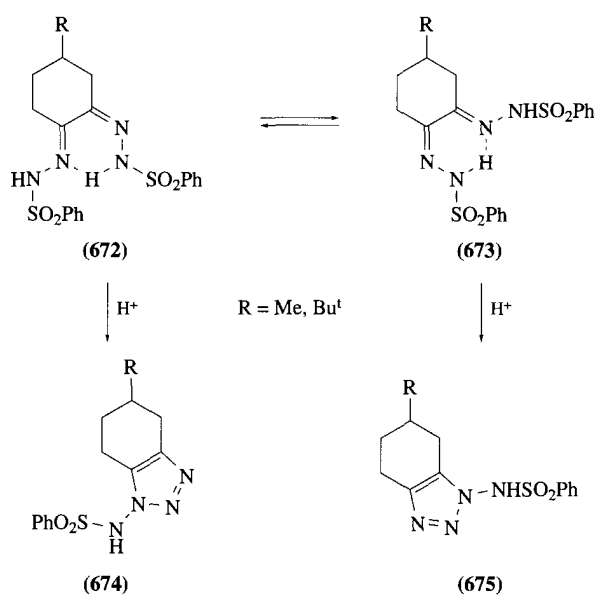
with phenylsulfonylhydrazine in an acidic medium at room temperature to give a monophenylsulfonylhydrazone, which, on gentle heating, results in the formation of triazole (**670**) as the sole product (Scheme 133). The formation of its regioisomer (**671**) is not observed. Direct heating of the starting diketone with an excess of phenylsulfonylhydrazine under acidic conditions achieves the same result. 4-Methyl- and 4-*t*-butyl-1,2-cyclohexanedione react with phenylsulfonylhydrazine to give bishydrazones (**672**) and (**673**) which, on heating, readily undergo heterocyclization to the corresponding isomeric 1,2,3-triazoles (**674**) and (**675**), respectively (Scheme 134) <89JHC301>.



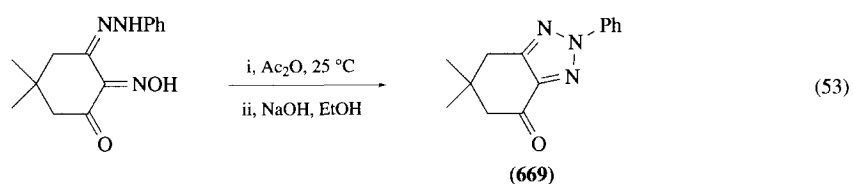
Scheme 132



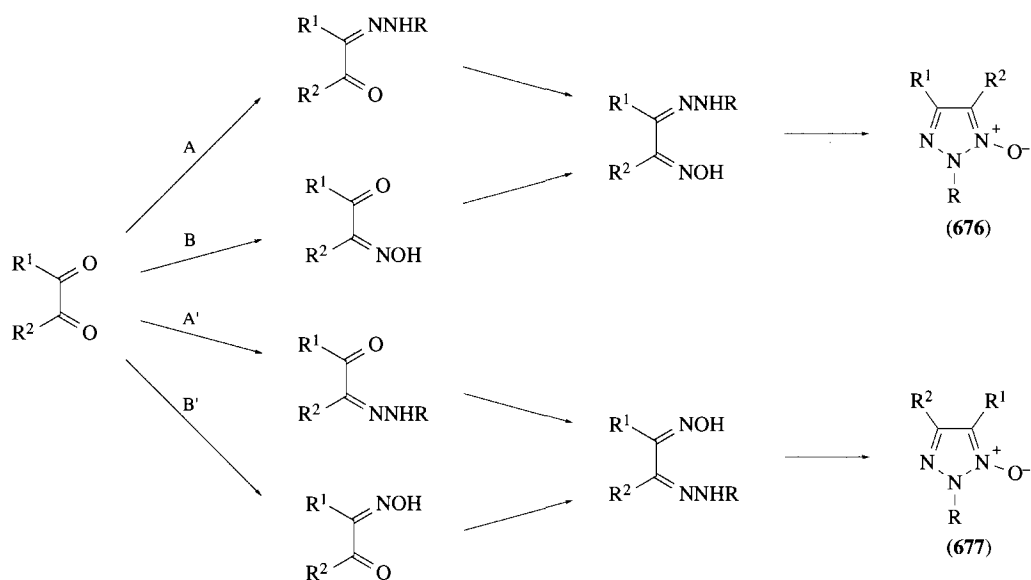
Scheme 133



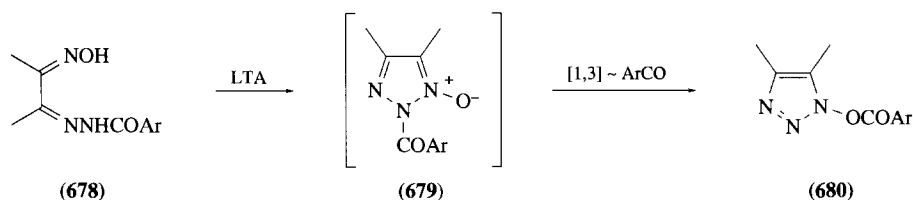
Scheme 134



There are two alternative routes leading to 2-alkyltriazole 1-oxides from α -dicarbonyl compounds (Scheme 135, routes A and B). Unsymmetrical dicarbonyl compounds may, although not always, give rise to two isomeric hydrazones and two isomeric oximes and hence to two isomeric 1,2,3-triazole 1-oxides (**676**) and (**677**) <81JCS(P1)503>. 2-Phenyltriazole 1-oxide is obtained from glyoxal via route A. However, 2-methyltriazole 1-oxide is prepared from glyoxal by route B in a one-pot process under neutral conditions. 2-Benzyltriazole 1-oxide is obtained similarly. 2,5-Dimethyltriazole 1-oxides are accessible through both routes <86ACS(B)262>. Lead tetraacetate oxidation of α -hydroxyimino aroylhydrazones (**678**) gives 1-aroxyloxy-4,5-dimethyl-1,2,3-triazoles (**680**, 35–48% yield) in acetic acid/dichloromethane (Scheme 136). An intramolecular [1,3]-aroxy migration in the intermediate (**679**) is proposed <89JCS(P1)619>.



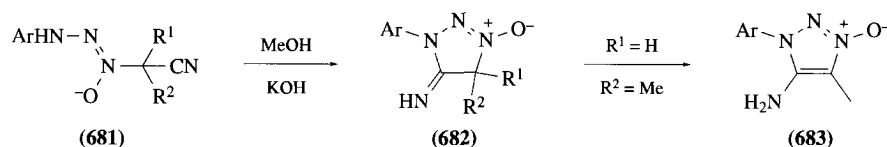
Scheme 135



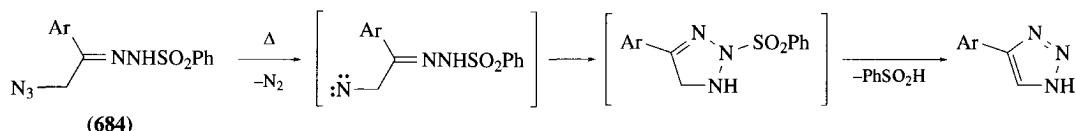
Scheme 136

1-(*t*-1'-Cyanoalkyl)-3-aryltriazene 1-oxides (**681**) give the corresponding 4-imino-4,5-dihydro-1,2,3-triazole 1-oxides (**682**) in good yields (50–89%) on treatment with KOH in methanol (Scheme 137). When $R^1 = H$ and $R^2 = Me$, the initially formed iminotriazolines (**682**) undergo isomerization to 4-amino-1,2,3-triazole 1-oxides (**683**). The starting compounds (**681**) are available from the reaction of 2-cyano-2-hydroxyaminopropane or 1-cyano-1-hydroxyaminoethanol with tetrafluoroborate salts of the corresponding aryl diazonium ions <92MC131>. Thermolysis of α -azidoacetophenone phenylsulfonylhydrazones (**684**), prepared by reaction of the α -bromo compounds

with sodium azide in DMF, in refluxing benzene leads to the formation of 4-aryl-1*H*-1,2,3-triazoles in 82–94% yields by elimination of nitrogen and benzenesulfonic acid (Scheme 138) <90CL453>.

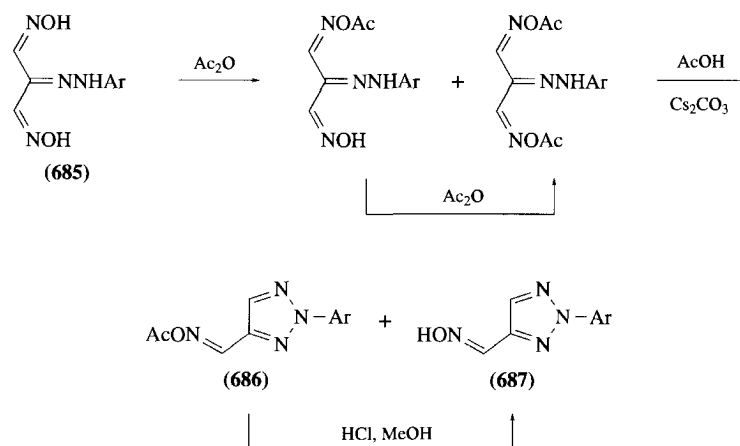


Scheme 137



Scheme 138

Mesomalonodialdehyde 1,3-dioxime is treated with arylhydrazines to give the mesoaldehyde 1,3-dioxime-2-arylhydrazones (**685**), which are *O*-acetylated with acetic anhydride to afford the mono- and di-acetyl derivatives (Scheme 139). Both intermediates are cyclized to 2-aryl-1,2,3-triazole-4-carbaldehyde oximes (**686**) and (**687**) with caesium carbonate. Triazoles (**687**) are converted to 4-cyanotriazoles by refluxing with acetic anhydride followed by pyrolysis <83JHC1561>.

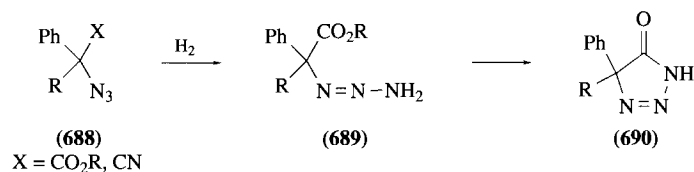


Scheme 139

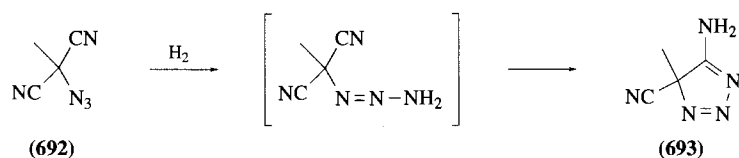
Catalytic hydrogenation of α -azido- α -phenylalkancarboxylates (**688**, X = CO₂R) gives intermediates (**689**), which undergo intramolecular nucleophilic substitution to yield 4*H*-1,2,3-triazol-4-ones (**690**) (Scheme 140). Similar reaction of 2-azido-2,2-diphenylacetonitrile (**688**, X = CN, R = Ph) gives 5-amino-4,4-diphenyl-4*H*-1,2,3-triazole (**691**) and its tautomer <86LA1891, 93CB103>. Hydrogenation of 2-azidopropionitrile with 10% Pd/C in methanol provides a mixture of 4-methyl-5-amino-1,2,3-triazole and 2-aminopropionitrile. 2-Azido-2-cyanopropionitrile (**692**) similarly gives 5-amino-4-cyano-4-methyl-4*H*-1,2,3-triazole (**693**) (Scheme 141) <85JOC4986>. 2-Azido-2,3-dihydrophenalene (**694**) is *O*-formylated by treatment with sodium hexamethyldisilazane and Bu⁺CO₂CHO to give azide (**695**) (Scheme 142). Triethylphosphite converts (**695**) to (**696**) via an intramolecular cyclization and subsequent *O*- to *N*-formyl transfer. Similarly 5-phenyl-1*H*-1,2,3-triazole is prepared from (*Z*)- β -(formyloxy)vinyl azide <91JOC2680>.

4.01.8.2 Formation of Two Bonds

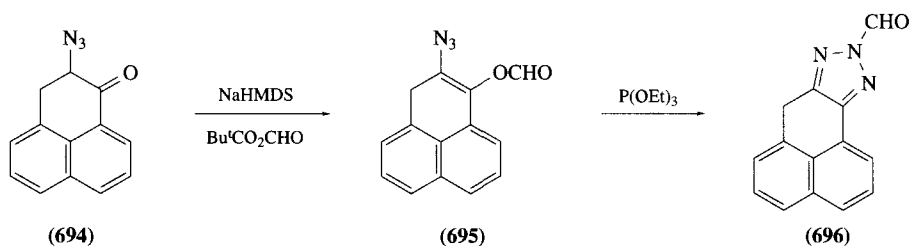
The cycloaddition of azides to C=C and C $\equiv$ C bonds has become the most important and versatile synthetic route to a wide range of 1,2,3-triazoles and triazolines, and is discussed in detail



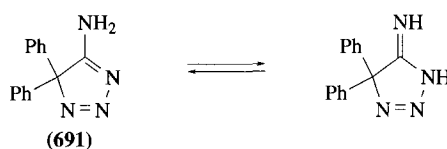
Scheme 140



Scheme 141



Scheme 142

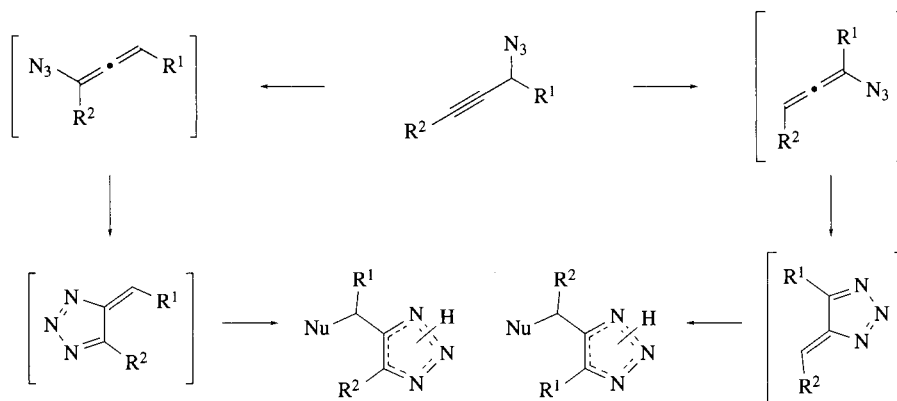
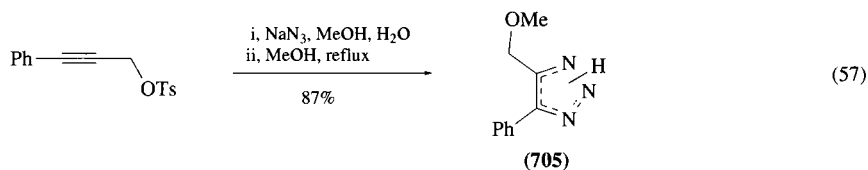


in CHEC-I <84CHEC-I(5)708>. The mechanism and synthetic applications of the 1,3-dipolar cycloaddition to form triazoles are also well documented in reviews <B-84MI 401-01>.

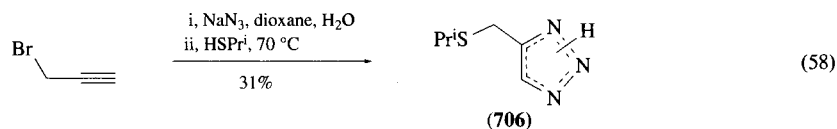
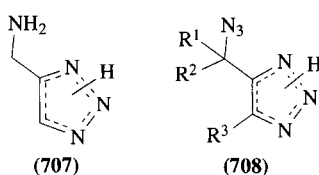
4.01.8.2.1 Addition of azides to $\text{C}\equiv\text{C}$ triple bonds

Numerous organic and inorganic azides undergo 1,3-dipolar cycloaddition to alkynes to give 1,2,3-triazoles. The regioselectivity of the reaction is low and regioisomers are usually obtained. This is easily understood in terms of the mechanism and energies of the HOMO–LUMO interactions <B-84MI 401-01>.

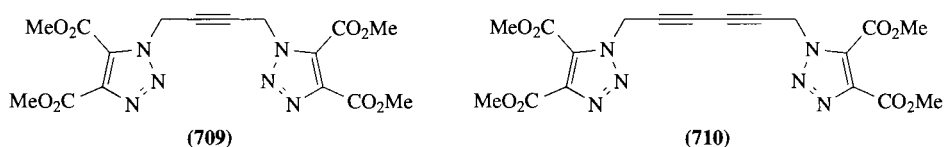
Cycloaddition of *p*-methoxyphenyl azide to alkyne dipolarophiles at room temperature gives triazoles (697) and (698) (Equation (54)). A regiospecific addition is only observed in the case of $\text{Z} = \text{CH}(\text{OMe})_2$ <89H(29)967>. Phenyl azide and substituted benzyl azides undergo 1,3-dipolar cycloadditions with DMAD, phenylacetylene, and ethyl propiolate to afford 1-phenyl- and 1-benzyl-1,2,3-triazoles, respectively. Again, only the reactions of these azides with ethyl propiolate are regiospecific, giving 4-ethoxycarbonyl triazoles as the sole products <89JHC1461, 90JHC687>. 2-Nitrobenzyl azide adds to unsymmetrical alkynes resulting in the formation of two isomeric triazoles which can be separated by column chromatography <89JHC1605>.



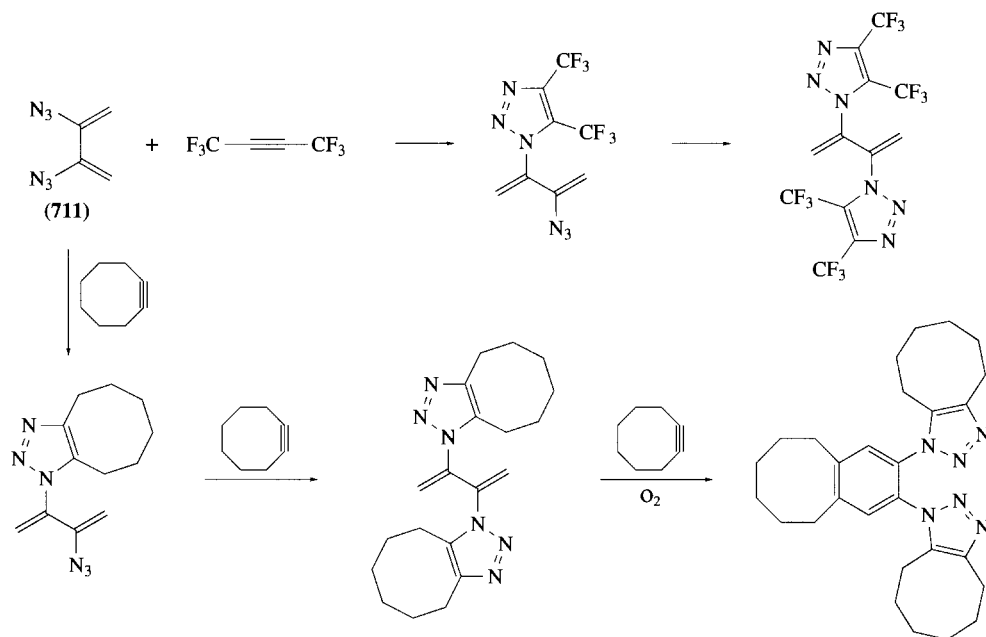
Scheme 144



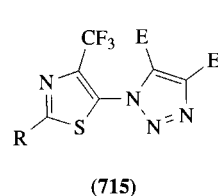
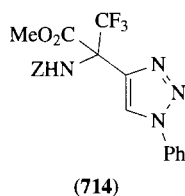
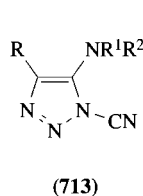
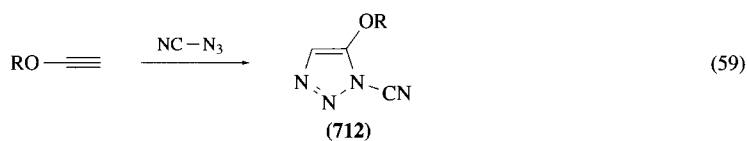
1,4-Diazido-2-butyne and 1,6-diazido-2,4-hexadiyne readily undergo cycloaddition with DMAD to afford bistriazoles (709) and (710), respectively [84ACS(B)623]. 2,3-Diazido-1,3-butadiene (711) undergoes cycloaddition with electron-deficient or angle-strained alkynes, such as di(trifluoromethyl)acetylene and cyclooctyne, to afford a variety of mono- and bis-triazoles as shown in Scheme 145 [89CB123]. Phenyltrifluoromethylacetylene and phenyl azide give trifluoromethylated 1,2,3-triazoles in good yields [84CPB4402].



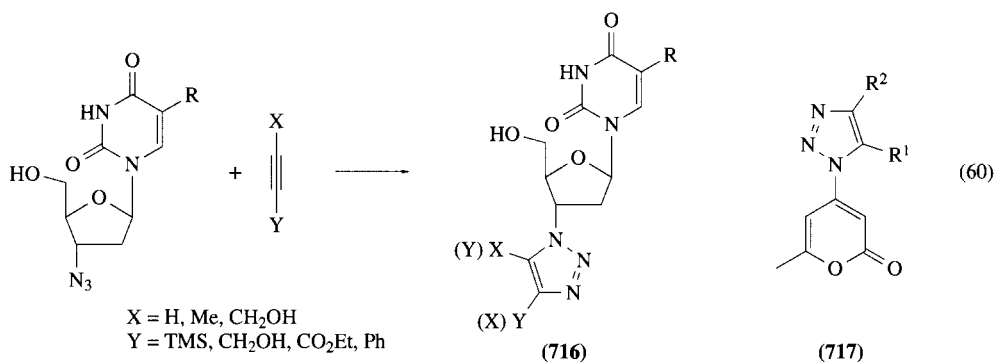
Cyanazide adds to electron-rich alkynes to give *N*-cyanotriazoles. The cycloadditions of alkoxyalkynes or aminoalkynes with cyanazide are regioselective and only 5-alkoxy- or 5-amino-1-cyano-1,2,3-triazoles (712) and (713) are produced (Equation (59)) [79AG(E)320, 81BSB615]. Trifluoromethyl-substituted alkynyl α -amino acids and phenyl azide react regioselectively to give the corresponding triazolyl amino acid derivatives (714) [92LA947]. 5-Azido-4-trifluoromethyl-1,3-thiazoles react with electron-deficient alkynes to give 1-(1,3-thiazol-5-yl)-1,2,3-triazoles (715) [90ZN(B)1695].



Scheme 145

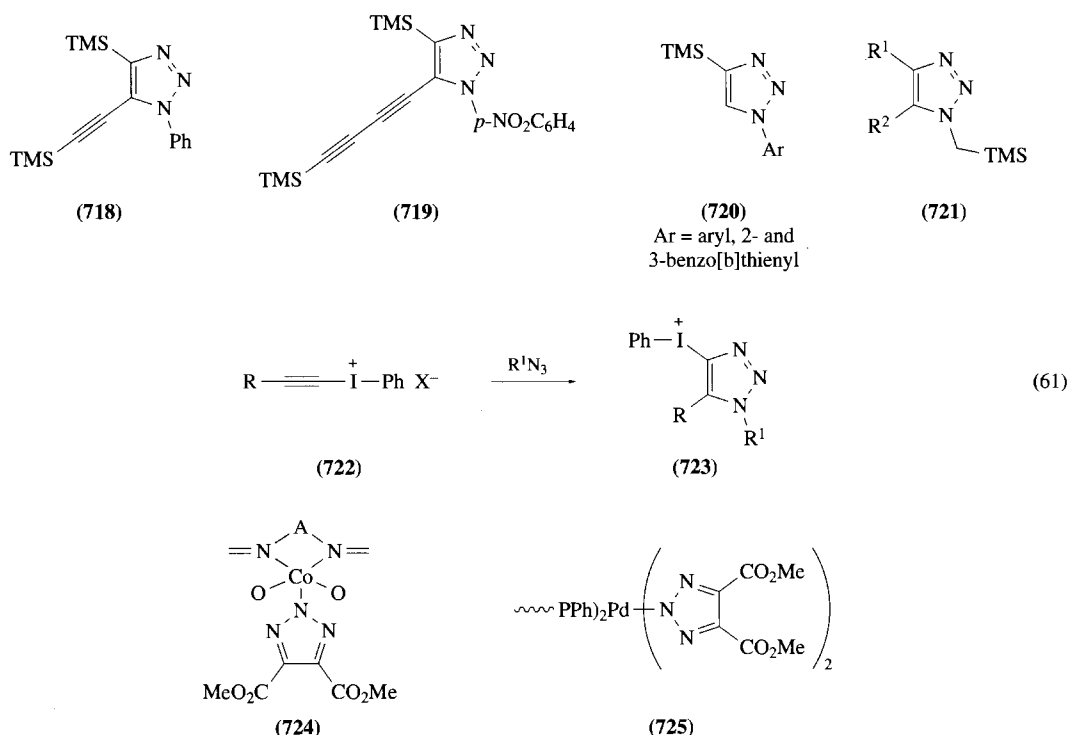


Cycloaddition of a variety of alkynes to the azido function of 3'-azido-2',3'-dideoxythymidine and 3'-azido-2,3-dideoxyuridine yields products (e.g., **716**) with a 1,2,3-triazol-1-yl substituent in the 3'-position (Equation (60)). By contrast to the parent compounds, these triazolyl derivatives have no appreciable activity against human immunodeficiency virus [89JHC1635]. Cycloadditions of 4-azido-6-methyl-2H-pyran-2-one with alkynes leads to triazoles (**717**) [93JHC317].



Phenyl azide reacts slowly with bis(trimethylsilyl)butadiyne at elevated temperature to give 1,2,3-triazole (**718**) as the only product. Similar reaction of 4-nitrophenyl azide and bis(trimethyl-

silyl)hexatriyne affords the triazole (**719**) with cycloaddition taking place exclusively at the triple bond adjacent to silicon. The regio- and site-specificity is attributed to orbital rather than to steric control. The cycloaddition is controlled by azide(HOMO)–diyne(LUMO) or azide(HOMO)–triyne(LUMO) interactions <88JOM(341)247>. Aryl azides and 2- and 3-azidobenzo[*b*]thiophenes undergo cycloaddition with (trimethylsilyl)acetylene to afford 1-aryl (or heteroaryl)-4-trimethylsilyl-1,2,3-triazoles (**720**) in nearly quantitative yields <91JCS(P1)2789>. Trimethylsilylmethyl azide undergoes 1,3-dipolar cycloadditions with alkynes to give triazoles (**721**) <83CL1131>. The cycloadditions of methyl or phenyl azide to ethynyl(phenyl)iodonium triflate salts (**722**) give (1,2,3-triazolyl-4-yl)iodonium salts (**723**) in low yields (Equation (61)) <92T3527>. The cycloaddition of DMAD to the azide ligand of polymeric Schiff's base, cobalt(III), and phosphine palladium complexes, gives the corresponding triazolate complexes (**724**) and (**725**), from which the triazoles are cleaved by HCl <87ZN(B)55>.



Various 1-(1-naphthyl)-1,2,3-triazoles with electron-withdrawing groups at the 4- and/or 5-positions (e.g. (**135**)) are synthesized from 1-azidonaphthalene and alkynes <87JCS(P1)413>. 1-(Naphthyl)-benzotriazoles (**127**) are prepared by cycloaddition of the appropriate 1-azidonaphthalenes to benzyne or substituted benzyne, generated from 3-methylantranilic acid. 1-(1-Naphthyl)-naphthotriazole is similarly prepared by cycloaddition to 2,3-dihydronaphthalene. 1,3-Dipolar cycloadditions of 8-azidoquinolinone with benzyne and DMAD give benzotriazoles and triazoles (e.g., (**130**)), respectively <87JCS(P1)403>.

The 1,3-dipolar cycloaddition of $RNH_2^+CH_2C\equiv CH$ and $RNH_2CH_2CH_2N_3$ is found to be substantially accelerated by the polycyclic molecular receptor, cucurbituril. The reaction also becomes regiospecific yielding only the 1,4-disubstituted-1,2,3-triazole <89JOC5302>. Almost all organic and inorganic azides undergo cycloaddition to the multiple bond under thermal conditions. However, irradiation of triarylbi-muth diazide $[Ar_3Bi(N_3)_2]$ in benzene in the presence of alkynes results in the transfer of one of the azido ligands to the triple bond, leading to *N*-unsubstituted 1,2,3-triazoles in moderate yields. In contrast to the thermal addition, the diazide does not react with electron-withdrawing substituted alkynes <93TL1055>.

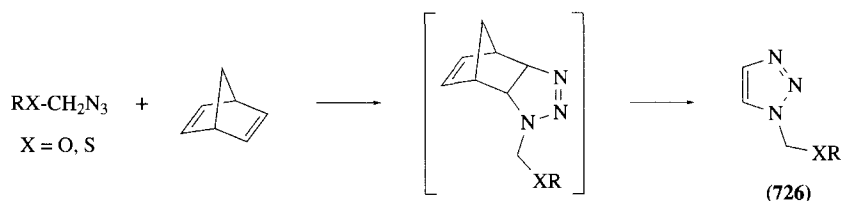
4.01.8.2.2 Addition of azides to $C=C$ double bonds

Alkenic bonds undergo 1,3-dipolar cycloadditions with azides to give Δ^2 -1,2,3-triazolines. Azides can add to a wide range of angle-strained, unstrained, and inactivated double bonds; to electron-

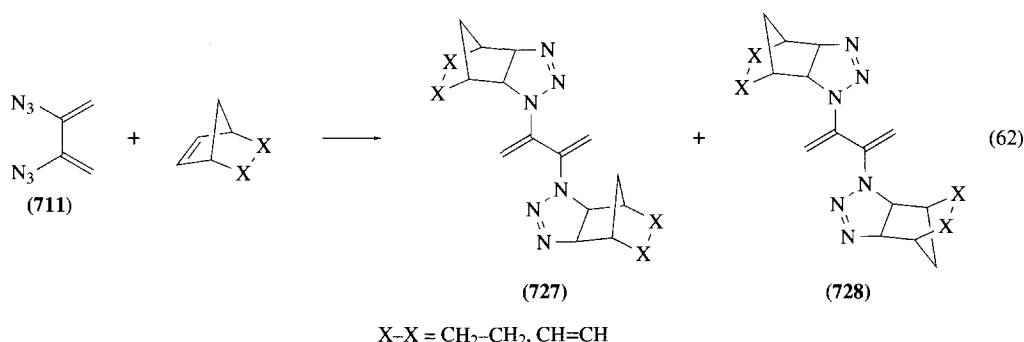
rich double bonds such as enamines, enamides, enol ethers, and ketene acetals; and to alkenes bearing one or two electron-withdrawing groups. The addition is, unlike the case of alkynes, usually regioselective giving 1,5-disubstituted triazolines. The synthesis of Δ^2 -1,2,3-triazolines by the cycloaddition of azides to double bonds has been extensively reviewed (84AHC(37)217, B-84MI 401-01, 84CHEC-I(5)708). Δ^2 -1,2,3-Triazolines are generally unstable; thus, many cycloadditions of azides with alkenes give 1,2,3-triazoles by aromatization of the initially formed Δ^2 -1,2,3-triazolines.

Azide-alkene dipolar cycloadditions are significantly accelerated by pressure. Thus, methacrylates and other electron-deficient alkenes react with azides at 12 kbar in various solvents to give triazolines in good yields (55–96%) in shorter periods (24 h). An increase in pressure has little effect on the regio- and stereoselectivity (91JOC6946). High-pressure reactions of arylsulfonyl azides with electron-rich silylenol ethers have also been reported. However, the triazolines formed decompose under these conditions (82JOC5042, 91TL2457).

α -Alkoxy- and α -alkylthio-substituted azides, on reaction with norbornadiene in refluxing 1,4-dioxane, give the 4,5-unsubstituted 1,2,3-triazoles (726) in high yield via a retro Diels-Alder reaction of the initially formed 1,2,3-triazolines (Scheme 146) (90H(31)1669). 2,3-Diazido-1,3-butadiene reacts with norbornene and norbornadiene to give isomeric bistriazolines (727) and (728) (Equation (62)) (89CB123).

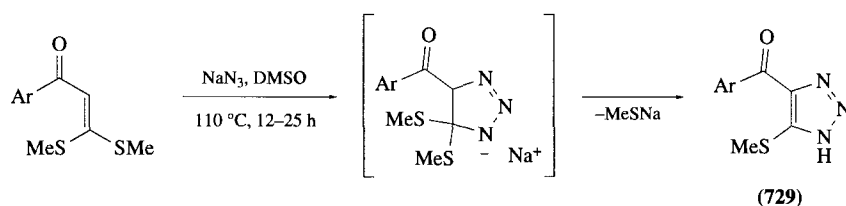


Scheme 146

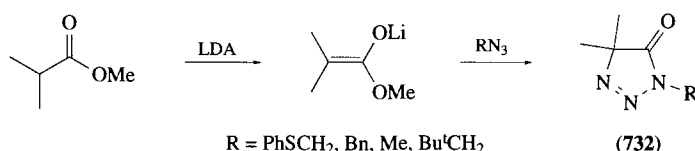


Cycloadditions of 4-azido-6-methyl-2H-pyran-2-one with enol ether and vinyl acetate, followed by elimination of an alcohol or acetic acid, give 1,2,3-triazoles (717) (93JHC317). [3 + 2] Cycloaddition of aroylketene dithioacetals with sodium azide in DMSO produces 4-aroyle-5-methylthio-1,2,3-triazoles (729) by elimination of one methylthio group from the triazoline intermediates (Scheme 147). The corresponding 1-acetyl-2,2-bis(methylthio)ethylene, however, yields the unstable azidoalkenes (88S453). Cycloaddition of acylketene *S,N*-acetals with tosyl azide under alkaline conditions gives 4-acyl-1-alkyl-5-tosylamino-1,2,3-triazoles in 44–70% yield. The similar reaction of cyclic *S,N*-acetals with tosyl azide in dioxane affords the 3,4-annulated 1,2,3-triazoles (730) (88S851). However, cycloaddition of ketene *S,N*-acetals with sodium azide gives tetrazoles instead of triazoles (88S453). Aryl azides containing no electron-withdrawing groups add to the enolate ion of acetaldehyde to give 1-aryl-4,5-dihydro-5-hydroxy-1,2,3-triazoles (731) which can be isolated and characterized (70–99%) (Scheme 148) (86T3913). Azides also undergo cycloadditions with lithium enolate, generated from the ester upon treatment with LDA, to form 1,4,4-trialkyl-4H-1,2,3-triazol-5-ones (732) (82TL4681, 86LA1891, 93CB103).

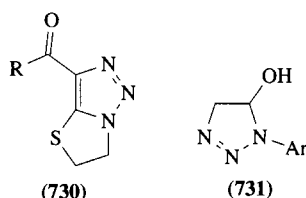
The 1,3-dipolar cycloaddition of equimolar amounts of enamide and aryl azide at room temperature, over a period of time (3 days to 10 months), affords the Δ^2 -1,2,3-triazolines (733) as stable crystalline products (Equation (63)). In refluxing ethanol, however, the reaction yields the corresponding triazoles as the major product with loss of the amides (92JOC3075). 5-Amino-1-aryl-1,2,3-triazolines (e.g., (734)–(735)) are readily prepared from the [3 + 2] cycloaddition of azides to



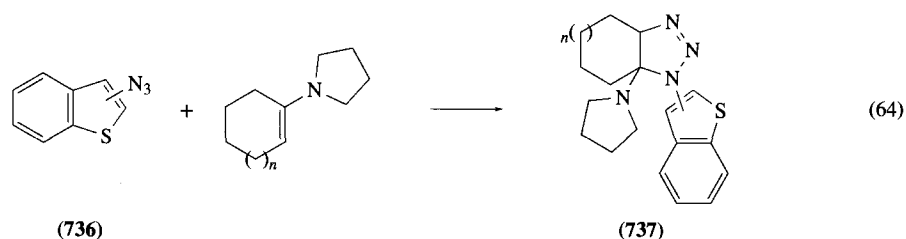
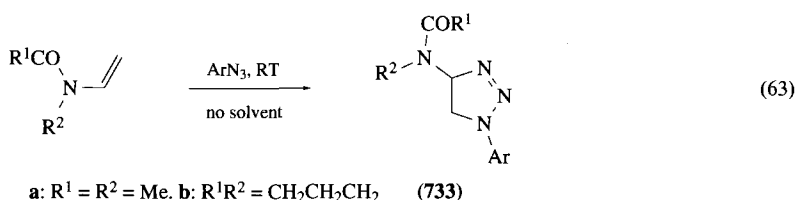
Scheme 147



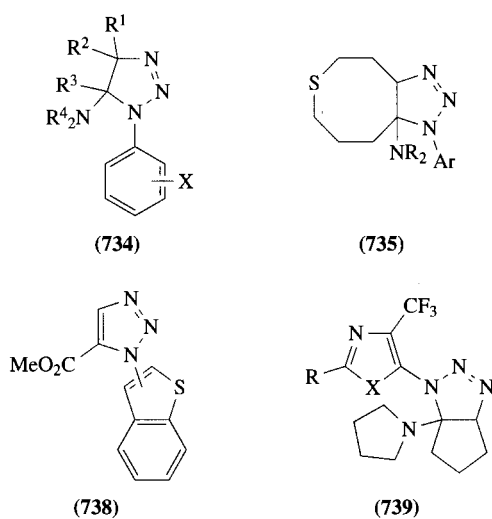
Scheme 148



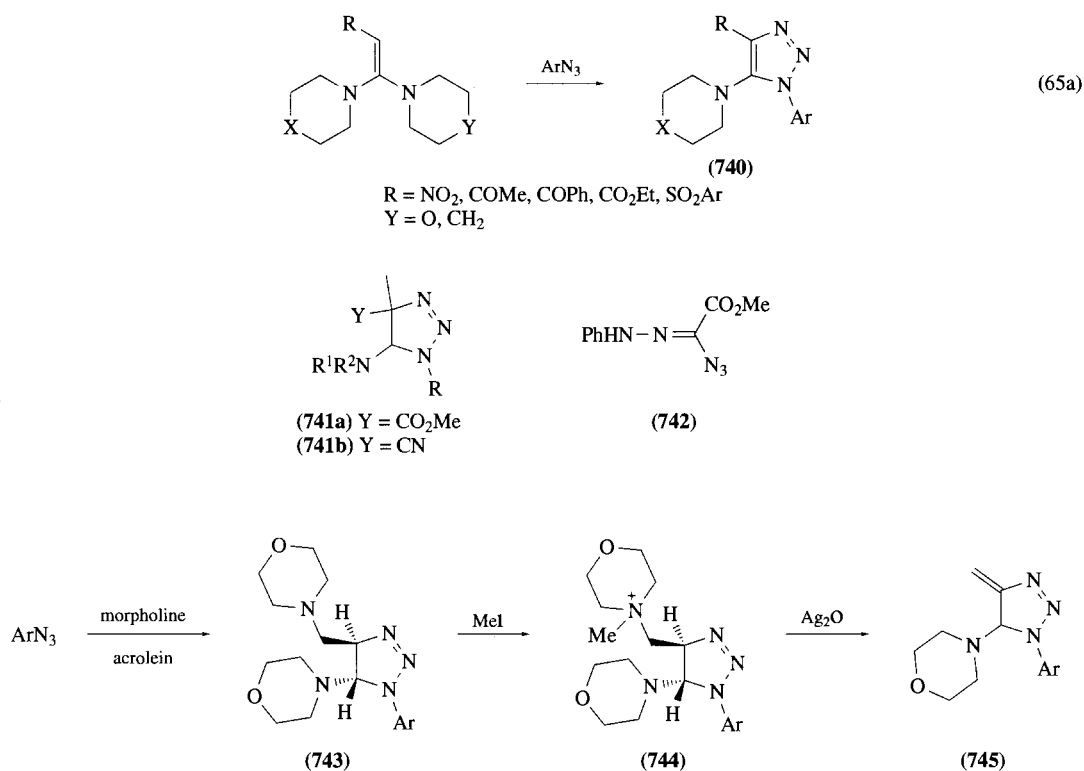
enamines <81BCJ261, 84AHC(37)217, 84JHC1121, 92JCS(P1)2709>. 2-Azido- and 3-azido-benzo[*b*]thiophenes (736) undergo regiospecific [3 + 2] cycloadditions to 1-pyrrolidinyl-cyclopentene or cyclohexene in benzene to furnish the corresponding triazolines (737) in quantitative yield (Equation (64)). By contrast, treatment of azides (736) with methyl (*E*)-3-(1-pyrrolidinyl)acrylate affords triazoles (738) arising from an intermediate triazoline by elimination of pyrrolidine <90JCS(P1)2971>. Cycloadditions of 5-azido-4-trifluoromethyl-1,3-azoles with enamines give triazolines (739) at low temperature <90ZN(B)1695>.



Aryl azides undergo 1,3-dipolar cycloaddition with 1,1-diaminoethenes bearing an electron-withdrawing group at C(2) to give unstable 5,5-diamino-Δ²-1,2,3-triazolines. Subsequent elimination of one amino group gives 5-amino-1-aryl-1,2,3-triazoles (740) containing a functional group at the C-4 position (Equation (65a)) <86S1010>. Aryl azides react with methyl β-aminomethacrylate and β-aminomethacronitrile to produce Δ²-1,2,3-triazolines (741). Similar additions of aroyl azides to enamines give only amidines and diazo compounds; no triazoline is isolated <84JHC513>. The reaction of azide (742) with enamines leads to mixtures of ring-closure products, namely 1,2,4-triazines, 1,2,3-triazoles, and 1,2,4-triazoles. Triazolines are also formed at low temperature <85JCS(P1)1903>.

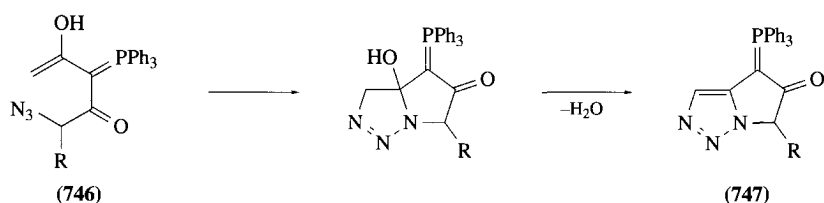


p-Substituted phenyl azides react with acrolein and morpholine to give Δ^2 -1,2,3-triazolines (**743**) (Scheme 149). Hoffmann elimination of *N*-methylmorpholine from the quaternized intermediates (**744**) by treatment with Ag_2O affords 4-methylene triazoles (**745**) [86JCR(S)132].

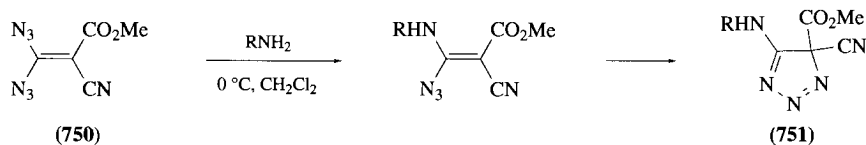
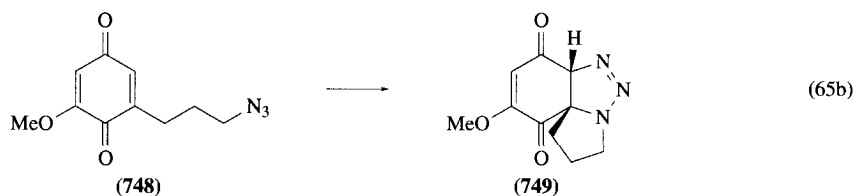


Scheme 149

Intramolecular cycloaddition of the azido group of compounds (**746**) to the tautomeric enol double bond affords triazoles (**747**) after loss of water (Scheme 150) [83BSB881, 84BSB579]. In either benzene at 40°C or refluxing CH_2Cl_2 , the 2-(azidoalkyl)quinone (**748**) undergoes intramolecular azide-alkene cycloaddition to give triazoline (**749**) (Scheme 151) [84JOC1676]. Vinyl azides do not generally cyclize to 1*H*-triazoles; instead, they eliminate nitrogen to give 2*H*-azirines. However, introduction of an electron donor into the α -position increases the nucleophilicity at the β -carbon, and 1,5-ring closure is possible. Thus, the reactions of methyl 3,3-diazo-2-cyanoacrylate (**750**) with amines in CH_2Cl_2 at 0°C lead to the 4*H*-triazoles (**751**) [82AG(E)288].

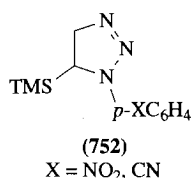


Scheme 150

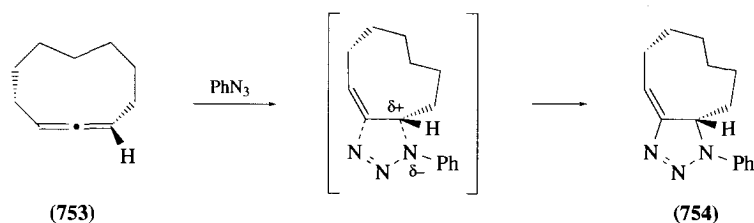


Scheme 151

The reactions of 4-nitro- and 4-cyano-phenyl azide with neat trimethyl(vinyl)silane at 25 °C for 9–10 days give the corresponding 1,2,3-triazolines (**752**) in 95% and 87% yields, respectively. However, similar reactions with other aryl azides without strongly electron-withdrawing substituents produce pyrazolines and aziridines <91JCS(P1)2789>. 4-Methoxyphenyl azide reacts with equimolar amounts of dibenzoyl ethene in benzene at room temperature to yield, after 8 days, the *trans*-dibenzoyltriazoline in 35% yield. Treatment of 4-nitro- and 4-chlorophenyl azide with dibenzoyl ethene gives only benzoyltriazoles and diazo compounds <89JCS(P1)2235>.



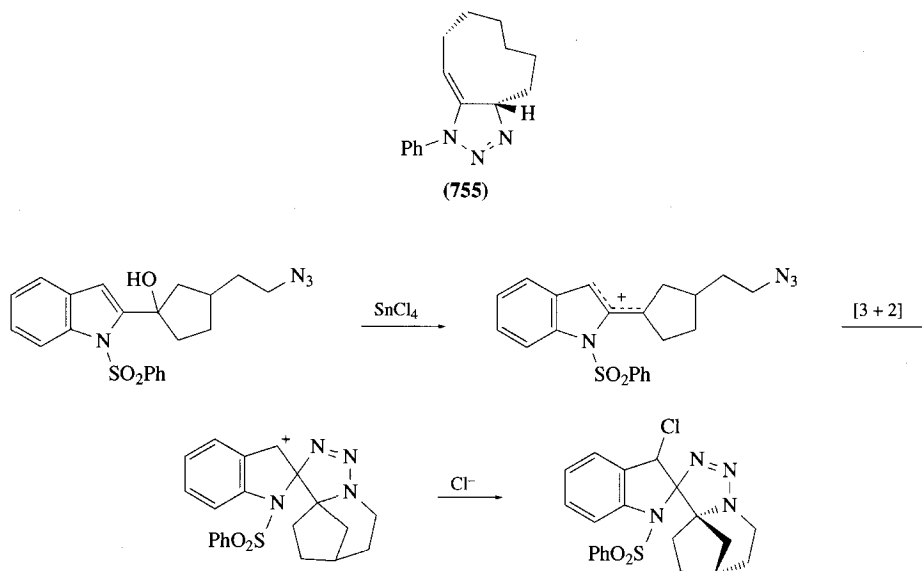
1,2-Cyclononadiene (**753**) and phenyl or 4-bromophenyl azide give a 1 : 1 adduct (**754**) (Scheme 152). This reaction is regiospecific and isomer (**755**) is not formed. When optically active (*R*)-(+)-cyclononadiene (**753**) reacts with phenyl azide, the optically active (*S*)-(+)-triazoline (**754**) is obtained, suggesting a concerted cycloaddition mechanism. The bicyclo triazoline (**754**) is stable under the reaction conditions, but is readily isomerized to the corresponding triazole with base <91JOC4463>. Azides undergo unprecedented low-temperature [3 + 2] cycloadditions with allylic carbocations to give triazolines (Scheme 153) <94JOC2682>. 4,5-Unsubstituted 1-alkyl-1,2,3-triazolines are prepared, albeit in low yield, from the reactions of alkyl azides with a slight excess of dimethyl sulfoxonium methylide. In this way, 1-methyl-, 1-ethyl-, 1-propyl-, 1-butyl-, 1-isopropyl-, 1-*tert*-butyl-, and 1-benzyl-1,2,3-triazolines are obtained in 20–30% yields <93JOC2097>.



Scheme 152

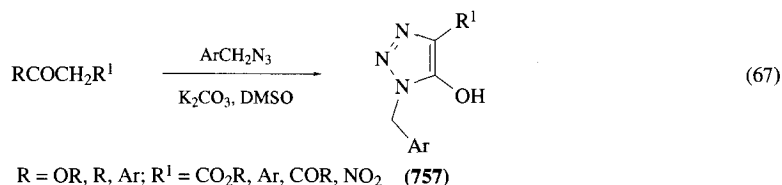
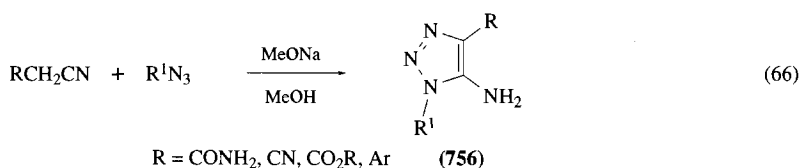
4.01.8.2.3 Reactions of azides with active methylene groups

The synthesis of triazoles from organic azides and active methylene compounds under basic conditions is well known. Although the condensation is stepwise, the reaction is usually regioselective,



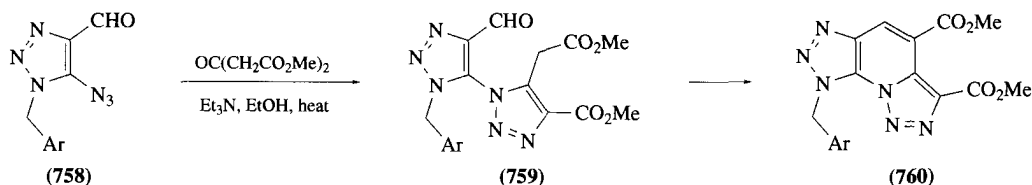
and most useful for the preparation of 5-amino- or 5-hydroxy-1,2,3-triazoles with an electron-withdrawing group at the 4-position. A wide range of azides and active methylene compounds can be employed.

1-Aryl-5-aminotriazoles (**756**) are prepared by the condensation of active methylene nitriles with aryl azides in $\text{CH}_3\text{OH}/\text{CH}_3\text{ONa}$ (Equation (66)). Care should be taken to avoid the Dimroth rearrangement by carrying out the reaction at low temperatures (0 – 20°C) <89T749>. Although sodium alkoxides are widely used as bases in the condensation, potassium carbonate in DMSO is found to be effective for the preparation of 5-amino-1*H*-1,2,3-triazoles from cyanoacetamide, malonitrile and phenylacetonitrile (48–94%). 5-Hydroxy-1*H*-1,2,3-triazoles are similarly obtained from azides and diethyl malonate (77–96%) or ethyl acetoacetate (84–89%) <91JHC301>. When *t*-butylacetonitrile is treated with LDA and methyl azide, 5-amino-1-methyl-4-*t*-butyl-1,2,3-triazole is formed in 35% yield <88CB1285>. A modified method for the preparation of 5-hydroxytriazoles (**757**) utilizing the reaction of azides and diethyl malonate or other active methylene compounds is described (88–91% yield) (Equation (67)) <84JHC1603>.

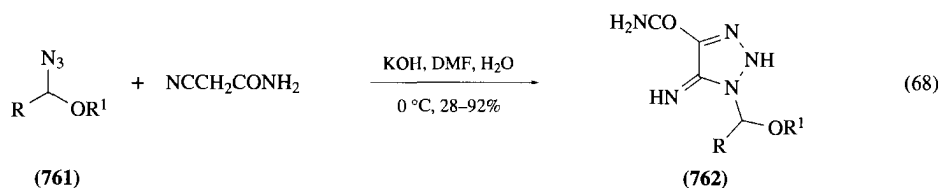


Active methylene nitriles condense with *o*-substituted aryl and heteroaryl azides in a two-step process to give tricyclic triazolopyrimidines without isolation of the triazole intermediates <85BSB441, 87BSB587>. 5-Azido-4-formyltriazoles (**758**) condense with dimethyl 3-oxopentanedioate and triethylamine in ethanol to give 5-(triazol-1-yl)-4-formyltriazoles (**759**), which undergo cyclization to

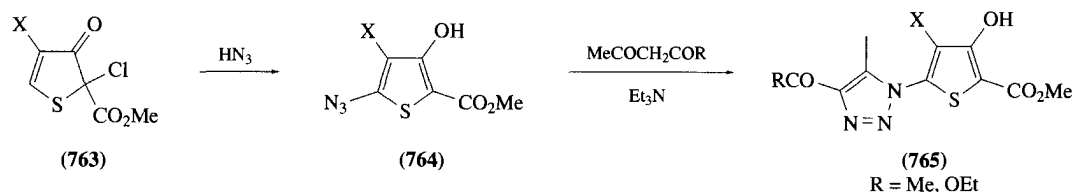
give pyridineditriazoles (**760**) (Scheme 154) <93ACS323>. α -Alkoxyalkyl azides (**761**) condense at 0°C with cyanoacetamide in the presence of KOH to give the corresponding 5-amino-1,2,3-triazoles (**762**) in good yield (Equation (68)) <88S879>. Compounds (**762**) can be isolated and characterized <90H(31)1669>.



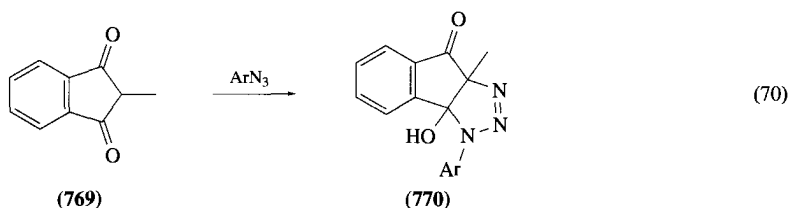
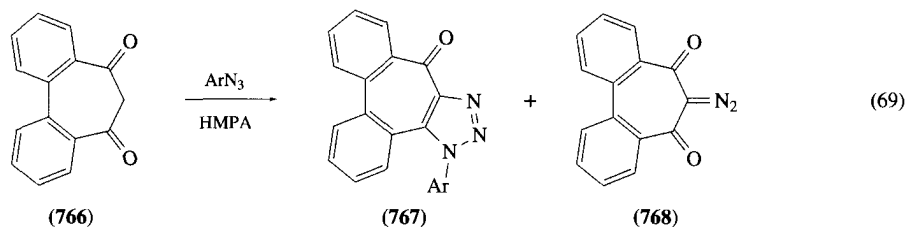
Scheme 154



Hydrazoic acid, generated from sodium azide in acetic acid, reacts with compounds (**763**) to give 5-azidothiophenes (**764**), which condense with acetylacetone and ethyl acetoacetate in the presence of triethylamine at room temperature to afford the corresponding triazoles (**765**) (Scheme 155) <87JHC1301>. *p*-Nitrophenyl azide reacts with cycloheptanedione (**766**) in HMPA to afford 1,2,3-triazole (**767**, Ar = *p*-NO₂C₆H₄) in 90% yield accompanied by 8% of the corresponding diazo derivative (**768**). By contrast, the reaction of tosyl azide and (**766**) gives only the diazo compound (97%) (Equation (69)). Under similar conditions, treatment of *p*-nitrophenyl azide with 1,3-cyclohexanedione and open chain β -diketones or β -ketoesters affords, in most cases, the corresponding triazoles as the major or sole products. With malonates, however, only diazo compounds are formed <92G249>. Reactions of aryl azides with 2-methylindane-1,3-dione (**769**) in HMPA at 55°C result in the formation of fairly stable tricyclic 4-acyl-5-hydroxytriazolines (**770**) in generally good yields (Equation (70)). Strongly electrophilic azides, such as tosyl azide, do not give triazolines on reaction with 2-methylindanedione <92JCS(P1)2845>.



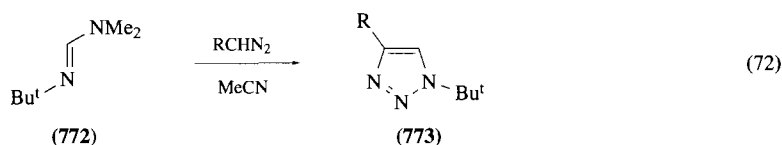
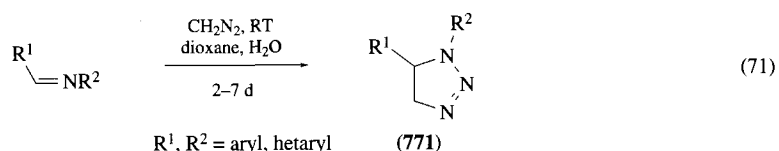
Scheme 155



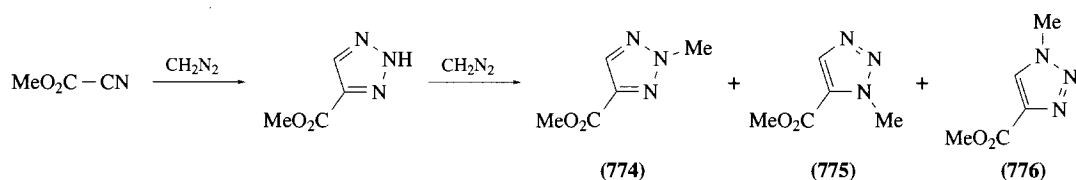
4.01.8.2.4 Cycloaddition of diazoalkanes to C=N bonds and relevant reactions

The [3 + 2] cycloaddition of diazo compounds to imines or nitriles is an alternative approach to the preparation of 1,2,3-triazoles and 1,2,3-triazolines. For reviews, see CHEC-I <84CHEC-I(5)717>.

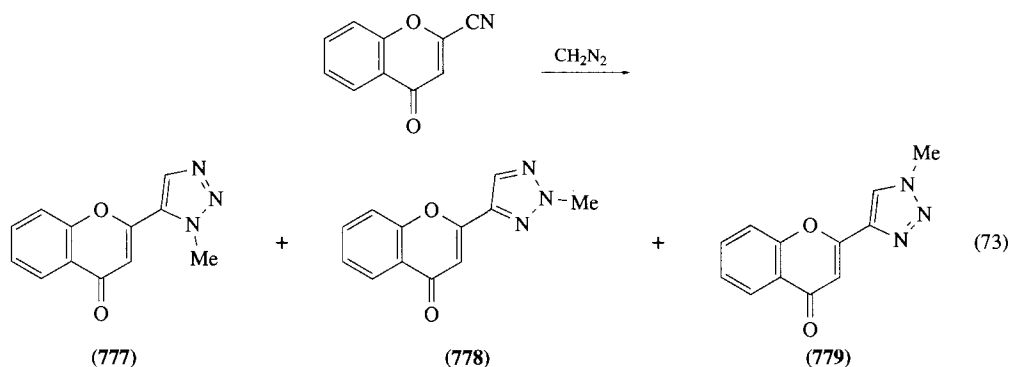
Diazomethane reacts with heteroaromatic imines in dioxane in the presence of a catalytic amount of water at room temperature, to give 1,5-disubstituted Δ^2 -1,2,3-triazolines (**771**) (Equation (71)) <90JOC5891, 93JHC1121>. Reaction of aromatic aldehyde azines in DMSO with phenyldiazomethane and Bu^tOK gives 4,5-diphenyl-1,2,3-triazoles in 92% yield <88JCS(P1)2917>. Substituted diazomethanes react with *t*-butyliminoamine (**772**) in acetonitrile to give 1-*t*-butyl-1,2,3-triazoles (**773**) in good yields (Equation (72)) <85S178>.



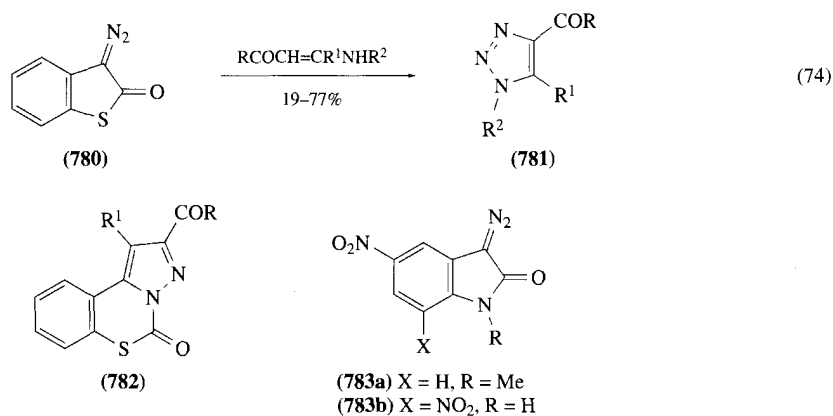
An excess of diazomethane with methyl cyanoformate gives *N*-methyl-1,2,3-triazolecarboxylic esters (**774**)–(**776**) (Scheme 156) <87CB159>. However, unactivated nitriles generally do not react with diazomethane or other diazoalkanes without the participation of a catalyst <88JHC1167>. A mixture of aryldiazomethanes, benzonitriles and Bu^tOK (1 : 1 : 1 molar ratio) in toluene gives 4,5-diaryl-1,2,3-triazoles in 26–75% yields <88JCS(P1)2917>. Cycloaddition of diazomethane to 2-cyanochromone in diethyl ether affords all three isomeric *N*-methyltriazoles (**777**)–(**779**) (Equation (73)) <88JHC1167>.



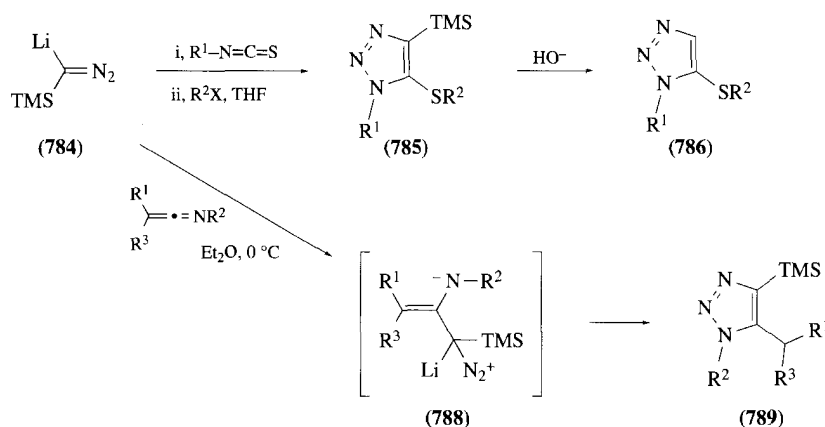
Scheme 156



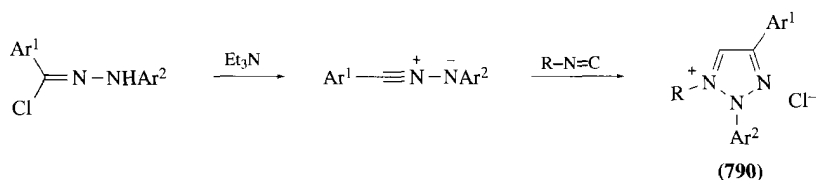
The reactions of 3-diazobenzo[*b*]thiophene-2-one (**780**) with enaminones leads to the formation of 1,2,3-triazoles (**781**) (19–77%) as the major products along with by-products (**782**) (Equation (74)). The nitro derivatives (**783**) react with various enaminones to give generally good yields of 1,2,3-triazoles (55–82%). The mechanism for the formation of the triazoles is described <93JOC7079>.



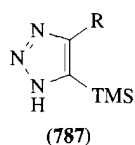
Lithium trimethylsilyldiazomethane (**784**) reacts with isothiocyanates in THF to produce 4-trimethylsilyl-5-alkylthiotriazoles (**785**) after quenching with alkyl halides (Scheme 157). Desilylation of (**785**) with aqueous KOH in methanol gives 1-substituted 5-alkylthio-1,2,3-triazoles (**786**) in excellent yields <85H(23)2371>. Lithiotrimethylsilyldiazomethane (**784**) undergoes cycloadditions with nitriles to yield 4-alkyl-5-trimethylsilyl-1*H*-triazoles (**787**) <85S717>. Ketenimines (**788**) and diazomethane (**784**) give 4-trimethylsilyl-1,2,3-triazoles (**789**) in good yields via intermediate (**788**) <89H(28)133>. However, ketenimines bearing an EWG at the C(2) position react with (**784**) to give pyrazoles as the main products <91S1163>. Diarylnitrilimines, prepared from *N*-phenylbenzohydrazonoyl chloride and triethylamine, react with alkyl isocyanides to form the 1,2,4-trisubstituted 1,2,3-triazolium salts (**790**) <87H(26)1751>.



Scheme 157

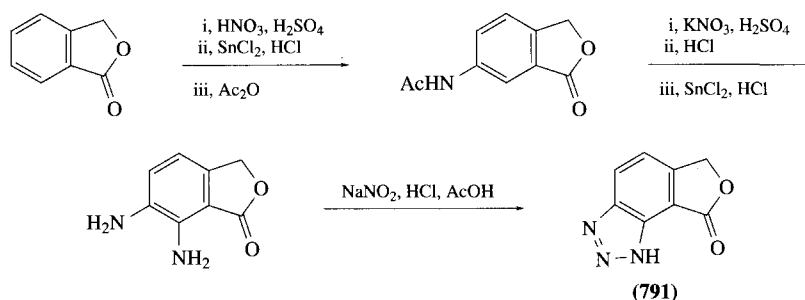


Scheme 158

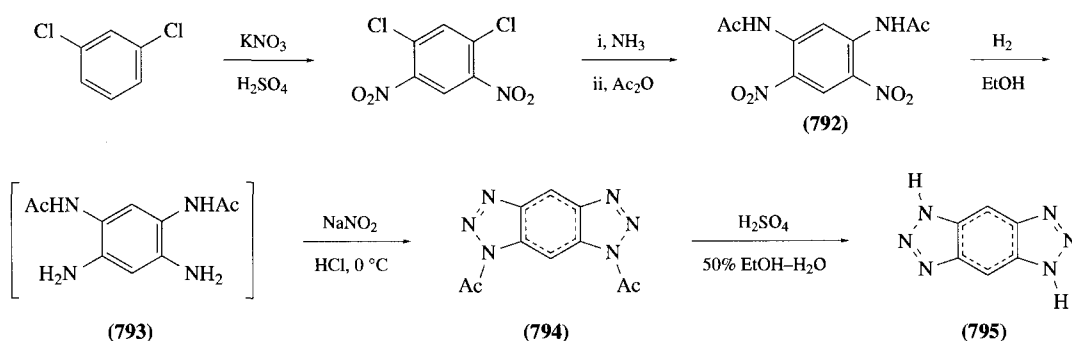


4.01.8.3 Synthesis of the Benzotriazole Ring

The diazotization of *o*-diaminobenzene derivatives is the most common synthetic route to benzotriazoles. Triazolo[6,7-*d*]phthalide (**791**) is synthesized in a seven-step sequence from phthalide in 24% overall yield as shown in Scheme 159. Triazolo[6,7-*d*]dihydrocoumarin is similarly prepared in nine steps from dihydrocoumarin in 20% overall yield <92JHC1519>. Benzo[1,2-*d*:4,5-*d'*]bistriazole (**795**) is synthesized from *m*-dichlorobenzene in five steps and 54% overall yield (Scheme 160). The hydrogenation of (**792**) is carried out in ethanol to give (**793**), which, without isolation, is diazotized at 0 °C to afford diacetyl bistriazole (**794**) in 96% yield <86JOC979>.

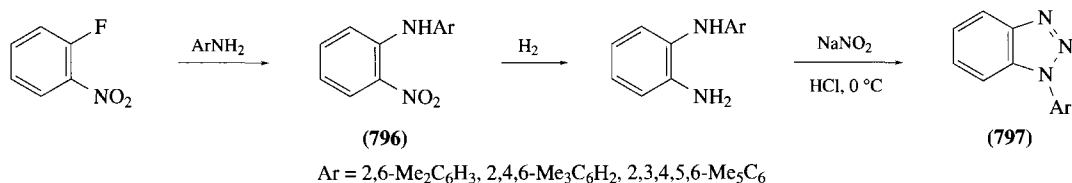


Scheme 159



Scheme 160

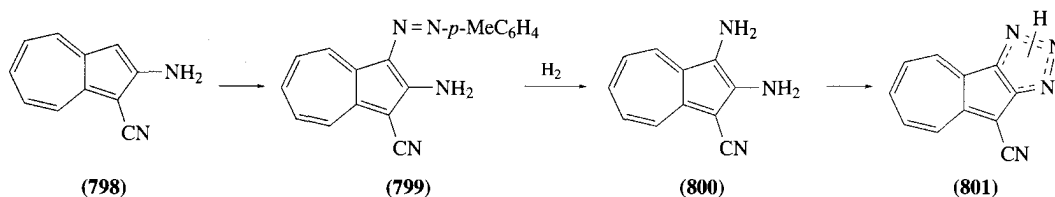
1-Arylbenzotriazoles (**797**) are prepared via 2-nitro- and 2-amino-diphenylamines (Scheme 161). The 2-nitrodiphenylamines (**796**) are prepared from the appropriate aniline by reaction with 2-fluoronitrobenzene in the presence of KF <80S215, 85JCS(P1)2725>. Azo-coupling of 2-amino-1-cyanoazulene (**798**) with *p*-tolyldiazonium chloride gives (**799**) (Scheme 162). Catalytic reduction of (**799**) quantitatively yields the diamino derivative (**800**), which on diazotization affords 9-cyanoazuleno[1,2-*d*]triazole (**801**) in 77% yield <85TL335>.



Scheme 161

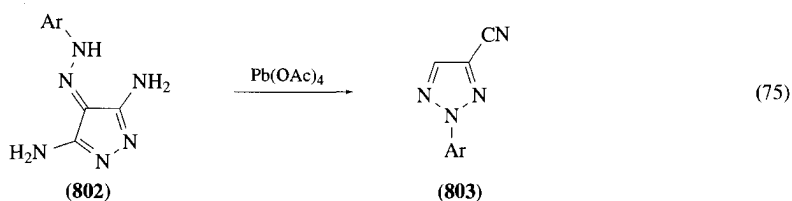
4.01.9 SYNTHESIS OF TRIAZOLES BY TRANSFORMATION OF OTHER HETEROCYCLES

For reviews on ring transformation of five-membered heterocycles, see <93AHC(56)49> and CHEC-I <84CHEC-I(5)718>.

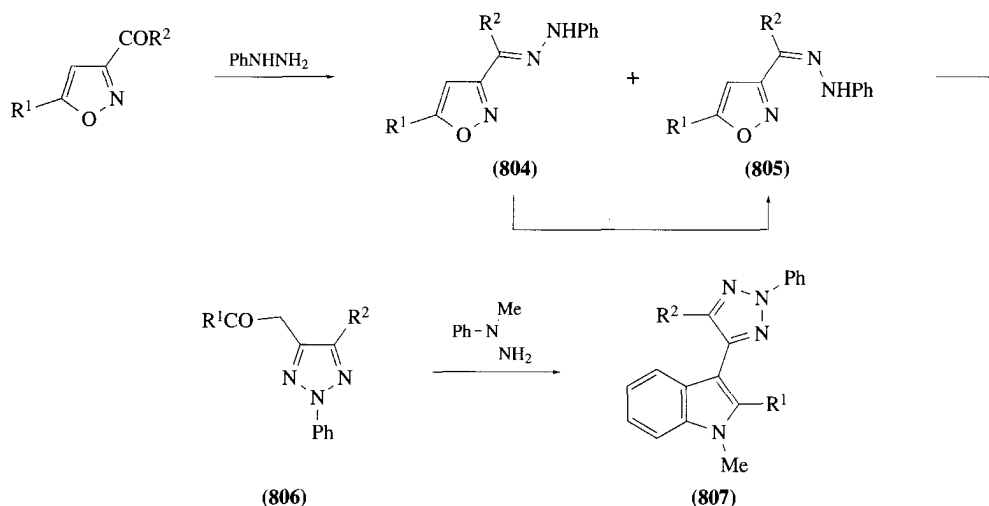


Scheme 162

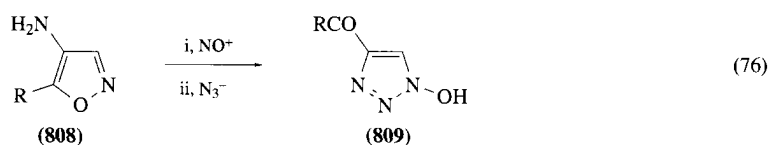
Oxidation of 3,5-diamino-4-arylhydrazonopyrazoles (**802**) with lead tetraacetate gives 2-aryl-4-cyano-2*H*-1,2,3-triazoles (**803**) in moderate yield (Equation (75)). A mechanism involving pyrazolotriazole and/or nitrene intermediates is proposed <86JCS(P1)1379>.

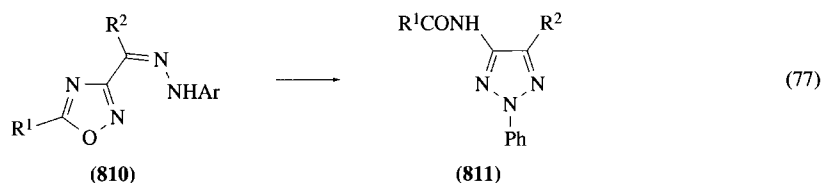


The reaction of 3-benzoyl-5-phenylisoxazole and 3-acetyl-5-methylisoxazole with phenylhydrazine in acetic acid gives both *E*- and *Z*-hydrazones (**804**) and (**805**) (Scheme 163). The mixture of (**804**) and (**805**) rearranges into 2-phenyl-1,2,3-triazoles (**806**). Similar reactions also occur with *N*-methyl-*N*-phenylhydrazine to afford (**806**) after demethylation. In the presence of an excess of *N*-methyl-*N*-phenylhydrazine, triazoles (**806**) can undergo Fischer indolization to give (**807**) <83JHC931>. 1-Hydroxy-1,2,3-triazoles (**809**) are prepared from 4-amino-2-alkylisoxazoles (**808**) using the combined procedures of nitrosation and treatment with sodium azide at 0–5°C to form a diazo-oxime intermediate (Equation (76)) <84BSB593>. The mechanism of the mononuclear heterocyclic rearrangement of isoxazole hydrazones to 1,2,3-triazoles has been studied <87JCS(P2)537, 88JCS(P2)1683>. The rearrangement (Equation (77)) of *Z*-arylhydrazones of 3-aryl-1,2,4-oxadiazoles (**810**) into 4-aryl- or acyl-amino-1,2,3-triazoles (**811**) in acidic and basic solution or by heating has been described in CHEC-I and reviewed <93AHC(56)49>. The kinetics of the rearrangement, substituent effects and solvent effects have been studied <83JCS(P2)1203, 84JCS(P2)541, 84JCS(P2)785>.



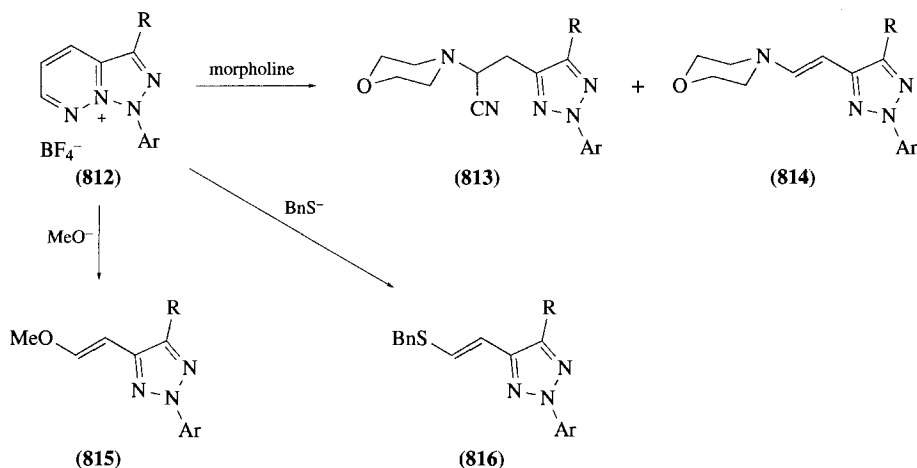
Scheme 163



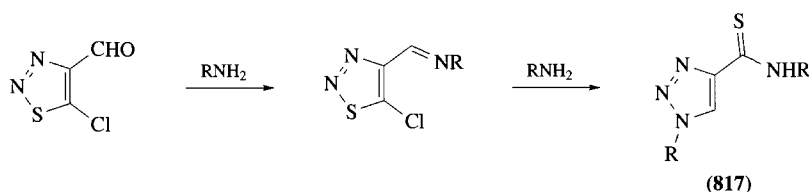


The triazolopyridazinium salts (**812**), when treated with morpholine, undergo ring opening of the pyridazine ring and to yield a mixture of triazoles (**813**) and (**814**) depending on the nature of the R group (Scheme 164). When the reaction is carried out with the morpholine anion, generated by NaH in TFF to minimize the presence of protons, only the triazolyl enamines (**814**) are formed. Compounds (**812**) also undergo similar ring opening reactions with other nucleophiles to give functionalized ethenyl-1,2,3-triazoles (e.g., (**815**) and (**816**)) <93JHC819>. The Dimroth rearrangement is widely used to synthesize 1,2,3-triazoles from 1,2,3-thiadiazoles as discussed in Section 4.01.4.1.1. 5-Chloro-1,2,3-thiadiazole-4-carbaldehyde reacts with alkyl- and aryl-amines and -hydrazines to give 1,2,3-triazole-4-thiocarboxamides (**817**) (Scheme 165) <91JCS(P1)607>.

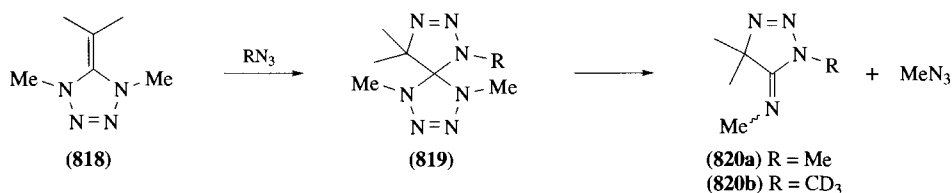
5-Iminodihydro-1,2,3-triazoles (**820**) are prepared from the 5-isopropylidenedihydrotetrazole (**818**) and alkyl azides through a ring transformation involving cycloaddition and cycloreversion via the spiro intermediates (**819**) (Scheme 166). The reaction is highly stereoselective with (*E*)/(*Z*) = 95 : 5 for (**820a**) and 100 : 0 for (**820b**) <90CB2195, 92CB2749>.



Scheme 164

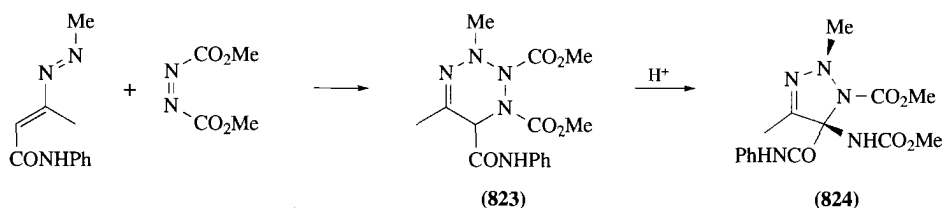
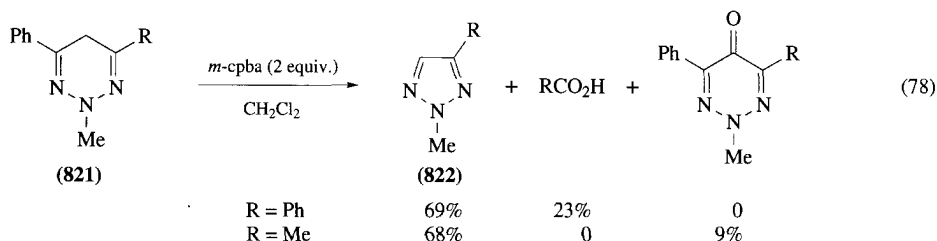


Scheme 165

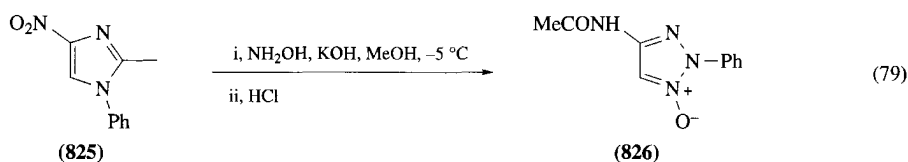


Scheme 166

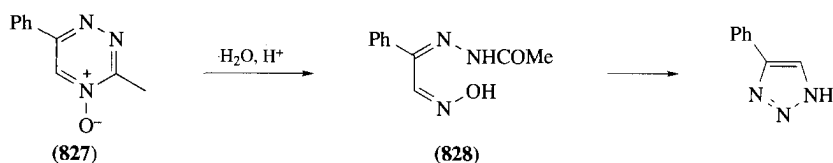
2-Methyl-2,5-dihydro-1,2,3-triazines (**821**) are oxidized by *m*-chloroperbenzoic acid in methylene chloride to give 2-methyl-4-substituted-1,2,3-triazoles (**822**) in good yields if at least one of the substituents is a phenyl group (Equation (78)) <86H(24)33>. The 1,2,3,6-tetrahydro-1,2,3,4-tetrazine (**823**), obtained from the cycloaddition of an azoalkene and azo esters (Scheme 167), undergoes rearrangement on acidic work up to form 4,5-dihydro-1,2,3-triazole (**824**) <91JCS(P1)3361>. 2-Methyl-4-nitro-1-phenylimidazole (**825**) reacts with hydroxyamine in the presence of KOH in methanol to form 4-acetylamino-2-phenyl-2*H*-1,2,3-triazole 1-oxide (**826**) in 57% yield <92TL7941>.



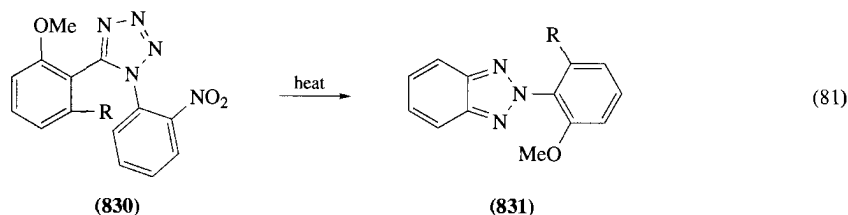
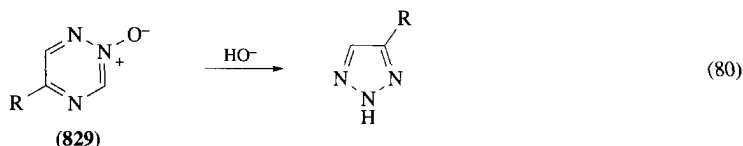
Scheme 167



Acid hydrolysis of 3-methyl-6-phenyl-1,2,4-triazine 4-oxide (**827**) yields 4-phenyl-1,2,3-triazole through an acyclic intermediate (**828**) (Scheme 168) <89AHC(46)73>. 1,2,4-Triazine 2-oxides (**829**) undergo rearrangement in basic conditions (Equation (80)) to form 4-substituted 2*H*-1,2,3-triazoles <89AHC(46)73>. 1-(2-Nitrophenyl)-5-aryltetrazoles (**830**) and 1-aryl-5-(2-nitrophenyl)tetrazoles are converted into 2-arylbenzotriazoles (**831**) by refluxing in nitrobenzene (Equation (81)) <81AJC691>.



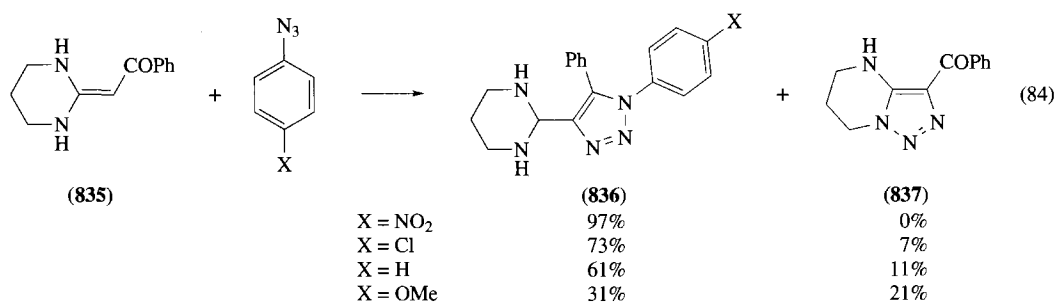
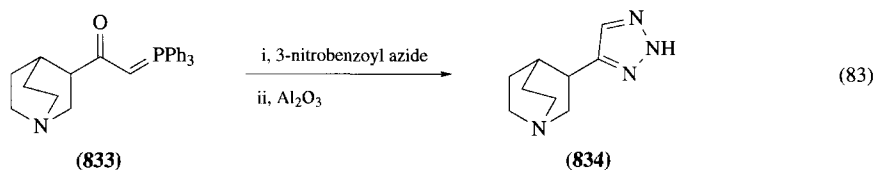
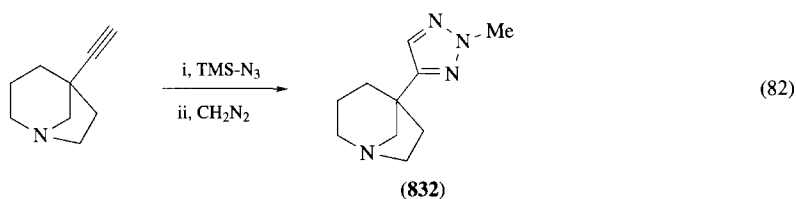
Scheme 168



4.01.10 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

4.01.10.1 Synthesis of 1,2,3-Triazoles

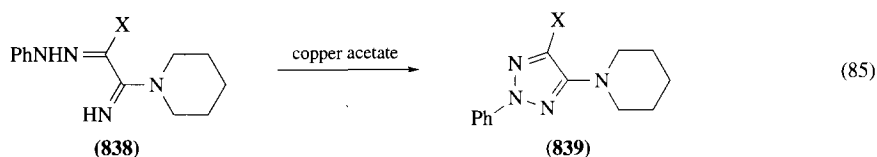
The most common method for the synthesis of 1,2,3-triazoles is the cycloaddition of an alkyne to an azide. The reaction works extremely well for arylalkynes and for alkynes which are activated with electron-withdrawing groups such as alkoxycarbonyl. However, forcing conditions are required for alkynes substituted with electron-releasing groups. For example, treatment of 5-ethynyl-1-azabicyclo[3.2.1]octane with TMS azide at 140°C for 8 h followed by CH_2N_2 gives only triazole (**832**) in 7% yield (Equation (82)) <92JMC2392>. An alternative synthesis is based on the cycloaddition of an electron-rich alkyne equivalent, such as an α -keto phosphorus ylide, to an electron-deficient azide. Thus, treatment of the α -keto ylide (**833**) with 3-nitrobenzoyl azide gives a substituted triazole from which the protecting group is removed during purification on an alumina column to afford triazole (**834**) (Equation (83)) <92JMC1280>. Ketene aminal (**835**) reacts (Equation (84)) with 4-nitrophenyl azide to give 1,2,3-triazole (**836**) in 97% yield. However, the reactions of (**835**) with other phenyl azides proceed more slowly, and triazolo[1,5-*a*]pyrimidine (**837**) is formed in addition to the corresponding triazoles (**836**) <92JOC184>.



Further disadvantage of the alkyne-azide cycloaddition is the lack of regioselectivity. On the other hand, cycloadditions of azides to alkenes are, in most cases, regioselective and afford 1,5-disubstituted triazolines <B-84MI 401-01>. Therefore, the regioselective cycloaddition of an azide to an alkene, followed by aromatization (see Section 4.01.5.3.1) is an alternative method for the synthesis of 1,2,3-triazoles.

5-Amino-1,2,3-triazoles with a substituent at the 4-position have been prepared: (i) from azides and active methylene nitriles; (ii) from azides and ynamines; (iii) from diazomethane and carbodiimides; (iv) from azides and 1,1-diaminoethenes; and (v) from the rearrangement of 3-hydrazono-1,2,4-oxadiazoles. Among these, the first method, a regioselective process, is the most versatile and convenient although it is suitable only for 5-NH₂-substituted triazoles. Other methods are used to prepare 5-NHR¹-, 5-NR¹R²- and 5-NHCOR-substituted triazoles. Intramolecular cyclization of suitable precursors also gives 5-aminotriazoles. For example, α -imino- α -piperidyl phenylhydrazones (**838**), in the presence of copper acetate, give 5-piperidyl-triazoles (**839**) (Equation (85)) <94H(38)739>.

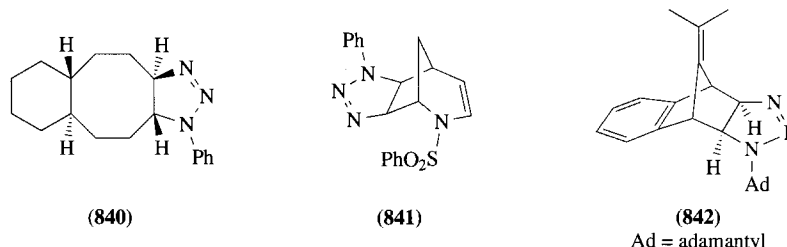
5-Hydroxy-1,2,3-triazoles with an aryl or carbonyl function at C(4) are similarly synthesized from azides and 1,3-dicarbonyl compounds.



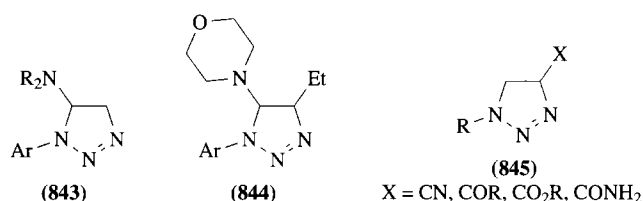
There are three general approaches to synthesize *N*-amino-1,2,3-triazoles: (i) Intramolecular cyclization of 1,2-bishydrazones or bissemicarbazones by treatment with oxidants, such as lead tetraacetate (see Section 4.01.8.1). (ii) Dimroth rearrangement of 5-chloro-1,2,3-triazoles or 5-chloro-1,2,3-thiadiazoles upon treatment with hydrazine. This method is ideally suited to 1-amino-1,2,3-triazoles with an amino or thio group at the 5-position as discussed in Section 4.01.4.1.1 <89BSB343, 89JHC1811>. (iii) Direct amination of triazoles <86JOC979>. In this case, however, a mixture of 1- and 2-aminotriazoles is formed. The oxidative cyclization of α -hydroxyimino hydrazones is a general route to 2-alkyltriazole 1-oxides <86ACS(B)262> and 1-aryloxytriazoles <89JCS(P)619>.

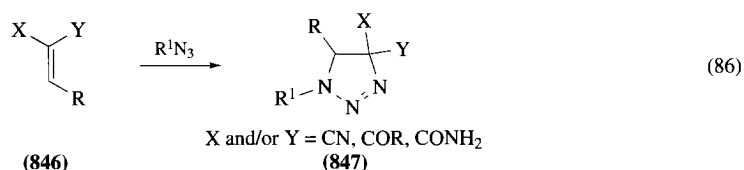
4.01.10.2 Synthesis of 1,2,3-Triazolines

The 4,5-dihydro-1,2,3-triazoline ring is synthesized by two main approaches: (i) Azide-alkene cycloaddition. This reaction involves the union of the C—C and N—N—N components. (ii) Imine-diazoalkane coupling. In this approach, the ring is constructed from the C—N and C—N—N fragments. The type of substitution desired on the triazoline ring at both the nitrogen and carbon atoms will determine which method is appropriate. Cycloalkenes and strained bicyclic alkenes are particularly reactive towards azide addition, and in many cases, the reactions proceed quantitatively. Therefore, hydrocarbon fused-ring triazolines, such as compounds (840)–(842) and (754)–(755) are best synthesized in this way. 1,3-Cycloadditions of azides to strained double bonds have been reviewed in great detail <84AHC(37)217>. Intramolecular reactions of azidoalkenes give 1,5-fused triazolines <84JOC1676, 86JOC1120>.

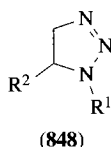


Electron-rich double bonds, such as those found in enamines, dienamines, enol ethers, and enol thioethers, are very reactive towards azides. The reaction is both regio- and stereoselective, giving 1,5- or 1,4,5-substituted triazolines such as (843) and (844) (see more examples in Section 4.01.8.2.2). Triazolines prepared from azides and enamines are generally isolable, although further aromatization leads to the formation of 1,2,3-triazoles. A considerable number of triazolines with an amino, amido, alkoxy, or alkylthio group at the 5-position have been obtained in this way. Electron-deficient double bonds also show high reactivity in cycloaddition reactions with azides. The products are generally 1,4-substituted triazolines. Thus, the cycloaddition of organic azides to acrylic esters, ketones, nitriles, and amides is a versatile approach to 1,2,3-triazolines of the general structure (845). Alkenes bearing two geminal EWGs (e.g. (846)), undergo cycloaddition with azides to give the stable 4,4-disubstituted triazolines (Equation (86)) (847).





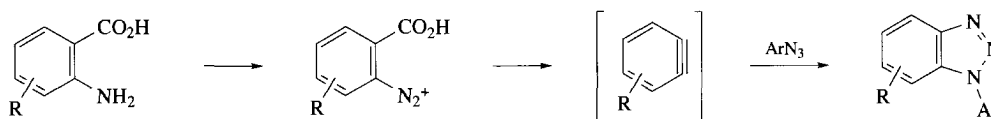
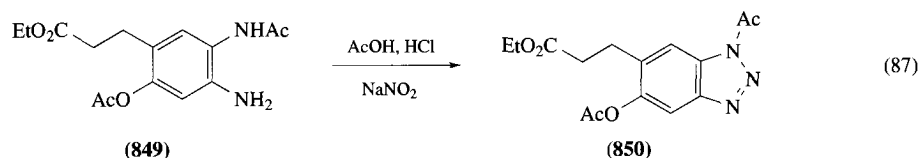
C=C double bonds which are neither strained nor activated by an EWG or EDG react slowly with azides. The reaction may take weeks or even months. The use of high temperatures is restricted as 1,2,3-triazolines are thermally unstable. In such cases, the imine-diazoalkane reaction is a suitable alternative. This method is a versatile route for the preparation of 1,5-substituted triazolines, especially 1,5-diaryltriazolines (**848**), from the reaction of a Schiff's base and diazomethane under mild conditions (93JHC1191). A wide range of substituents can be incorporated from readily available imines.



There is no general and convenient method for the synthesis of Δ^3 - and Δ^4 -triazolines.

4.01.10.3 Synthesis of Substituted Benzotriazoles

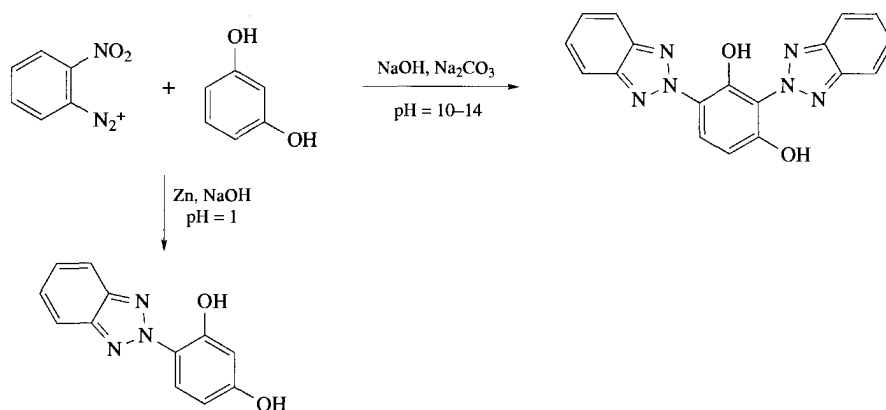
1*H*-Benzotriazole and its derivatives are usually obtained by diazotization of *o*-phenylenediamines as discussed in Section 4.01.8.3 and in CHEC-I (84CHEC-I(5)722). Substituted *o*-phenylenediamines (e.g., **849**) similarly give 1-substituted benzotriazoles (**850**) upon treatment with NaNO₂ (Equation (87)) (92JHC1519). 1-Arylbenzotriazoles are alternatively synthesized from the cycloaddition of an aryl azide to benzyne or substituted benzyne, generated from the diazotization of anthranilic acid or its appropriately substituted derivatives (Scheme 169) (86CC399, 87JCS(P1)403, CHEC-I).



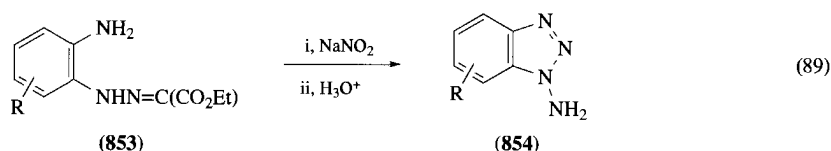
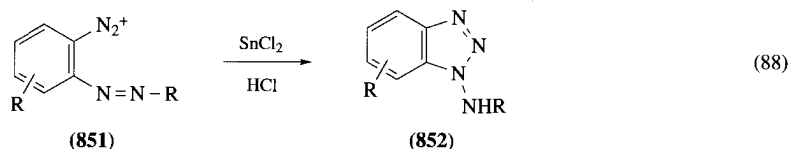
Scheme 169

2-Arylbenzotriazoles are readily prepared from the cyclization of 1,2-azoaminobenzotriazoles (84CHEC-I(5)723). Reactions of 2-nitrobenzenediazonium salt with phenols give 2-(2-hydroxyphenyl)-benzotriazoles. In the presence of an excess of 1,3-dihydroxybenzene, both mono- and di-benzotriazoles can be obtained, depending on the reaction conditions (Scheme 170) (85MI 401-01). 1-Alkyl- and 2-alkyl-benzotriazoles are generally prepared by the alkylation of benzotriazole followed by column chromatographic separation.

1-Aminobenzotriazoles can be synthesized by two methods: (i) direct amination of benzotriazole. This method is simple, however, all possible isomers are formed (86JOC979); (ii) Cyclization of 2-hydrazinobenzenediazonium salts. Reductive cyclization of 2-azobenzenediazoniums (**851**) gives compounds (**852**) (Equation (88)). The diazotization of protected 2-hydrazino-anilines (**853**) followed by hydrolysis allows the preparation of 1-aminobenzotriazoles (**854**) (Equation (89)).



Scheme 170



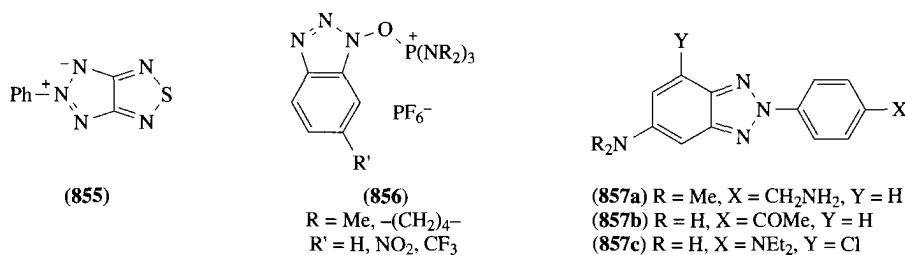
4.01.11 IMPORTANT COMPOUNDS AND APPLICATIONS

1,2,3-Triazoles and benzotriazoles are of great importance in organic synthesis, medicinal chemistry, and industry. Numerous publications have appeared in the decade from 1985–1995.

4.01.11.1 1,2,3-Triazoles and 1,2,3-Triazolines Utilized in Organic Synthesis

4-Aminotriazoles which are appropriately substituted at the C(5)-position are important intermediates for the synthesis of 8-azapurines. These reactions have been reviewed (86AHC(39)117). The pharmaceutically useful acyclonucleosides bearing 1,2,3-triazolines and 8-azapurines have been synthesized (88S879). 4,5-Diaminotriazoles react with 1,2-dicarbonyl reagents to give 1,2,3-triazolo[4,5-*b*]pyrazines. 4,5-Diamino-2-phenyltriazole and sulfur monochloride afford the triazolo[4,5-*c*][1,2,5]thiadiazole (855) (86AHC(40)129). The synthesis of triazolopyridines from triazoles has been described in a review (83AHC(34)79). For further applications of substituted triazoles in preparations of complex heterocycles, see Section 4.01.4.

The synthetic applications of substituted 1,2,3-triazole 1-oxides and 1,2,3-triazolium-1-imides in the preparations of 1,2,3-triazines, 1,3,4,5-oxo- and -thia-triazines, and 1,2,3,5-tetrazines have been discussed in Section 4.01.4.12. Conversions of 1,2,3-triazolines into aziridines either thermally or photochemically were described in detail in CHEC-I (84CHEC-I(5)691) and in a review (84AHC(37)217). Some recent developments are discussed in Section 4.01.5.



4.01.11.2 Benzotriazoles Utilized in Organic Synthesis

Benzotriazole has been developed as an inexpensive and highly efficient synthetic auxiliary. Two-step reaction sequences consisting of Mannich condensation of benzotriazole, an aldehyde, and an NH compound, followed by displacement of the benzotriazole moiety by a nucleophile, have been shown to be convenient and high yielding methods for the *N*-substitution of nitrogen compounds. Benzotriazole has been widely used in the alkylation of primary and secondary amines, amides, and thioamides, in the amidoalkylation of various nucleophiles, in the preparation of ethers and sulfides, and in synthesis of other nitrogen-containing heterocycles. Benzotriazole has also been used for stabilizing carbanions. The synthetic application of benzotriazole and its derivatives is described in detail in Section 4.01.7 and in several reviews.

1-Hydroxybenzotriazole and its derivatives are of importance in peptide synthesis (see 4.01.7.1). Phosphorus-based peptide coupling reagents (**856**) have been widely used either in solution or in solid-phase <90TL205> peptide synthesis. Endothiopeptides have been obtained using (**856**) promoted coupling between Fmoc-protected amino monothio acids and amino acid or peptide esters <91TL7617>. Compounds (**856**) also activate the ambident nucleophilic monothio acid group as a thiocarbonyl functionality, and are therefore suitable for use in thioacylations to thioamides <94JOC1257>. 1-Chlorobenzotriazole, a versatile oxidizing agent, reacts with a variety of functional groups under different conditions <90MI 401-02>. 1-Chlorobenzotriazole has also been used as a chlorinating agent <82JOC4895>.

Oxidation of 1-aminobenzotriazole with lead tetraacetate has been widely used in organic synthesis as a convenient and high yielding method for generating benzyne <89JOC4019>. A modified procedure for generating benzyne from 1-aminobenzotriazole by the use of two syringe pumps to effect simultaneous addition has been developed and applied to benzyne-oxazole Diels-Alder cyclo-additions <88JOC5595, 90JOC929>. Benzotriazole has been used as a catalyst for the preparation of addition products of epoxide oligomers and (meth)acrylic acid <91GEP4004091>.

4.01.11.3 1,2,3-Triazoles and Benzotriazoles Utilized in Analytical Chemistry

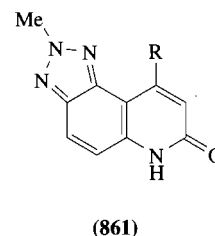
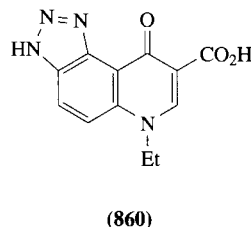
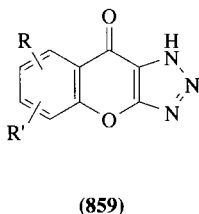
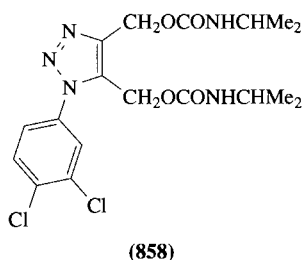
A simple but accurate potentiometric method for the estimation of mercaptans in 0.01 M perchloric acid is based on their quantitative oxidation to disulfide with 1-chlorobenzotriazole. A backtitration procedure can also be used <90MI 401-03>.

2-(*p*-Aminomethylphenyl)-5-amino-2*H*-benzotriazoles (**857a**) are highly sensitive fluorescence derivatization reagents for carboxylic acids and have been used for the determination of carboxylic acids in HPLC. The detection limit for carboxylic acids is 15 fmol per injection <89CPB831>. 2-(4-Acetylphenyl)-5-amino-2*H*-benzotriazole (**857b**) shows a much higher ratio of fluorescence intensity in organic solvent to water (F_o/F_w) than 8-anilino-1-naphthalenesulfonate. A water-soluble derivative (**857b**) has been used in drug-protein studies <89CPB1005>. 7-Chloro-2-(*p*-diethylaminophenyl)-5-aminobenzotriazole (**857c**) is useful as a fluorescence probe for basic drug- α_1 -acid glycoprotein-binding measurements <89CPB1009>. *S*-(–)[4-(1-Aminoethyl)naphthyl]-6-methoxy-*N*-methyl-2*H*-benzotriazolyl-5-amine dichloride has been reported as a fluorescence chiral derivatization reagent for carboxylic acids in HPLC studies <89MI 401-03>.

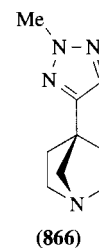
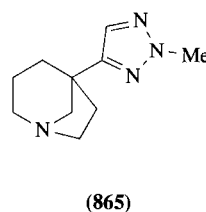
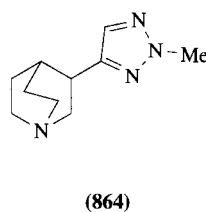
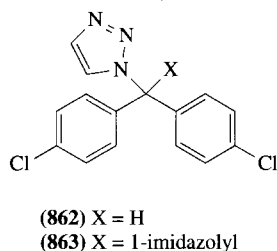
4.01.11.4 Medicinal Applications

Many 1,2,3-triazoles and benzotriazoles have been reported to show various biological activities and have therefore found applications in medicinal chemistry. *In vitro* antileukemic and antitumor activities of 1-aryl-1,2,3-triazole-4,5-dimethanol-4,5-bis(isopropylcarbamates) (e.g., **858**) have been evaluated. The cytotoxic activity of compound (**858**) has been tested on HL-60, a human myeloid cell line, and YAC-1, a mouse lymphoma cell line. The compound kills 75% of the cells in 7 days when used at 10×10^{-6} M <90JHC687>. Some benzopyrano[2,3-*d*]-1,2,3-triazol-9-ones (e.g., **859**) show antiallergic activity by the rat passive cutaneous anaphylaxis screen. The most potent compounds, 6-mesyloxy-9-oxobenzopyrano[2,3-*d*]-1,2,3-triazole and its 5-methyl homologs, are ten times more potent than disodium cromoglycate <83JMC251>. These triazoles also show combined H_1 -antihistamine and mast cell-stabilizing properties <86JMC2262>. 6-Ethyltriazolo[4,5-*f*]quinolin-9-one-8-carboxylic acid (**860**) shows selective activity against *Escherichia coli* (MIC 12.5 μ g/ml) in *in vitro* tests <89FES619>. 1,2,3-Triazolo[4,5-*f*]quinolines (**861**) are also reported as new bioisosters of

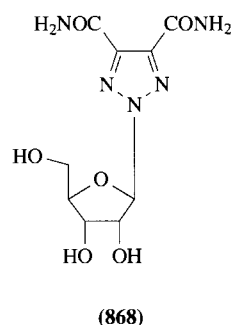
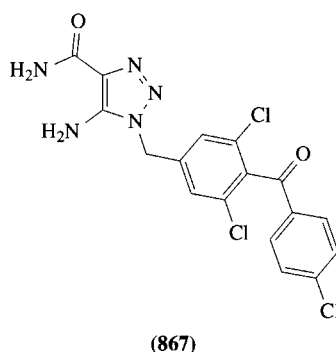
known pyrazolo-, pyrrolo-, and imidazo-quinolines possessing various biological activities <89FES609>. The anti-inflammatory effects of 1-phenyl-1,2,3-triazole derivatives have been reported.



Some 1,2,3-triazole derivatives are found to be highly active aromatase inhibitors, for example, compounds **(862)** and **(863)** exhibit EC_{50} potencies for aromatase inhibition at low nanomolar levels ($0.018 \mu M$), which are at least as high as other nonsteroidal aromatase inhibitors reported previously <90JMC416>. 2-Methyl-4-(quinuclidin-3-yl)-1,2,3-triazole **(864)** has a much higher muscarinic activity than its 1-methyl- and 3-methyl analogs <92JMC1280>. Other azabicyclic triazole-based muscarinic receptor ligands (e.g., **(865)** and **(866)**) are also found to be potent and efficacious <92JMC2392>.

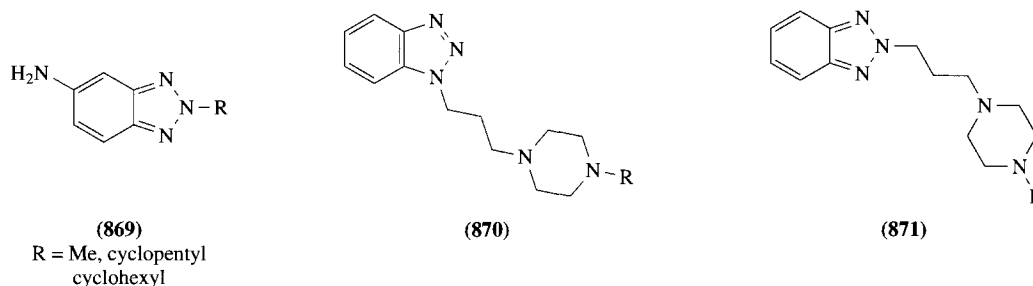


Substituted 5-amino-4-carbamoyl-1,2,3-triazole **(867)** is an anticoccidiostat, but displays unacceptable tissue residues. Compound **(867)** has also been found to have antiproliferative activity in several disease models and to possess antimetastatic activity in a model of ovarian cancer progression <91JMC2843>. 1,2,3-Triazol-2-ylribonucleoside containing two carbamoyl groups **(868)** shows extensive inter- and intra-molecular hydrogen bonding both in solution and in the solid state. Although it exhibits no significant cytotoxic properties against L1210 and WI-L2 leukemia cells in culture, it is found to be an inducer of cellular differentiation in HL-60 cells at $32 \mu M$ concentration <90JMC336>.



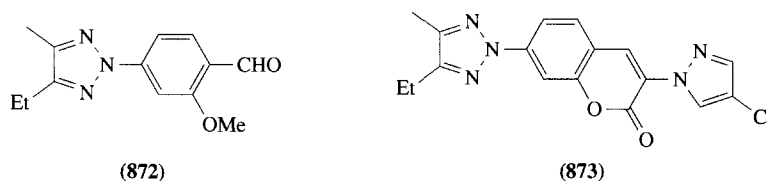
Some 2-alkyl-5-amidobenzotriazoles **(869)** are characterized by interesting antimicrobial activities. Their *in vitro* antimicrobial activity against Gram-positive and Gram-negative and *Candida albicans* are correlated with the corresponding partition coefficients <90EJM343, 92EJM161>. 1- and 2-[3-(1-Piperazinyl)propyl]benzotriazoles **(870)** and **(871)** have been tested for their antiserotonergic, antiadrenergic, and antihistaminic *in vitro* activity, as well as for their analgesic *in vivo* action. The compounds bearing a phenyl ring on the 4-piperazine nitrogen show a pharmacological profile

similar to that of the antidepressant, trazodone <93EJM969>. A nitrotriazole derivative is the active ingredient in a radiation sensitizer which has been used to accelerate inactivation of intractable hypoxic cells in a malignant tumor by irradiation <87EUP212558>.



4.01.11.5 Dyestuffs and Fluorescent Whiteners

Several disperse azo dyes and pigments have been prepared by coupling diazotized amino derivatives of 1,2,3-triazole with various reagents <82MI 401-01>. Triazole and benzotriazole have been used as brighteners for electroplating a tin-lead alloy <88JAP88128194>, and as components of polishing agents for optical glass <89JAP89287190>. 2*H*-1,2,3-Triazoles (872) and (873) are useful fluorescent whitening agents for thermoplastic resins <82GEP3104992, 87GEP3527530>.



4.01.11.6 Corrosion Inhibition

Benzotriazole and its derivatives have found widespread use as corrosion inhibitors for copper and its alloys. A huge number of patents have appeared since the mid-1980s. Polymeric tapes or sheets coated with adhesive containing acrylic polymer emulsions of benzotriazole and tripolyphosphate salts can protect copper and copper alloys against discoloration <87JAP8707780>. Benzotriazoles with an alkyl group, especially *n*-butyl, at the benzene ring have been used to inhibit corrosion of copper in aqueous systems <88EUP258021>. An inhibitor mixture consisting of triethanolamine, NaNO₂, benzotriazole, sodium salicylate, and polyethylene glycol protects copper, solder, brass, steel, cast iron, and aluminum in heating systems <81JAP81108882>.

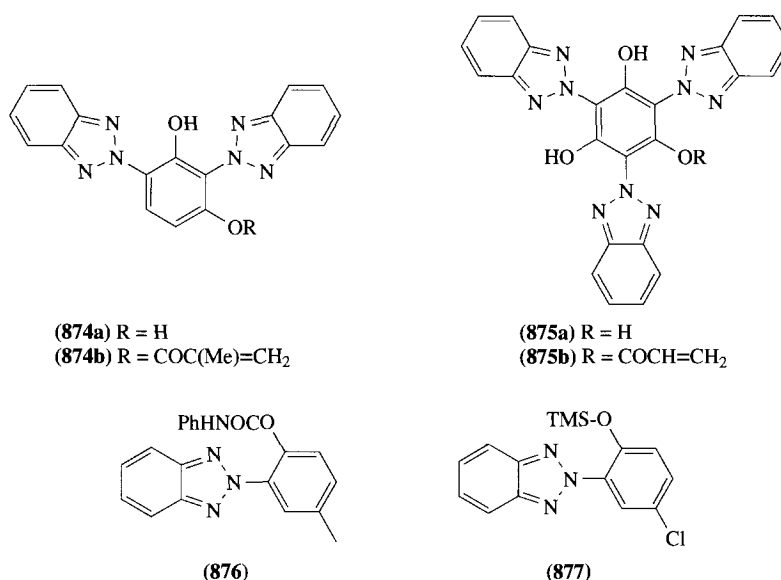
5-Alkoxybenzotriazoles are effective corrosion inhibitors of copper and copper alloy <90EUP397455>. The anticorrosion of benzotriazole on copper has been studied by surface-enhanced Raman spectroscopy, ellipsometry, and electrochemical techniques <86MI 401-01>.

Benzotriazole has also been used as an additive in anticorrosive coatings for silver layered on plastic film <89JAP8909733>. An anticorrosive, electromagnetic wave-shielding coating containing tolyltriazole has been developed for aluminum <91EUP437979>.

4.01.11.7 Photostabilizers

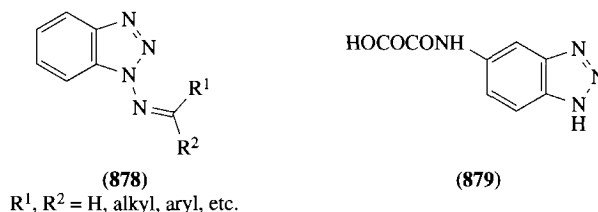
Hydroxyphenylbenzotriazoles have long been used as photostabilizers of polymers. For further details, see the 1990 review by Rabek <B-90MI 401-01>. The photostabilizing mechanism of *o*-hydroxyphenylbenzotriazoles has been well investigated <87JPC1408>. The absorption and fluorescence spectra of these photostabilizers have been the subjects of many publications (see Section 4.01.2.9). There are a great number of commercially available 2-(*o*-hydroxyphenyl)benzotriazoles. They have been widely used in the photostabilization of polypropylene, polystyrene, polyacrylates,

PVC, polyamides, unsaturated crosslinked polyesters, ABS, and wood (B-90MI 401-01). Di- and tri-benzotriazole photostabilizers, such as (874) and (875) are synthesized from 2-nitrobenzenediazonium salts and an excess of 1,3-dihydroxybenzene or 1,3,5-trihydroxybenzene (85MI 401-01). The dibenzotriazole derivatives (874b and 875b) can be used as polymerizable acrylic UV absorbers (84PB237). A few *ortho*-urethane and -trimethylsilane substituted 2-phenylbenzotriazoles (876 and 877) show similar photostabilization activity (B-90MI 401-01). Weather resistance of low-density polyethylene is improved by the addition of a benzotriazole-type photostabilizer (90MI 401-04).



4.01.11.8 Photographic Applications

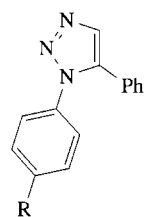
1-Iminobenzotriazoles (878) have been used to form a charge-transporting layer to give an electrophotographic photoreceptor (88JAP88292143). 2-Aryl-2*H*-benzotriazoles are resistant to heat and are useful as antireflective absorbing agents which increase the accuracy of photoresist patterning. Thus, they have been used as additives in photosensitive resins (91JAP9164753). The benzotriazole derivative (879) is a useful fog inhibitor in the rapid processing of Ag(Br, Cl, I) photographic material at high temperature which gives an image with high sensitivity (89JAP89239551).



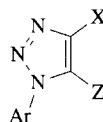
4.01.11.9 Agrochemicals

Several 1,2,3-triazole derivatives of aryloxyalcanoic acid (880) show interesting antimicrobial, insecticide, and herbicide activities (83JHC1729). Benzotriazoles containing branched alkyl substituents at the N atoms (e.g., *N*-cyclopentyl, -cyclohexyl and —CHMe(CH₂)_{*n*}COR, R = OH, OEt and NH₂) are potential plant auxins (88FES29). 1,2,3-Triazole derivatives (881) are pesticides with insecticidal and acaricidal activity, showing LD₅₀ of <300 ppm against brown rice hoppers and the larvae of ticks and sheep blowflies (90EUP400842). 1-Aminobenzotriazole and its *N*-alkyl derivatives are potent inhibitors of cytochrome P450-dependent monooxygenase activity in hepatic microsomes

of guinea pigs <90MI 401-05>. The synergistic effects of 1-aminobenzotriazole on the phytotoxicity of chlorotoluron and isoproturon in a resistant population of black-grass is also reported <87MI 401-02>.



(880)
R = oxyalcanoic



(881)
Ar = Ph, pyridyl, pyrimidyl
X,Z = halo, CN, NO₂, CONH₂, SOR
SO₂R, SR, OR, etc.

4.01.11.10 Other Industrial Applications

Benzotriazole, as an antiwear additive for lubricating oil emulsions, can increase the rolling efficiency of a copper alloy rolling tool <87JAP87285991>. A mixture of higher alcohols and benzotriazole in water has been used as a polishing agent to improve the glass surface quality and prevent the loading of diamond wheels <89JAP89287190>. Triazole and benzotriazole have been included in heat-storage compositions <89JAP89161082>. 2*H*-1,2,3-Triazole derivative-based nonlinear optical materials have been reported <89JAP89187538>. Picryl-1,2,3-triazoles and 4-nitro-1- and -2-picryl-1,2,3-triazoles are powerful and sensitive explosives <89JPC1000>.

4.02

1,2,4-Triazoles

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University College London, UK

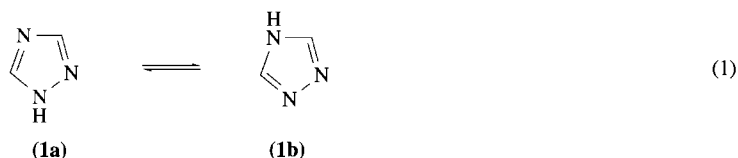
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4.02.1 INTRODUCTION

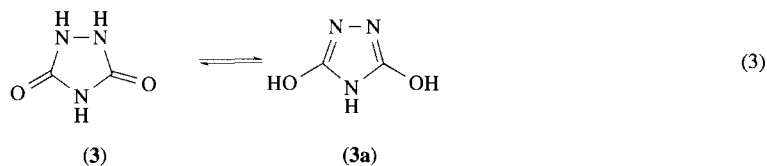
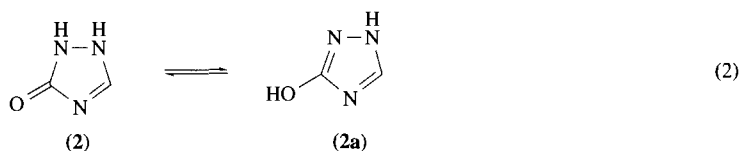
This chapter describes the chemistry of the simple, nonfused 1,2,4-triazoles including those triazoles annelated by a saturated ring. A résumé of the most important points discussed by Polya in the corresponding chapter in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-1(5)733> has been made and a substantial number of the earlier references have been retained, but this account will concentrate on those advances that have been made in this area since the early 1980s. A comprehensive review of 1,2,4-triazole was published in 1981 <81HC(37)1>.

1,2,4-Triazole can be considered to exist in a tautomeric equilibrium between **(1a)** and **(1b)**, in which the hydrogen is transferred from the hydrazine to amine nitrogen (Equation (1)). The chemistry of 1,2,4-triazole suggests that **(1a)** predominates, while *ab initio* theoretical studies <90JPC5499> and a temperature dependent ¹H NMR study <84JCS(P2)1025> suggest that it is the exclusive form.

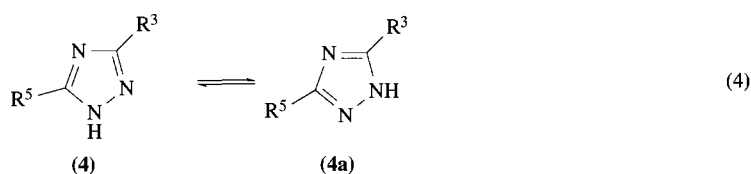


1,2,4-Triazole has also been called *s*-triazole, to distinguish it from the isomeric 1,2,3-triazole, termed *v*-triazole. In this chapter the *s* will be omitted and the term triazole will imply the *s* structure.

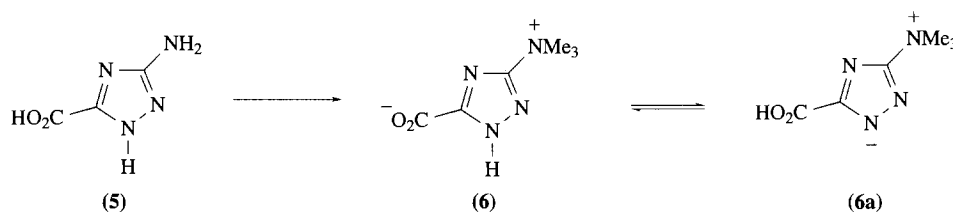
Partially or fully reduced triazoles are relatively unstable and have not aroused great interest except for those with exocyclic double bonds, which retain the potential aromatic character of the parent triazole. Compounds such as triazolinone (**2**) and 3,5-dioxo-1,2,4-triazolidine (urazole) (**3**) will be treated as triazoles, since they can be written in the tautomeric triazole forms **(2a)** and **(3a)** (Equations (2) and (3)).



In C-substituted triazoles, prototropy between the nitrogen centres to give the different tautomers **(4)** $\rightleftharpoons$ **(4a)** (Equation (4)) can affect the outcome of chemical reactions. The proportion of each tautomer will depend on the medium, and the nature of the substituents and the reaction conditions can also be important. Prototropy becomes more complex with substituents able to donate protons to nitrogen. Hydrogen bonding between substituents and annular nitrogen atoms or between NH groups and annular nitrogen can also produce tautomers with different energies.

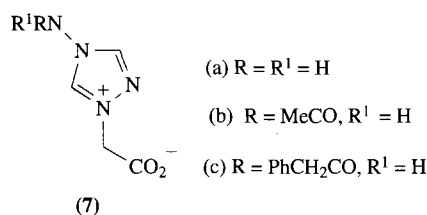


Quarternization of the triazole (5) gave the betaine (6) which is in tautomeric equilibrium with (6a) (Scheme 1).

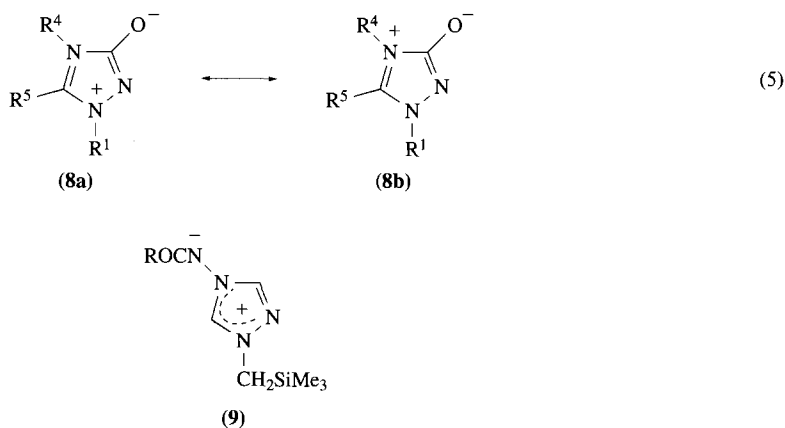


Scheme 1

A number of betaines of type (7) have been prepared as potential antibiotic analogues of β -lactams and were found to inhibit serine and aspartic proteases [92EJM193, 93JPP(45)466].



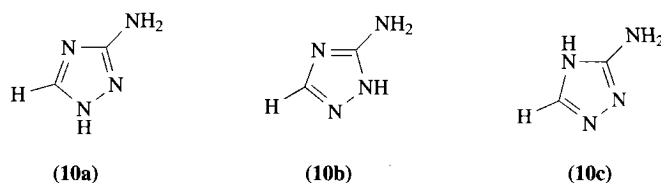
Substitution on N(1) and N(4) can produce mesomerically stabilised zwitterions when the negative charge can reside on an exocyclic heteroatom or carbanion. A large number of compounds of this type (e.g., (8a,b)) have been prepared (Equation (5)) [76AHC(19)3]. The zwitterion (9), in which the R group is a polymer $-(CH_2CH_2)-$, has been reported [90ZC285].



4.02.2 THEORETICAL METHODS

Theoretical studies favour the 1H-structure (1a) for triazole rather than the more symmetrical 4H-structure (1b). Calculations suggest that the destabilization of (1b) is due to the contiguous heteroatoms of the same hybridization type [86JA3237, 89JOC3553, 90JPC5499]. The 6-31G** level of *ab initio* calculation is considered to be needed to provide reasonable estimates of tautomeric equilibrium energy differences, whereas calculations at the 3-21G level are adequate for geometry optimization [90JPC5499]. Correlation effects, using Møller–Plesset perturbation, slightly reduce the energy separation between the two tautomers but zero point energy, obtained from the harmonic frequency at 3-21G, can be neglected. In the gas phase the energy difference between (1a) and (1b) was $-26.3 \text{ kJ mol}^{-1}$. The addition of terms for the solvent greatly reduces this difference in energy but, at -9.5 kJ mol^{-1} , it remains in favour of (1a). The current interest in triazoles for a wide

range of pharmaceutical applications reinforces the importance of the detailed structure of these compounds. *Ab initio* calculations at the 3.21G and 6.31G** levels on 3-amino-1,2,4-triazole, a compound of considerable biological interest, suggest that **(10a)** is about 1.7 kJ mol⁻¹ more stable than **(10b)** with **(10c)** about 30 kJ mol⁻¹ higher in energy <92JCS(P2)1681>. These values are modified in the presence of solvent and different predictions are given by different models, but **(10a)** remains the most stable structure. This is contrary to experiments in which **(10b)** appears to be preferred. HMO calculations for triazole derivatives have been reported <88M341>. The energies of various conformations of the NH₂ group in 4-aminotriazole have been calculated at the 3-21G level <89AJC1623>. (**(10a)**, **(10b)**, and **(10c)**).



Theoretical calculations for the dipole moment of the 1H- (**1a**) and 4H-tautomers (**1b**) gave values for the 1H-tautomer that were closely in agreement with the observed value of triazole, whereas the calculated values for the 4H-tautomer were much higher. *Ab initio* calculations made at the 6.31G* level gave a good agreement with the observed dipole moment of 2.71D for 3,5 bis(trifluoromethyl)triazole (see Section 4.02.4.5).

4.02.3 EXPERIMENTAL STRUCTURAL METHODS

4.02.3.1 X-ray

X-ray crystallographic structural analyses of triazole are in accord with the (**1a**) structure, with hydrogen bridges between N(1) and N(4) of neighbouring rings. The bond lengths indicate that N(1)—H is the hydrogen donor <65MI 402-01, 69AX(B)135>. With the growing interest in triazoles as high energy propellants, herbicides, fungicides, and as components of drugs for a variety of clinical conditions, crystallographic studies have been reported on a wide range of derivatives <83JHC97, 83MI 402-01, 85ACS(A)711, 88AX(B)672, 88AX(C)1673, 88AX(C)2187, 89AX(C)653, 89AX(C)782, 89CJC198, 90AX(C)1141, 91AX(C)1866, 91AX(C)2476, 92AX(C)184, 92AX(C)1265, 92AX(C)1540, 92AX(C)1682, 92AX(C)1683, 94AJC309>. The molecular geometry of 1,2,4-triazole at -160°C is shown in Table 1, and that for 3,4'-triazolyltriazole (**11**) in Table 2. The two triazole rings in (**11**) are virtually coplanar <91AX(C)1866>, unlike the 4,4'-derivative in which they are approximately orthogonal. The bond dimensions in the two triazole rings of (**11**) illustrate the change in structure when N(4) is substituted. In the 4-hydroxy derivative (**12**), the crystal is composed of both (**12a**) and the tautomer (**12b**), packed so that one hydrogen is shared between the N(2) atoms of two molecules and one hydrogen is shared between the oxygen atoms of two molecules (Equation (6)) <89AX(C)782>. When a series of N- and C-substituted triazoles was compared with the parent compound it was found that substitution had little effect on the ring geometry <83MI 402-01>. Triazole exists as the expected 1H-tautomer in a 1 : 1 complex with 1-(2,4-dimethylphenyl)but-2-yne-1-ol <87CL2317>.

Table 1 Molecular geometry of 1,2,4-triazole at -160°C.^a

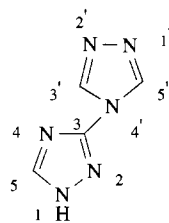
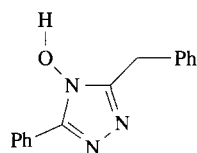
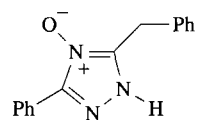
Angle (°) ^b		Bond	Bond length (pm)
5—1—4	110.2	1—2	135.9
1—2—3	102.1	2—3	132.3
2—3—4	114.6	3—4	135.9
3—4—5	103.0	4—5	132.4
4—5—1	110.1	5—1	133.1
		N1—H	103.0
		C3—H	93.0
		C5—H	93.0

^a<69AX(B)135>. ^bNumbers refer to atom centres as conventionally numbered in 1,2,4-triazole.

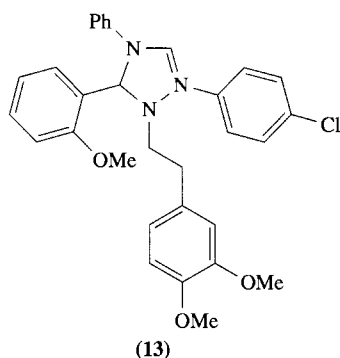
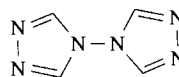
Table 2 Molecular geometry of 3,4'-triazolyltriazole (**11**).^a

Angle (°) ^b		Bond	Bond length (pm)
5—1—2	110.4	1—2	136.3
1—2—3	100.3	1—5	132.2
2—3—4	117.5	2—3	130.9
3—4—5	101.0	3—4	134.3
4—5—1	110.7	4—5	132.5
2—3—4'	121.2	1'—2'	139.2
3—4'—3'	127.3	1'—5'	129.8
3'—4'—5'	104.9	2'—3'	129.7
4'—3'—2'	110.8	3'—4'	135.7
3'—2'—1'	106.7	4'—5'	135.7
2'—1'—5'	107.3	3—4'	140.7
1'—5'—4'	110.3		

^a<91AX(C)1866>. ^bNumbers refer to atom centres as numbered in structure (**11**).

**(11)****(12a)****(12b)****(6)**

An x-ray crystallographic structure for the 4,5-dihydro derivative (**13**) has been reported <92AX(C)342>.

**(13)****(14)**

4.02.3.2 Electronic Spectra

The electronic spectra of representative 1,2,4-triazoles have been tabulated <61CRV87, B-76MI 402-01>. The parent triazole absorbs at 210 nm and does not exhibit intense $n \rightarrow \pi$ bands at longer

wavelengths. Aryl substituents cause a bathochromic shift that varies with the site of substitution in the order 3 (or 5) > 1 > 4 <54JCS4256>.

Hydroxytriazoles and their tautomeric triazolinones have a common mesomeric anion and the spectra change in the presence of base. The predominately dioxo structure of 4-phenyl-1,2,4-triazolidine-3,5-dione is supported by the electronic spectrum.

N-acylation of the triazole nucleus results in a bathochromic shift whereas acylation of substituent amino groups has little effect on the spectrum <55CR(241)1049>.

3,4'-Triazolotriazole (**11**) has an absorption maximum at 283 nm <91AX(C)1866> whereas the 4,4'-triazolotriazole (**14**) has an absorption maximum at 215 nm <77CSC503>. This difference reflects the difference in the crystal structures of (**11**) and (**14**), the former having the two rings virtually coplanar whereas in the latter they are almost orthogonal.

4.02.3.3 IR and Raman Spectra

A detailed comparison of the IR absorptions of triazole, halotriazole and their salts has been made <70KGS248>. The IR spectra of *N*-unsubstituted triazoles shows the involvement of hydrogen bonding which leads to a variety of effects <69JCS(C)1056, 71PMH(4)324, 77AJC421>. A study of the vibrational spectrum of 4-methyl-1,2,4-triazole, its 3,5-dideuterio analogue and their hydrochloride salts has been reported and stretching frequencies and ring vibrational modes have been identified <87CJC2509>.

N-unsubstituted triazoles show absorption in the region 2400–3200 cm⁻¹. A detailed study of *N*-unsubstituted triazoles has been carried out and differences in intensities of various bands have been recorded, probably originating in different modes of hydrogen bonding <71PMH(4)272>.

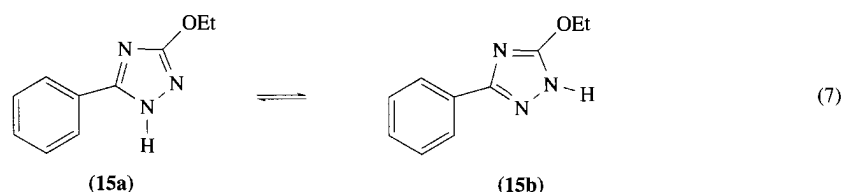
IR spectroscopy has been used to study the structures of urazoles, triazolinones <66T213>, and triazolinethiones <71JCS(C)1016>. *N*-alkylation reduces the problem of tautomeric structures and early views in favour of the oxo and thio rather than the hydroxyl and thiol forms have been confirmed, although there are exceptions <73CPBI342>.

IR data and force constant calculations suggest that the 3-nitrotriazole is preferred to the tautomeric 5-nitrotriazole structure <73KGS707>. In *N*-unsubstituted triazoles, protonation on N(1) or N(2) is favoured over protonation on N(4) but the choice between N(1) or N(2) depends, in general, on which is nearest to the best electron donating substituent on C(3) and C(5) <75CPB955>. Solvents and substituents capable of stabilizing one tautomer by intramolecular bonding can affect the choice of proton site.

4.02.3.4 NMR and Quadrapole Spectra

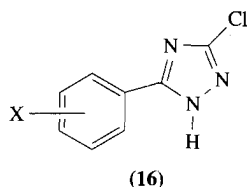
Proton NMR studies carried out in the late 1960s, had shown that the spectrum of (**1**) was temperature dependent, the H(3), H(5) protons being observed separately at -34°C <68JOC2956>. A 1984 detailed study of the temperature dependent ¹H NMR spectrum gave no evidence for the presence of the 4-H tautomer <84JCS(P2)1025>. At 10°C in THF-*d*₈ two signals of equal intensity were observed for H(3) (δ 8.63) and H(5) (δ 8.07), while at -70°C the upfield signal had split into a doublet with a splitting independent of the field strength, indicating a coupling to NH. These findings are largely in accord with earlier ¹H NMR temperature dependent studies <68JOC2956>, but differ from the conclusions reached by ¹⁵N and ¹⁴N NMR studies. In the earlier ¹⁴N NMR experiments, only one broad signal was observed for all three nitrogens and interpretation depended on accounting for the chemical shift <72T637>. The later ¹⁵N NMR study showed two types of nitrogens, a combined signal for N(1) and N(2) and a signal for N(4), and it was suggested that there might be a significant contribution (up to 0.08 mole fraction) from the 4-H tautomer (**1b**) <82JOC5132>. The subsequent ¹H NMR studies make this suggestion very unlikely.

Signals for both of the tautomers (**15a**) and (**15b**) can be observed in the ¹³C NMR spectrum at 29°C, the peaks having coalesced at 50°C to give seven signals with C(3) at δ 167.8 and C(5) at δ 153.4 (Equation (7)) <82JHC1215>. From the integration at 29°C, the ratio of (**15a**) to (**15b**) is 7:3.



The data for the ^1H and ^{13}C NMR spectra of 5-aminotriazole derivatives have been collected <85MRC194>.

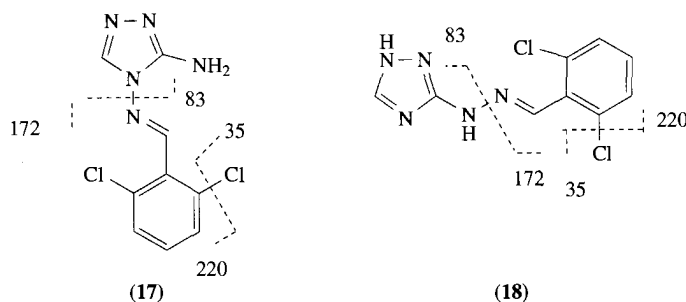
The ^{35}Cl nuclear quadrupole resonance spectrum of 3-chloro-5-aryltriazoles (absorption at 36.80 ± 0.4 MHz) is in accord with the tautomeric structure (16) <82CHE637> and in agreement with earlier studies. ^{14}N Quadrupole coupling tensors have been determined for triazole in the solid state and agree with theory and with earlier determinations <85CPH103>.



4.02.3.5 Mass Spectra

The mass spectrum of triazole, assuming autropy involving the identical 1H and 2H tautomers, leads to an interpretation of the data that assigns negligible weight to the 4H tautomer <72OMS(6)1139>. A study of alkyltriazoles concluded that the observed fragmentation patterns favour the presence of 1H, 2H, and 4H parent molecules <73OMS(7)57>. The mass spectrum of triazole supports an interpretation based on the 1H form <80OMS(15)172>.

Mass spectral studies can distinguish between the N(4) and NH_2 substitution of 3-aminotriazole in compounds (17) and (18) <88JHC565>. In (17) the base peak is at m/e 220, whereas this fragment is very small in (18), the base peak being at m/e 84.



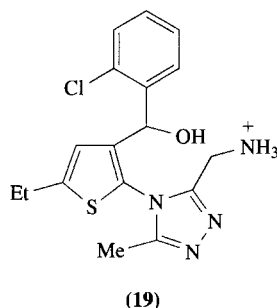
The mass spectra of a number of *N*-substituted isomeric derivatives based on the 3-thiomethyl-5-aminotriazole structure have been correlated with the type of cleavage of the substituent <83JCR(S)126>.

4.02.4 THERMODYNAMIC ASPECTS

4.02.4.1 Physical Properties

Triazole melts at $120\text{--}121^\circ\text{C}$ and boils at 260°C . It has a density of 1.132 and a specific conductivity of about $10^{-10} \Omega^{-1} \text{cm}^{-1}$, of the same order as imidazole. Triazole dissolves readily in water and ethanol but is only slightly soluble in ether. Substitution on N(1) usually lowers the melting point; this effect is usually much smaller for substitution at N(4), although 4-aminotriazole has a melting point of $84\text{--}86^\circ\text{C}$. 3-Aminotriazole has a melting point of 159°C and the 3-thiol derivative of 221--

224 °C, both of which probably reflect substantial hydrogen bonding in the crystal. Triazole gives the *N*-1-(2,4-dinitrophenyl) derivative with 2,4-dinitrofluorobenzene in DMSO <66AJC1935>. The derivative (19) exhibits atropisomerism, existing in two crystalline forms due to restriction around the N(4)—C(2) thiophene single bond <92CPB220>. X-ray structures of both atropisomers have been obtained.

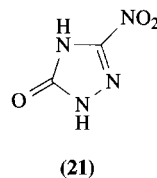
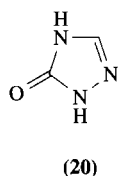


4.02.4.2 Thermochemistry

Estimates of resonance energy by different authors vary in the range 84–206 kJ mol⁻¹, the higher values comparing well with those for pyrazole and appearing more likely <61MI 402-01>. Thermochemical data support the preference of the 1H over the 4H tautomer <69JA796> and the tautomeric preference of the oxo and amino structures <70JA2929>.

The latest thermochemical study on 1,2,4-triazole gives an enthalpy of combustion, $\Delta_c H_m^\circ(298.15 \text{ K}) = -1324.4 \pm 0.3 \text{ kJ mol}^{-1}$ <89MI 402-01>, slightly higher than the previous value, $-1328.9 \pm 1.2 \text{ kJ mol}^{-1}$ <85JCS(P2)811> and in agreement with earlier studies, $-1325.0 \pm 0.9 \text{ kJ mol}^{-1}$ <82MI 402-01>.

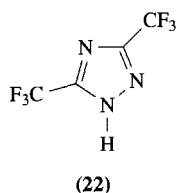
The enthalpies of formation of 5-triazolinone (20) [$-(142.4 \pm 0.7) \text{ kJ mol}^{-1}$], 3-nitro-5-triazolinone (21) [$-(129.4 \pm 1.1) \text{ kJ mol}^{-1}$] and the sodium and potassium salts of (21) have been determined <91JCT1169>. Compounds of this type are of interest as potential explosives with good handling properties.



4.02.4.3 Acidity

Triazole has pK_a values of 2.19 (as a base) and 10.26 (as an acid). A representative selection of acidity data <B-76MI 402-02> has been abstracted mainly from papers that consider the applicability of the Hammett treatment to the pK_a values of triazoles. The Hammett equation is more satisfactory for acidic than basic values of triazoles <65ZC381>. For triazoles with only annular NH as acidic groups the Hammett σ value is 6.00, while for 3-(or 5-) hydroxytriazoles it is 7.62. In both cases σ_m constants are most appropriate <65ZC304>; this is also true for nitrotriazoles <70KGS558>.

The gas phase basicity of 3,5-bis(trifluoromethyl)triazole (22) has been determined by Fourier transform ion cyclotron resonance mass spectrometry as $-50.2 \pm 0.8 \text{ kJ mol}^{-1}$ <94JOC1039>. The proton affinity related to ammonia was calculated as $-60.5 \text{ kJ mol}^{-1}$.



The pK_a acid values of a number of urazole derivatives have been measured in DMSO. The H(1)(2) and H(4) protons of urazole in this medium are of comparable acidity and the pK_a is 13.1. The N(1) and N(4) phenyl and methyl derivatives are more acidic, both substituent groups having surprisingly similar effects <90JOC5806>.

4.02.4.4 Dipole Moments

The observed dipole moment of (1) in dioxan is 10.57×10^{-30} C m and that obtained from the microwave spectrum of the vapour is 9.07×10^{-30} C m. Values have been tabulated <84CHEC-I(5)733 p. 743>. Theoretical calculations for the dipole moment of (1) gave values for the 1H-tautomer that were closely in agreement with the observed value of triazole, whereas the calculated values for the 4H-tautomer were much higher.

4.02.5 REACTIVITY OF FULLY CONJUGATED RING

4.02.5.1 General Considerations

1,2,4-Triazole effectively contains two pyridine type atoms and one pyrrole type nitrogen atom. It is deactivated against electrophilic attack and thus resembles pyridine. Nitration, sulfonation and *N*-oxidation do not occur with simple triazoles. Triazolate anions, however, do react readily with electrophiles, alkylation and acylation being the reactions that have been most investigated. There has been considerable interest in the regiospecific C-metallation of triazole using a variety of *N*-attached directing groups.

Further examples of the ease of exchange of substituents on carbon by nucleophiles under mild conditions have been reported. The reactivity of the ring towards nucleophiles is increased in triazolium cations and mesoionic derivatives.

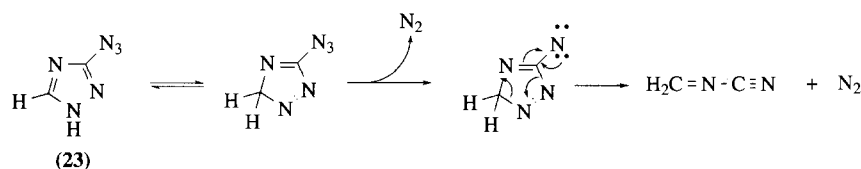
Reactions of substituents will be considered separately unless the reactions involve migration of the group from one ring atom to another or the substitution of the group by another, when they will be considered under the ring atoms concerned.

Tautomeric structures will not be considered separately but will be dealt with in the most appropriate section.

4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) has an extensive chemistry, largely as a dieneophile, and it will be treated separately.

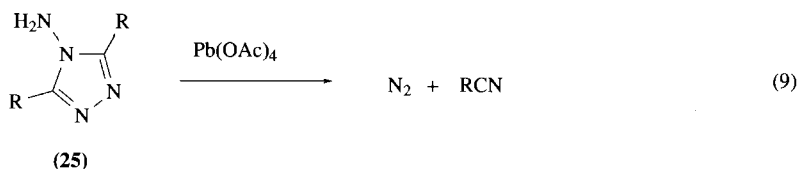
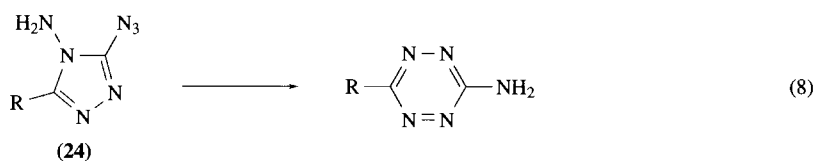
4.02.5.2 Thermal and Photochemical Reactions

Triazoles are thermally stable to ca. 300°C. Ring substituents may undergo changes in structure or position but the ring is unaffected. Gas phase pyrolysis under low pressure of 3-azidotriazole (23) at 800 K results in loss of N_2 followed by ring cleavage and loss of a further N_2 molecule <88CJC2123>. The process occurs by a 1,5-sigmatropic shift in the azido form followed by nitrene formation and ring cleavage (Scheme 2).

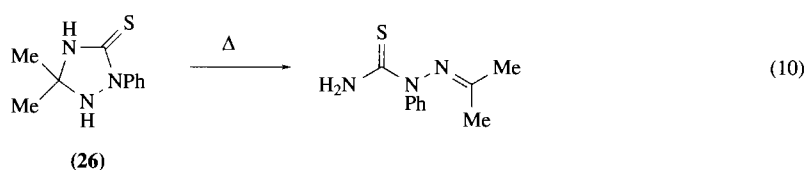


Scheme 2

Azides (24) thermally decompose to tetrazines (Equation (8)) <66TL5369> and 4-aminotriazoles (25) are cleaved by lead tetraacetate oxidation (Equation (9)) <70TL3851>, both presumably via the nitrene as intermediate.



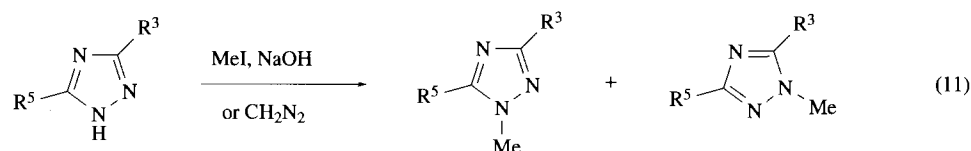
Triazolidones and their sulfur analogues are less thermally stable than triazoles as illustrated by the thermal cleavage of (26) (Equation (10)) <73BCJ2215>.



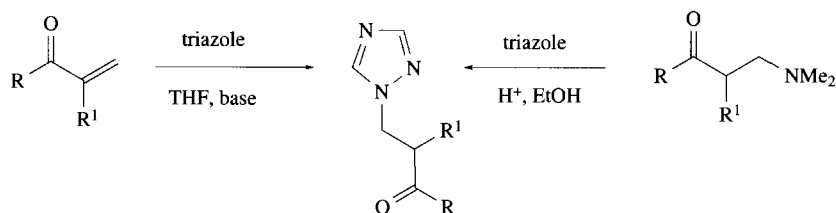
4.02.5.3 Electrophilic Attack at Nitrogen

Alkylation, arylation, and acylation of nitrogen in triazole have all been extensively explored and a wide range of reagents have been used. Both the protonated and deprotonated nitrogen substrates have been used.

N-alkylation of triazole occurs at N(1) rather than N(4) <61CRV87, B-76MI 402-01>. With 3- and 5-substituted triazoles the prediction of substitution between N(1) and N(2) is more difficult <54CI(L)1458, 54JCS3319>. Both products are obtained, the ratio depending on the alkylating agent (Equation (11)). 1-Benzenesulfonyltriazaoles give 1-alkyltriazaoles by treatment with the corresponding sodium alkoxide through nucleophilic attack at the sulfonyl group and alkylation of the resulting sodium triazolate by the alkyl benzenesulfonate produced <93H(36)1253>.

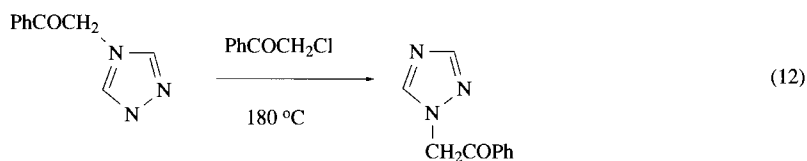


Triazole reacts with α,β -unsaturated ketones under basic conditions or the corresponding Mannich bases under acidic conditions to give *N*-alkylated triazoles (Scheme 3) <87SC809>. A method for the alkylation of N(1) with the 2-phenylethyl group has been described <94JHC1421>.

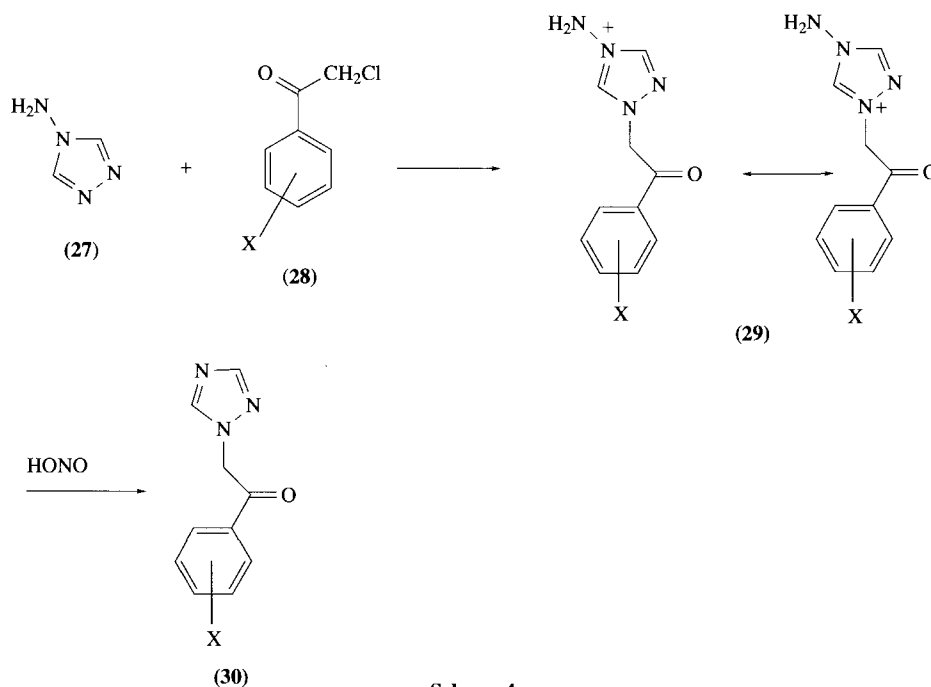


Scheme 3

Treatment of 4-alkylated triazoles with a catalytic amount of the alkylating halide at 150–180°C gave the corresponding 1-alkylated triazole <90CL347>. If triazole is alkylated with a slight excess of alkylating halide under similar conditions then the N(1) alkyl derivative is isolated. This reaction seems general (Equation (12)).

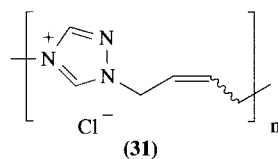


The importance of fluconazole as an antifungal agent has led to a renewed interest in triazole derivatives and a further exploration of methods of alkylation. Reaction of 4-aminotriazole (27) with chloroacetophenones (28) gave the corresponding triazolium cations (29) which could be deaminated to (30) with nitrous acid (Scheme 4) <93JHC1405>.



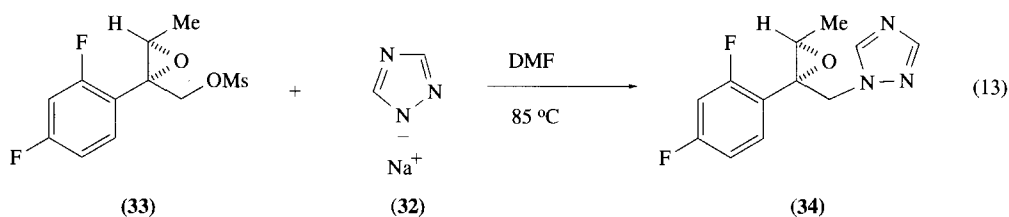
Scheme 4

Triazole is reported to give charged polymers (31) on reaction with 1,4-dichlorobut-2-ene, KOH and TEBAc in dioxane. Under controlled conditions 1,4-bis(*N*¹-triazolyl)-but-2-ene can be obtained <89CHE414>.

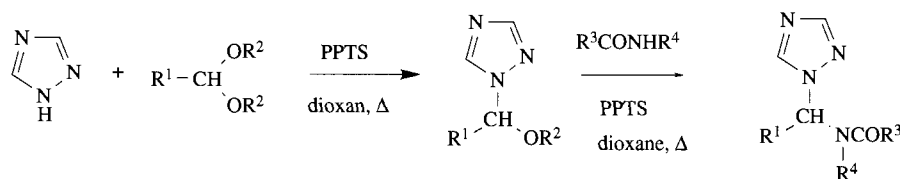


Triazole reacts with bis(trimethylsilyl)methyl chloride in the presence of potassium carbonate in DMF to give 1-bis(trimethylsilyl)methyltriazole <87JOC2314>. This is then used in the preparation of 1-vinyltriazoles.

Sodium triazolid (32) reacts with the mesylate (33) to give (34), an intermediate in the synthesis of compounds with activity against *Candida albicans* infection (Equation (13)) <92CPB562, 92CPB661>.



Triazole reacts with acetals in the presence of ppts in dioxane by alkylation at N(1) with replacement of one of the acetal alkoxy groups <90H(31)2029>. The second acetal group can then be replaced by an amide (Scheme 5).



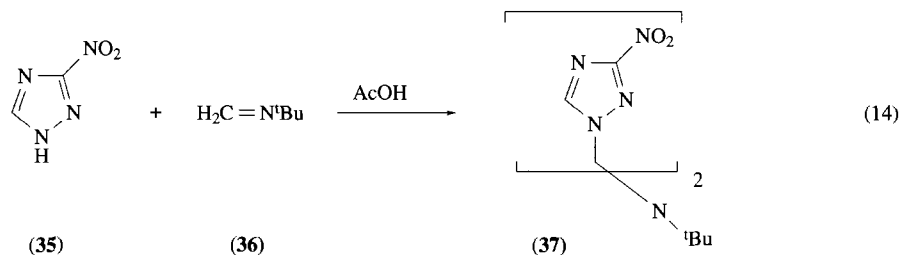
Scheme 5

3-Nitrotriazole reacts with propylene oxide in EtOH at 70°C to give a mixture of N(1) and N(2) alkylated derivatives, attack on the oxirane ring being predominately at the less hindered site <94H(38)481>. The N(2) derivative was converted into a prostaglandin analogue with a triazole ring. Reaction of triazoline with propylene oxide gave a mixture of the N(1) and N(4) alkylated products, the former predominating. Reaction with more complex oxiranes has been described <92CPB661>.

Picryl fluoride undergoes nucleophilic attack by 3-nitrotriazol-5-one to give 3-nitro-1-picryl-triazol-5-one, a potential safe explosive <90JHC575>. This reaction does not occur with picryl chloride, 2-chloro-4,6-dinitrophenol being the unexplained product.

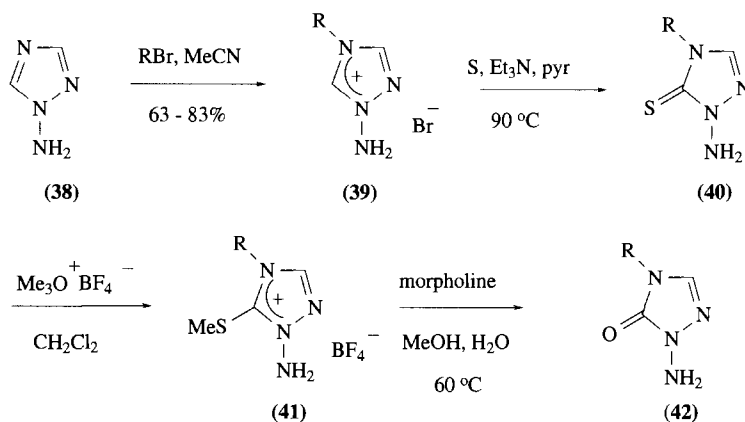
N-alkylation of 3-halotriazoles <75BSF647, 75EGP111074> gives a mixture of all three isomers and the N(4) isomer can be obtained in up to 60% yield if methylation is carried out with dimethyl sulfate in the absence of base.

Treatment of 3-nitrotriazole (35) with *N*-methylene-*t*-butylamine (36) in acetic acid gave the bis-triazole (37), presumably via the methylenamine cation (Equation (14)) <91JOU195>.



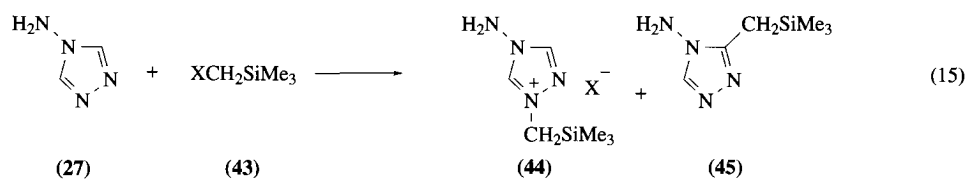
Methylation of 3-aminotriazole gives a mixture of all three annular *N*-methyl derivatives but not the methylamino derivative <73BSF1849>.

1-Aminotriazole (38) can be alkylated at N(4) with benzyl or acyl bromides in moderate to good yield to give the corresponding bromides (39) <89S269, 90S707>. These salts can be converted into the corresponding 5-triazolinethiones (40) and into 5-triazolinones (42) via (41) (Scheme 6).

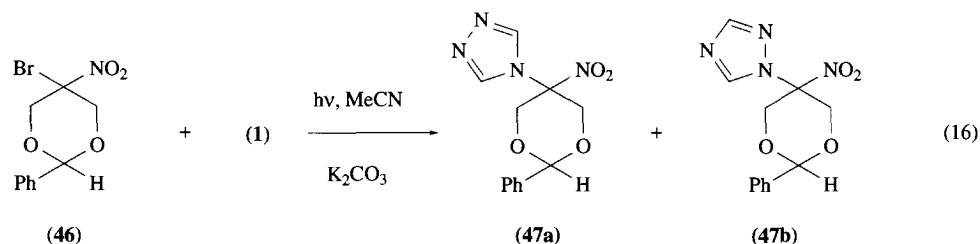


Scheme 6

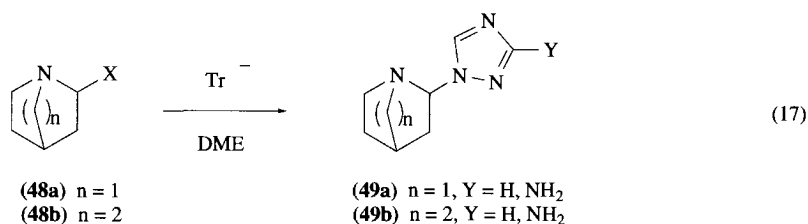
4-Aminotriazole (27) reacts with halomethyltrimethylsilanes (43) to give a mixture of the N(1) (44) and C(3) alkylated (45) derivatives, the former predominating (Equation (15)) <90ZC285>.



Photoirradiation of a mixture of the 1,3-dioxane (46) and triazole in acetonitrile containing potassium carbonate gave a mixture of the N(1) and N(4) derivatives (47a) and (47b) probably by an $S_{\text{RN}}1$ reaction (Equation (16)) <86TL6209>.

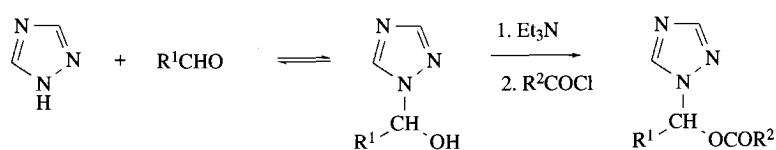


Reaction of sodium triazolidate or 3-aminotriazolidate with the bicyclic amine derivatives (48a) and (48b) gave the N(1) substituted derivatives (49a) and (49b) (Equation (17)) <92JMC2392>.



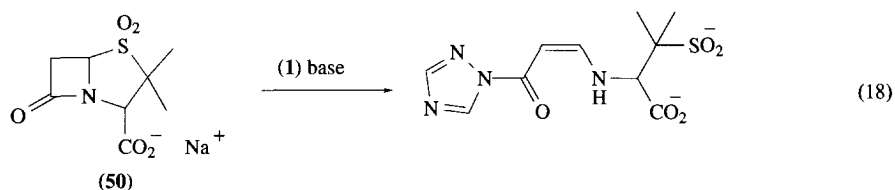
The kinetics of the base-catalysed alkylation of 5-substituted 3-nitrotriazoles with methyl vinyl ketone to give the N(1)-3-butanone derivative has been studied and the reaction was shown to be first order in both mvk and the 3-nitrotriazolium anion <90JOU1170>.

Triazole can undergo nucleophilic addition with aldehydes, but the reaction is reversible and the products cannot be isolated. They can be trapped, however, with acid chlorides (Scheme 7) <90CL351>.



Scheme 7

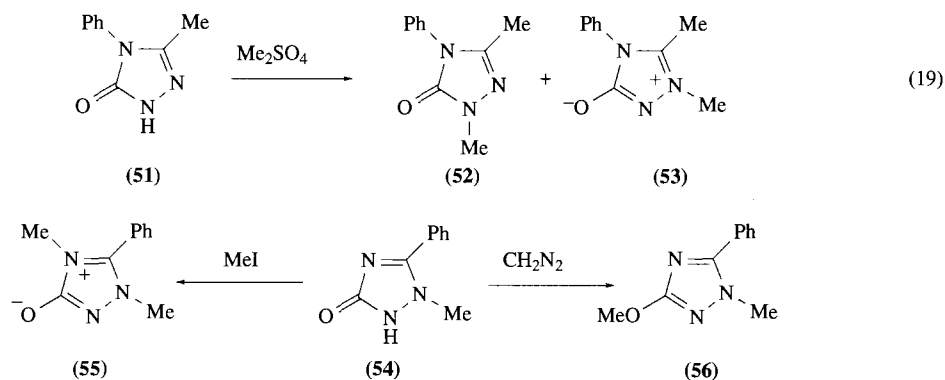
Triazole opens the sulbactam (50) ring systems under weakly basic conditions (Equation (18)) <85CPB4923>. This reaction can be used to determine the concentration of sulbactam in urine and plasma by monitoring the absorbance at 326 nm.



Treatment of 2-aminotriazoline with hydroxylamine sulfate at 70°C for 1 h gave a mixture of 1,5- and 1,3-diaminotriazole <90JHC1109>. The relative amount of the 1,5-isomer increased at lower temperatures and times but the overall yield fell.

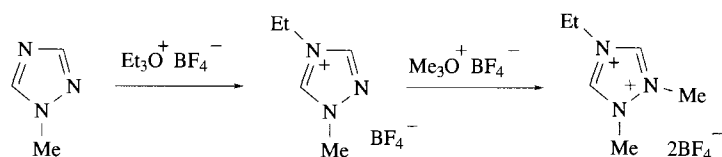
Triazoles with alkyl, aryl, or acyl substituents on N(1) or N(4) can be readily quaternized with powerful quaternizing agents such as trialkyloxonium tetrafluoroborates. Quaternization takes place such that maximum separation of the substituents occurs.

Alkylation of 3-methyl-4-phenyltriazolin-5-one (**51**) with dimethyl sulfate gave a mixture of (**52**) and the mesoionic compound (**53**) (Equation (19)) $\langle 66\text{AC(R)199} \rangle$ whereas the isomer (**54**) gave the mesoionic compound (**55**) with methyl iodide but the methoxytriazole (**56**) with diazomethane (Scheme 8) $\langle 76\text{CPB1336} \rangle$.



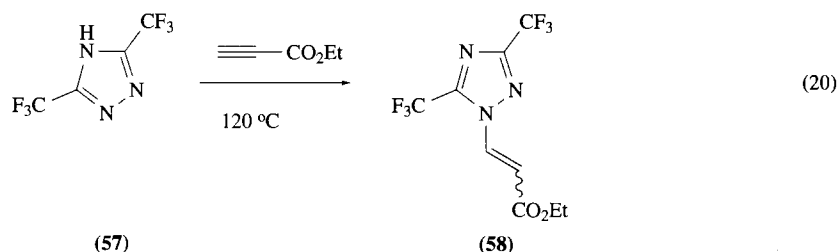
Scheme 8

Alkylation of all three triazole annular nitrogens can be effected by trialkyloxonium tetrafluoroborates (Scheme 9) $\langle 72\text{JOC2259} \rangle$.

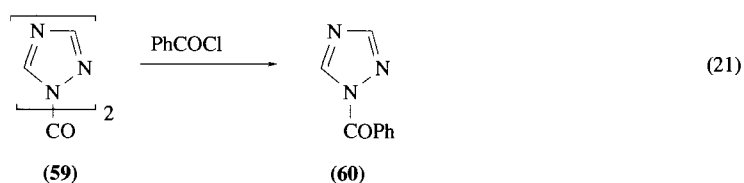


Scheme 9

1,5-Bis(trifluoromethyl)triazole has the 4-H structure (**57**) and reacts with ethyl propiolate at 120°C in a sealed tube to give an *E,Z* mixture of the vinyl ester (**58**) (Equation (20)) $\langle 90\text{JFC(48)149} \rangle$. The sodium salt of (**57**) also alkylates at N(1) with ethyl bromoacetate.



Acylation of triazole is generally facile and can be performed by reaction of anhydrides or acyl halides with triazoles or by treatment of triazoles with acyl halides in an inert solvent. Carbonylditriazole (**59**) reacts with benzoyl chloride to give 1-benzoyltriazole (**60**) via transacylation (Equation (21)) $\langle 62\text{CB1275} \rangle$.



The acylation of 3-aminotriazole has been extensively investigated <B-76MI 402-01, p120> and the general pattern for N(1) or N(2) acylation has been confirmed <70JHC1149>. Acylation with methyl isocyanate also occurs at N(1) or N(2) depending on the reaction conditions whereas methyl isothiocyanate acylates the NH₂ group <72JHC99, 73JCS(P1)1209>.

N-Halogenation can be carried out, but for chlorine and bromine the initial compounds usually rearrange to the C-halo derivatives <67CB2250, 67ZC184, 69KGS1114, 69ZC300, 69ZC325, 72JPR923, 75BSF647>. The N-iodotriazoles, however, are relatively stable and do not rearrange to the C-iodo derivatives on warming <69ZC300>.

4.02.5.4 Electrophilic Attack at Carbon

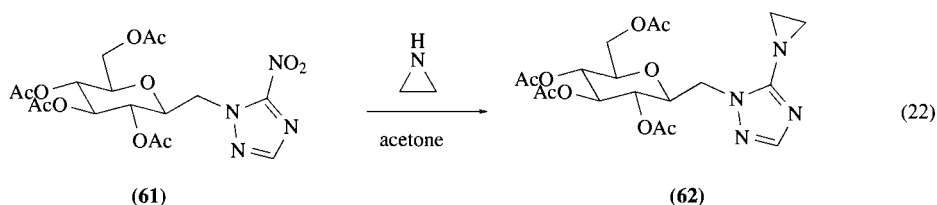
Nitration of triazole and its C-monoalkyl derivatives fails. Aryltriazoles are nitrated on the aryl ring in preference to the triazole, but 3-*p*-nitrophenyltriazole in which each ring is deactivated gives 1-nitro-3-*p*-nitrophenyltriazole which rearranges at 120 °C to 3-nitro-5-*p*-nitrophenyltriazole <72CC37>.

Halogenation usually proceeds through the N-halotriazoles, as described in Section 4.02.5.3. The bromination of N-substituted triazoles by NBS in CHCl₃ is also believed to involve N-bromotriazolium intermediates <75BSF647>.

4.02.5.5 Nucleophilic Attack at Carbon

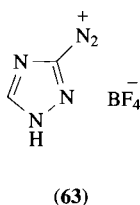
Many triazole derivatives are accessible by exchange of 3- or 5- halo, hydroxy, alkoxy, aryloxy, alkylthio, amino, or cyano groups <67EGP59288, 69BRP1157256, 70KGS1701, 75BSF1649>. A kinetic comparison of haloazole reactivities has been reported <67JCS(B)641>.

Nitro groups in triazoles can be readily exchanged, for example by hydrazine <67CB2250, 70KGS269, 70KGS997, 70KGS1701>. The N-glycoside (**61**) can exchange the triazole 5-nitro group for aziridine (giving (**62**)) or chloride, and is hydrolysed readily to the triazolinone (Equation (22)) <83JHC1307>.



Triazolinones are obtained by the alkaline hydrolysis of methyl-sulfinyl or -sulfonyl derivatives <73JMC312>. Hydrolysis of alkoxytriazoles to triazolinones is of practical importance <68AP(301)911>.

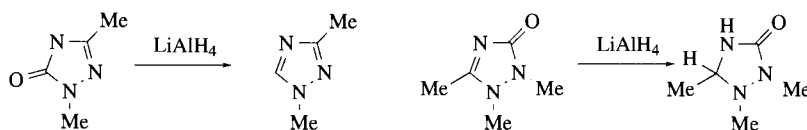
Diazonium salts, prepared from the corresponding nitrosamine, on treatment with halogen acids give the corresponding halotriazole. 3-Fluorotriazole was prepared by photoirradiation of 3-diazoniumtriazole tetrafluoroborate (**63**) <81HC(37)1>. Treatment of (**63**) with sodium nitrite gave 3-nitrotriazole <69AJC2251> and other nitro and dinitrotriazoles can be prepared in a similar manner <65LA(682)123, 67CB2250>.



N-substituted triazoles on treatment with sulfur give the thione <66MI 402-01, 70JCS(C)2403>, but the corresponding oxidation and amination reactions appear not to be known.

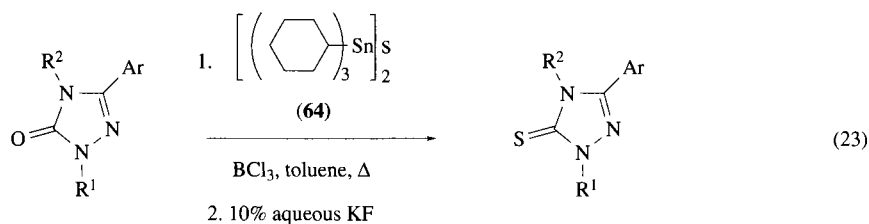
Triazolones are reduced by lithium aluminum hydride and triazoles can be the product, pre-

sumably from dehydration of the intermediate hydroxytriazoline. When a ring proton is not available 1,4-reduction can occur (Scheme 10) <71BSF3296>.



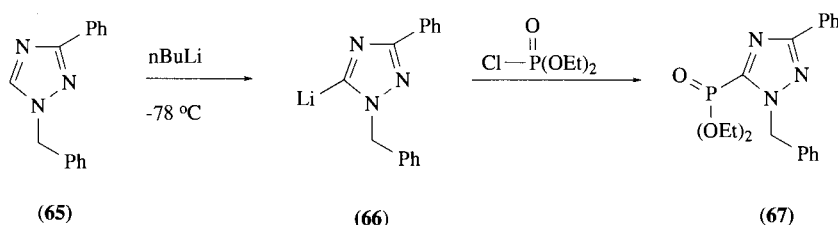
Scheme 10

The oxygen atom of 5-triazolones can be replaced by sulfur by reaction with bis-(tricyclohexyltin) sulfide (**64**) (Equation (23)) <87S912>.



4.02.5.6 Nucleophilic Attack at Hydrogen

There has been considerable interest in the use of C-metallated triazoles as nucleophiles following work with 1-(2-pyridyl)triazole <72AG(E)846>. 1-(2-Propyl)triazole is lithiated at C(5) with butyl lithium and reacts with aryl ketones to give the corresponding 1-(2-propyl)-5-substituted triazoles <82LA1387>. Treatment of 1-benzyl-3-phenyltriazole (**65**) with *n*-BuLi at -78°C gave the 5-lithiated derivative (**66**) which on treatment diethyl chlorophosphate gave (**67**) in 54% yield (Scheme 11) <86JHC1257>. 1-Benzyl, 1-methyl- and 4-benzyl-3-phenyl-triazoles react in a similar way. Treatment of (**67**) with LDA causes rearrangement of phosphorus to the exocyclic benzyl methylene group <92JHC177>.

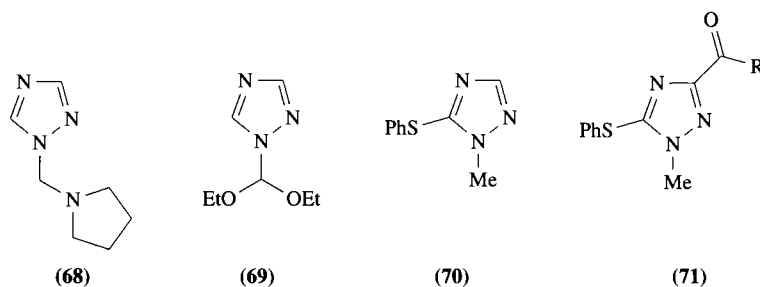


Scheme 11

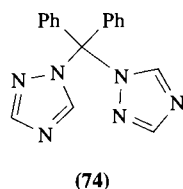
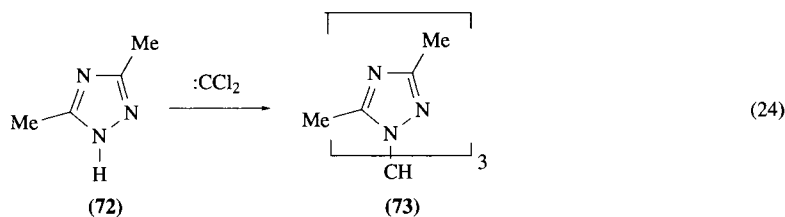
The 1-pyrrolidine derivative (**68**) lithiates with *n*-BuLi at C(5) and the lithiated species can be trapped by electrophiles <90T641>. Rearrangement between C(5) and C(3) occurs readily. The pyrrolidine group can be removed by treatment with NaBH_4 . Triazole reacts with ethyl orthoformate to give 1-bis(ethoxy)methyltriazole (**69**) which lithiates with *n*-BuLi at C(5) <93CPB1226>. Acylation gives the C(3) derivative. 1-Methyltriazole lithiates at C(5) and the lithiated species can be trapped with diphenyl disulfide to give the 5-phenylthio derivative (**70**) in high yield. Treatment of (**70**) with LTMP in THF containing TMEDA at -78°C gave the 3-lithiated species which could be acylated to give (**71**). The phenylthio group could be removed by Raney nickel desulfurization <93CPB1226>.

4.02.5.7 Reactions with Carbenes and Related Species

Insertion rather than addition of dichlorocarbene occurs with 3,5-dimethyltriazole (**72**) to give the tri-triazole (**73**) in low yield (Equation (24)) <69JCS(C)2251>, while diphenyldichloromethane reacts with triazole gives the bistriazole (**74**) <72BRP1269619>. Formation of (**73**) was suggested to



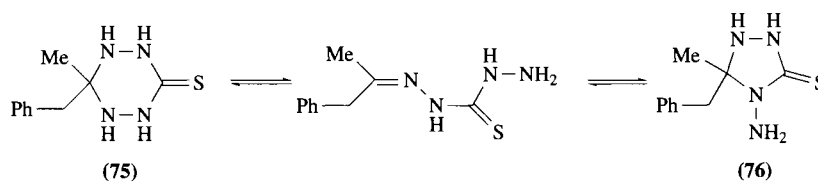
occur via the corresponding dichloromethyl anion which then loses chloride to give triazolyldichlorocarbene.



4.02.6 REACTIVITY OF NONCONJUGATED RINGS

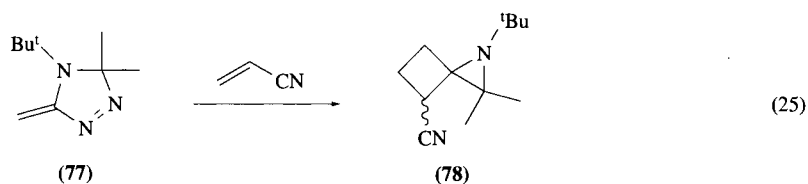
4.02.6.1 Triazolines (Dihydrotriazoles)

Only those compounds which do not have tautomeric aromatic triazole structures will be considered here, the others having been treated as triazoles. The triazolines are unstable and have been subjected to little study. Compounds which are disubstituted at the C(3) or C(5) atom are more stable than the mono- or unsubstituted analogues. The equilibrium has been observed by NMR spectroscopy between the six-membered tetrazine (75) and the triazolinethione (76) via the open-chain form, thus mirroring monosaccharide equilibria (Scheme 12) <90TL3927>.



Scheme 12

Treatment of 5-methylene-3,3-dimethyl-3,4-dihydrotriazole (77) with acrylonitrile gave aza-spiro[3.2]hexane (78) as a 1 : 1 mixture of diastereomers (Equation (25)) <86CC1721>.



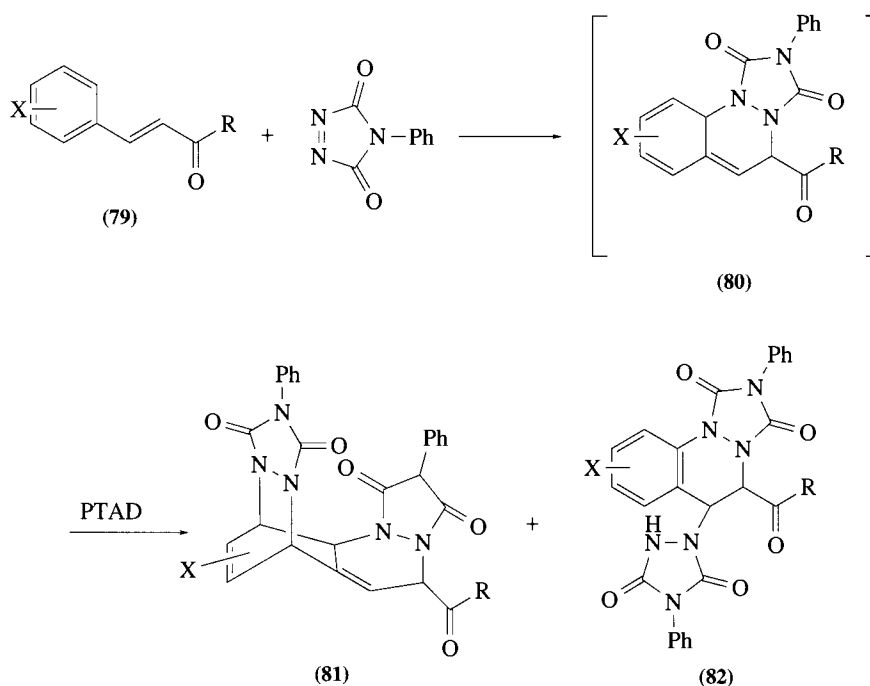
4.02.6.2 Triazolidinines (Tetrahydrotriazoles)

Again, as with the triazolines, only those compounds which do not have tautomeric aromatic triazole structures would be treated here and these systems are unstable and have been even less studied than their dihydrocounterparts. 4-Phenyltriazolidinedione is a precursor of PTAD (see Section 4.02.6.3).

4.02.6.3 4-Phenyltriazolinedione (PTAD) and Related Systems

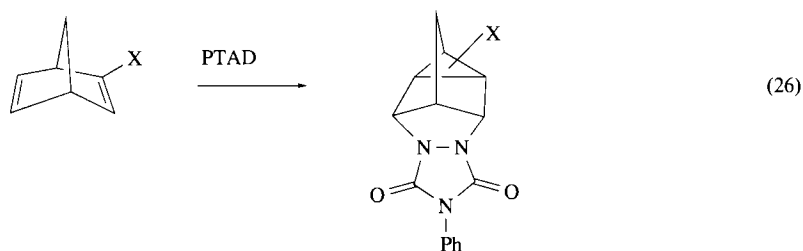
Although 4-phenyltriazolinedione (PTAD) has a tautomeric aromatic triazole structure it has been treated separately here because of its distinct and extensive chemistry.

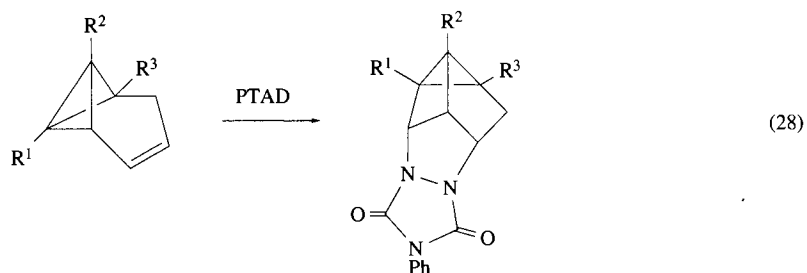
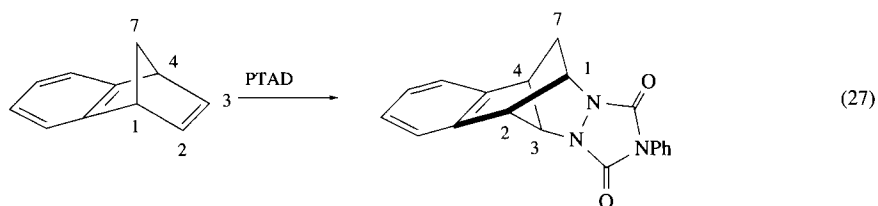
PTAD continues to find extensive use, particularly as a dieneophile, but a variety of other reactions have been reported. Treatment of the chalcone (79) with PTAD gives a mixture of the bis(adducts) (81) and (82) presumably via the intermediate (80) (Scheme 13) <91BCJ3188>. Diels–Alder reactions with a variety of dienes have been reported, giving unexceptional products <85JCS(P1)71>.



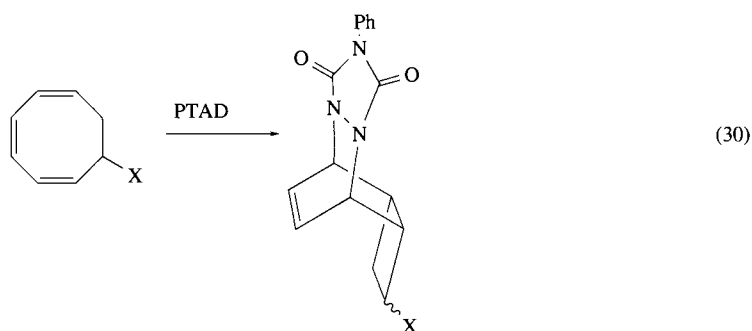
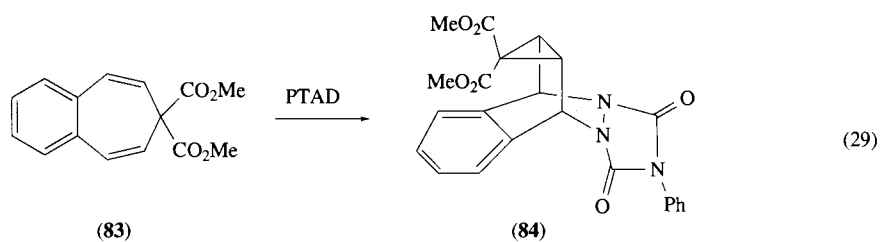
Scheme 13

The behaviour of PTAD with 7-vinylbenzonorbornadienes is complex and has been investigated in a series of papers by Adam and co-workers <86CB2932, 86S854, 89CB133>. With norbornadiene, the normal product is formed by a homo-Diels–Alder reaction across C(2,6) with concomitant bond formation between C(3,5), as illustrated in Equation (26). In the presence of electron-withdrawing substituents at C(2), 2 + 2 addition products across the C(2,3) double bond are also observed, together with rearranged and insertion products <87CB531>. With benzonorbornadiene a rearranged product is obtained, probably via the aziridinium ion (Equation (27)) <84CB1139>. With homo-benzvalene, a rearranged product is obtained (Equation (28)) <78JOC4522, 90CB1193>.

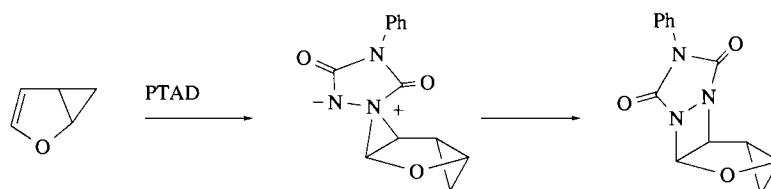




With the benzocycloheptatriene (**83**) 1,5-addition occurs with concomitant formation of the cyclopropanecyclooctatriene (**84**) (Equation (29)) <87TL555, 88AX(C)660>. Addition to the bicyclo[4.2.0]octa-2,4-diene tautomer is the predominant mode with cyclooctatrienes (Equation (30)) <85CB3357>.



In some cases apparent 2 + 2 cycloaddition occurs but this is likely to proceed through electrophilic addition followed by rearrangement, as exemplified by the addition to 2-oxabicyclo[3.1.0]hex-3-ene (Scheme 14) <86AG(E)989>.

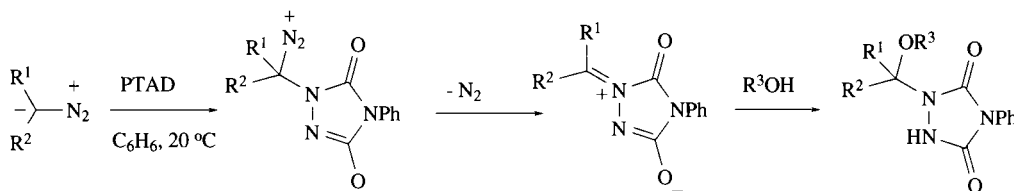


Scheme 14

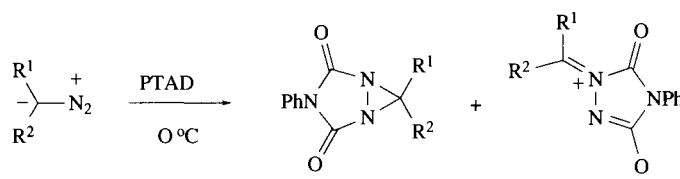
The products from the reaction of PTAD with substituted triazoles may arise from a 1,3-dipolar addition <92BCJ3315>. Abnormal reaction products also occur from the reaction with oxazoles <92BCJ2998>.

PTAD undergoes the ene-reaction with hindered alkenes and the stereochemistry of the products has been determined in the case 4-*t*-butylcyclohexylidene isomers <91JCS(P2)721>.

Diazoalkanes add to PTAD by electrophilic addition. The intermediate diazonium species can lose nitrogen and the resulting dipole can be trapped by solvent or form a diaziridine (Scheme 15) <85CB28, 85CB3396, 88JCS(P2)1415>. In many cases the phenyl group on the PTAD can be replaced by a substituted benzene and the same type of reaction occurs (Scheme 16).



Scheme 15

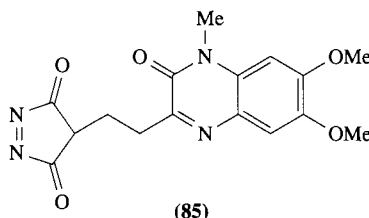


Scheme 16

There has been some dispute over the products resulting from the reaction of PTAD with alcohols, but an x-ray crystallographic study confirms the earlier work <87JOC1288>.

PTAD has been used as a protecting group for dienes in steroids since it can be readily removed under mild conditions by treatment with base (e.g., K_2CO_3 /DMSO) <85BSF849, 95JOC1828>.

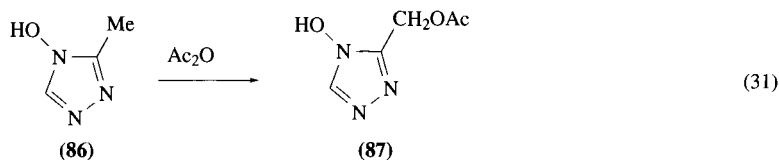
Instead of the phenyl ring, a fluorescent chromophore has been attached to N(4) (**85**) and this compound has then been used for detecting Vitamin D metabolites and retinoic acid <94TL1917>.



(85)

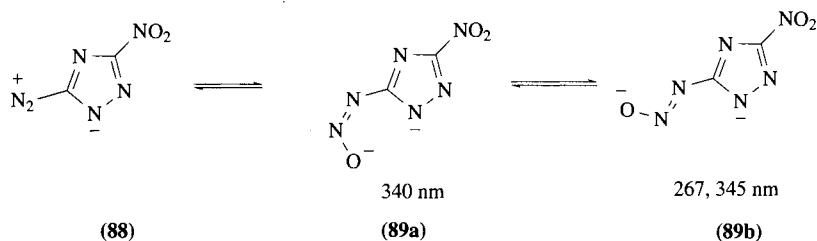
4.02.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING C ATOMS

Alkyl groups on triazole have similar properties to those on benzene and can be oxidised in a similar way. Derived functions such as CH_2OH and CH_2Br behave in the expected manner. The acetoxylation of (**86**) with acetic anhydride to give (**87**) is unexpected (Equation (31)) <70JPR610>.



(31)

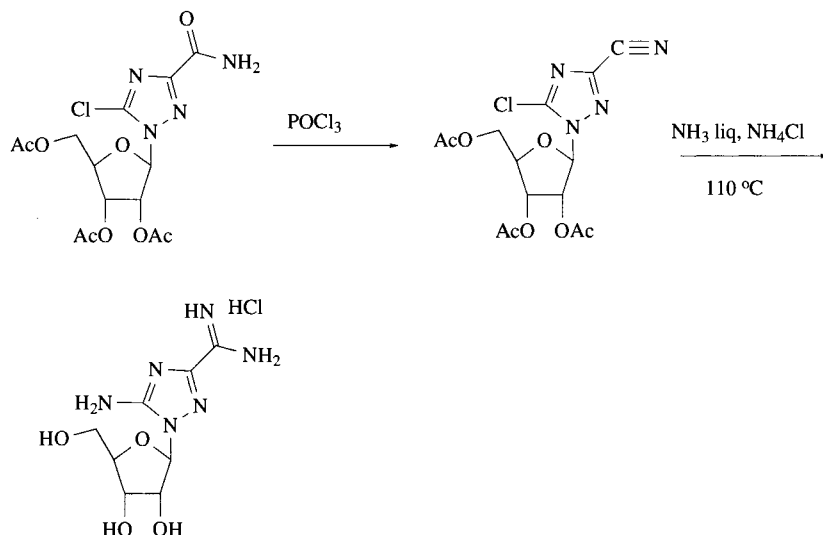
5-Amino-3-nitrotriazole is diazotized with sodium nitrite in 20% H_2SO_4 to give (**88**) which shows an IR absorption at 2285 cm^{-1} and a maximum at 282 nm in the electronic spectrum <90JOU1819>. Potentiometric titration with hydroxide gives the dianion (**89a**) which can be photoisomerized to its isomer (**89b**) (Scheme 17). For similar reactions of 3-amino-1-methyl- and 5-amino-1-methyl-triazoles, see <88JOU1928, 88JOU1935>. 3-Aminotriazole is oxidised by tetranitromethane in the presence of an alkali metal hydroxide to give the alkali metal *N*-nitrite <87JOU1977>.



Scheme 17

The aldehydes and ketones of triazole have many properties resembling those of the analogous benzene derivatives. Unlike benzaldehyde, however, triazole-5-carbaldehyde readily dimerizes $\langle 71AJC393 \rangle$. This preference for dimerization accounts for the failure of N-unsubstituted triazoles to undergo Cannizzaro reactions and benzoin rearrangements $\langle 71AJC393 \rangle$, or Döbner and Perkin reactions $\langle 62JCS575 \rangle$. The phenyl group migrates preferentially to the triazole group in the Beckmann rearrangement as is shown by the failure of one of the oximes of 3-benzoyl-1-phenyltriazole to rearrange $\langle 68JCS(C)824 \rangle$.

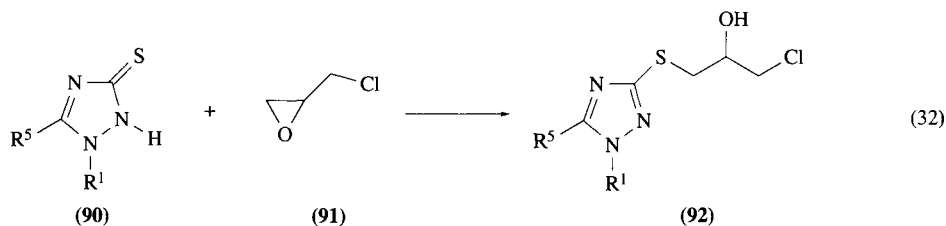
The carboxylic acids of triazoles are readily decarboxylated on heating but are otherwise stable. Esters, amides, nitriles, and hydrazides react normally. This is illustrated in Scheme 18 for the amide and nitrile functions $\langle 88JMC330 \rangle$.

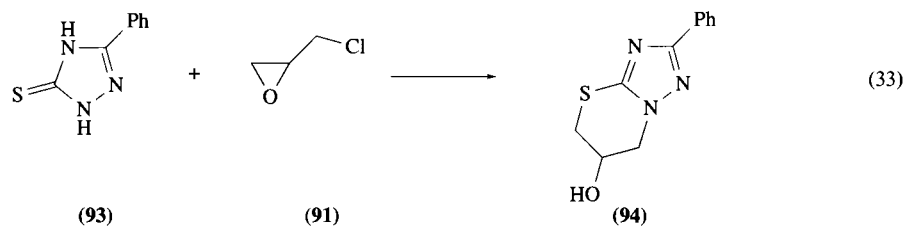


Scheme 18

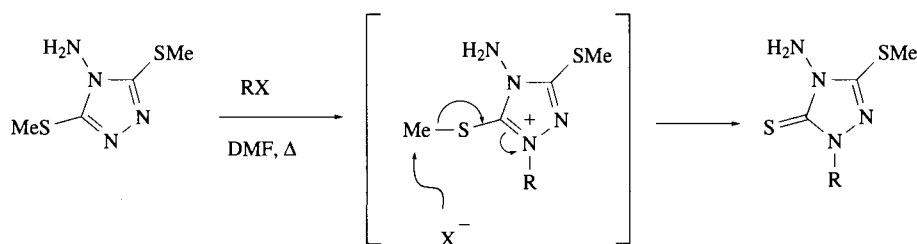
Scheme 18 also illustrates the nucleophilic replacement of halide which occurs more readily than in the analogous benzene derivatives. The kinetics of these processes have been investigated $\langle 67JCS(B)641, 73ZOR2535 \rangle$. Halogenated triazolones undergo still more ready replacement of halogen as exemplified by the replacement of bromine for chlorine on a ring activated by protonation $\langle 67CB2250 \rangle$.

The simple sulfur derivatives of triazoles exist as thiones $\langle 71JCS(C)1016 \rangle$ but behave as thiols in most of their reactions. The 3-thione derivative (90) reacts with chloropropylene oxide (91) at the least hindered oxide centre to give (92) (Equation (32)) $\langle 87CHE228 \rangle$. 3-Phenyl-5-triazolinethione (93) reacts with (91) to give the cyclic derivative (94), presumably through subsequent nucleophilic displacement of chloride by N(1) (Equation (33)) $\langle 90JOU1525 \rangle$.

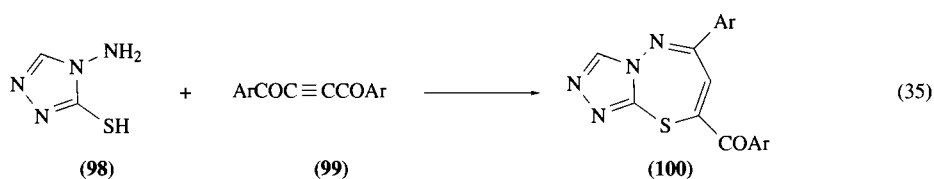
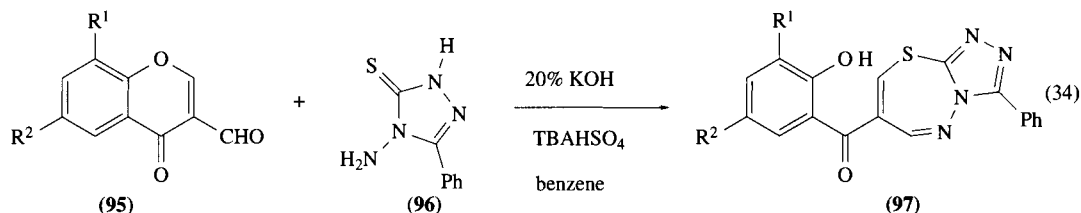




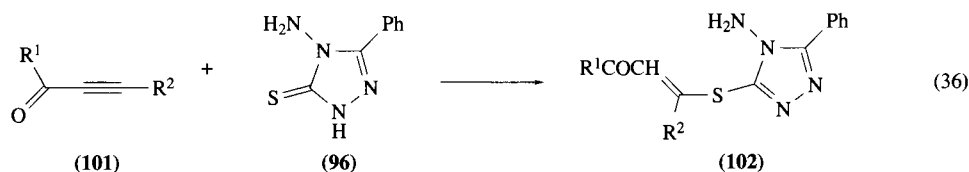
Reaction of 4-amino-3,5-bismethylthiotriazole with alkyl halides in DMF gives the 1-alkyl-5-thione derivatives, presumably by alkylation at N(1) followed by nucleophilic cleavage of the S—Me bond (Scheme 19) <83S414>.



Treatment of 3-formylchromone (95) and 4-amino-3-phenyl-5-triazolinethione (96) with KOH and TBAHSO₄ in benzene also gave a bicyclic derivative (97) (Equation (34)) <87SC1851>. 4-Amino-3-triazolinethione (98) reacts with the diketoacetylene (99) in a similar manner to give (100) (Equation (35)) <92CHE222>.

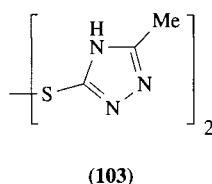


Reaction of (96) with ketoacetylenes (101) occurs by 1,4-addition of the thiol to the acetylene to give (102) (Equation (36)) <88JOU1941>. Similar results were obtained with (98) <92CHE222, 92CHE795> and with 3-methyl-5-triazolinethione <91JHC325>. Diethyl diazodicarboxylate oxidised 3-methyl-5-triazolinethione to the bis(3-methyltriazolyl)disulfide (103) <91JHC325>.



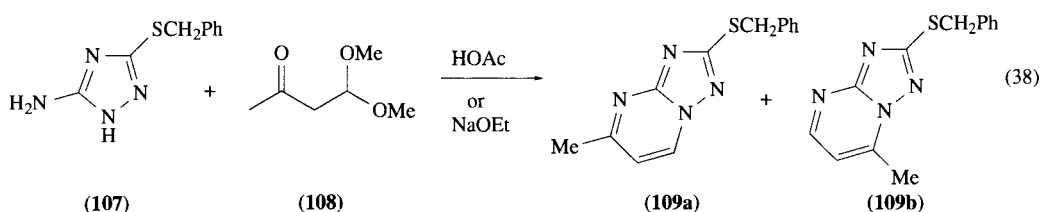
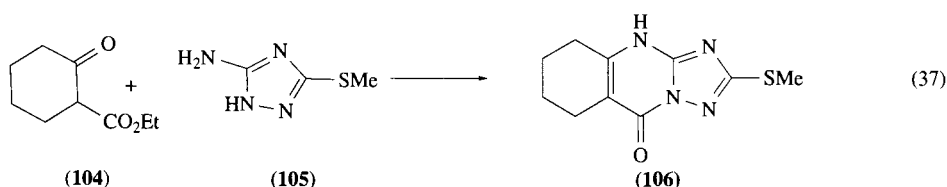
A comparison of the S-methylation of a trimethyltriazolinethione with a similar imidazole derivative suggested a later transition state for the triazolinethione <83JCS(P2)1217>.

Triazoline thiones can be converted to the corresponding triazoles with Raney nickel, nitric acid and hydrogen peroxide <75LA1264>. Sulfoxides can be obtained by controlled treatment with

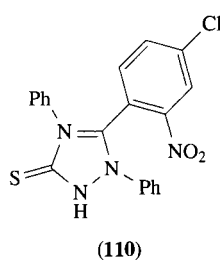


hydrogen peroxide <65JCS3912> and peroxyphthalic acid gives sulfoxides and sulfones <70JCS(C)2403>. Treatment of 3-amino-1-methyl-5-thiomethyltriazole with NaOH and H₂O₂ gave the corresponding 5-triazolinone <90JHC1063>.

5-Aminotriazoles react with β -ketoesters, as exemplified by the reaction of (104) with (105) to give (106) (Equation (37)) <89OPP163>, and with 1,3-diketones <89JHC1489> or β -ketoaldehyde acetals <89JHC1393>, as exemplified by the reaction of (107) with (108) to give (109a) and (109b) (Equation (38)). The relative amounts of the isomers (109a) and (109b) depend on the reaction conditions.



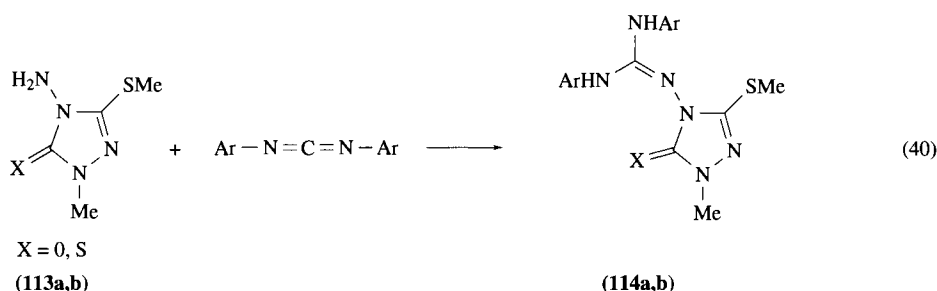
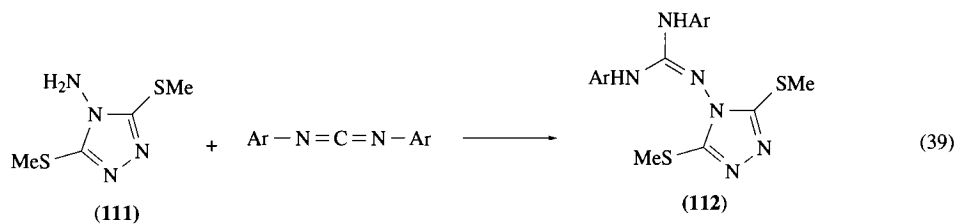
The 3-(4-chloro-2-nitrophenyl)triazole derivative (110) undergoes nucleophilic displacement of chloride by azide ion <89JCS(P2)1425>. The thermal and photochemical decomposition of 3-nitrotriazolone have been shown to occur via radical cations <91JPC5509>.



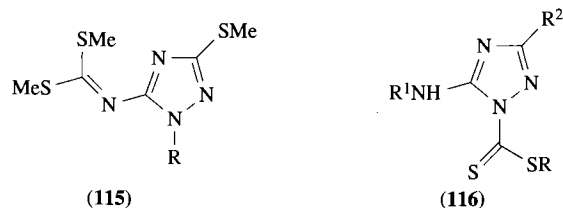
4.02.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING N ATOMS

Rearrangement of acyl and halo groups are the most common reactions of nitrogen substituents of triazoles.

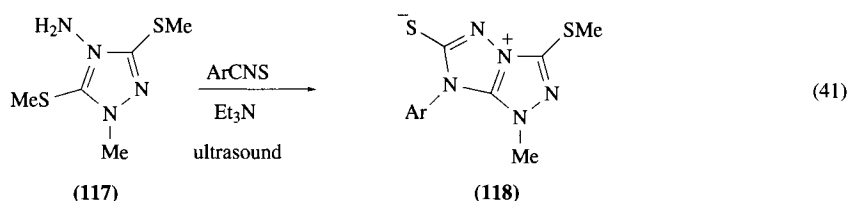
A number of examples of the reactions of 4-aminotriazoles have been given in the previous section. The 4-amino derivative (111) reacts with diimides to give the guanidine derivatives (112) (Equation (39)) <88H(27)161> and the 4-amino-5-triazolinone (113a) and 5-triazolinethione (113b) react in the same way with diimides and bisarylthioureas to give diarylguanidines (114a,b) (Equation (40)).



The dimethyl thioiminocarbonate derivative (**115**), which can be prepared from the corresponding aminotriazole <90JHC1689>, undergoes nucleophilic addition with amines and displacement of a thiomethyl group <92CCC134>. A similar reaction occurs with the 1-substituted derivative (**116**) <92JHC1677>.



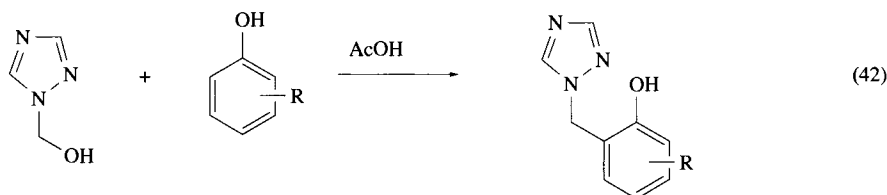
Treatment of the 4-amino derivative (**117**) with ArCNS under ultrasound activation gave the bicyclic mesoionic compound (**118**) (Equation (41)) <86T2121>.



N(1) acyl triazolines have been used as substrates in the investigation of factors influencing rates of hydrolysis. Sodium dodecyl sulfate inhibits the hydrolysis because of binding of the substrate in the micelle and this effect can be inhibited by the addition of a water soluble polymer, atactic poly(*N*-vinylpyrrolidone) <84JA2636>. For other investigations see <92JCS(P2)2035, 93JCS(P2)49, 93JOC7111>.

4-Aminotriazole can transfer the amino group to substituted 4-nitroimidazoles in the presence of sodium methoxide in DMSO <93T5339>.

1-Hydroxymethyltriazole acts as an alkylating reagent with phenols under acidic conditions, presumably via the iminium ion (Equation (42)) <94H(38)1813>.



N-(4-triazolyl)-2,4,6-trimethylpyridinium tetrafluoroborate decomposes at high temperature to give products consistent with the formation of the 4-triazolium cation <91JCS(P1)1761, 94TL2321>.

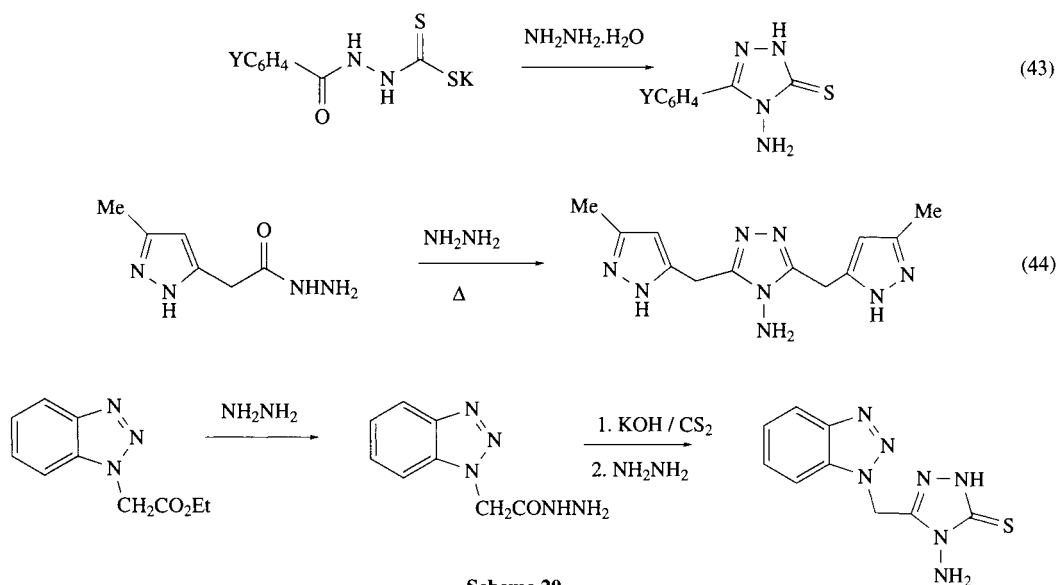
4.02.9 RING SYNTHESIS

4.02.9.1 General Considerations

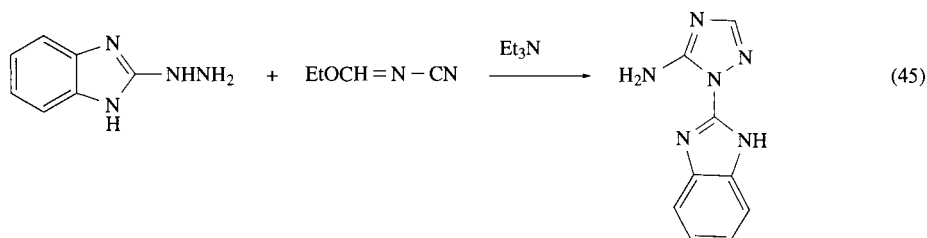
No theoretical scheme of the A-B plus C-D-E type will be used, for the reasons discussed by Polya in the CHEC-I <84CHEC-I(5)733>. For a review describing numerous triazole syntheses, see <89CHE714>. The synthesis of 1-substituted triazoles has been reviewed <94H(37)1951>. All of the methods used as examples in this chapter have been previously described and details of reactions used earlier can be found in the CHEC-I <84CHEC-I(5)733>.

4.02.9.2 Methods Employing Hydrazine Derivatives

The reaction of hydrazine or substituted hydrazines with suitable electrophiles remains the most common method of preparing triazoles. The hydrazine will usually form N(1) and N(2), but there are numerous examples of it becoming NH₂—N(4) (Equations (43), and (44); Scheme 20) <83S483, 86JHC361, 86JHC1451, 92JHC1101>. Examples where hydrazines provide all nitrogens have been described (Equations (43) and (44); Scheme 20) <89JHC177, 90JOC420, 92S398>.

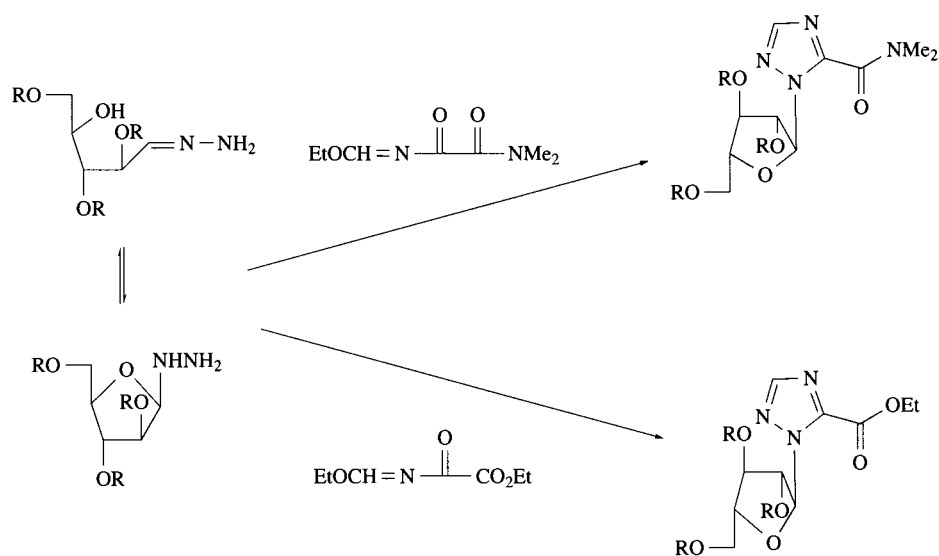


Treatment of ethyl-*N*-cyanoformimidate with a hydrazine in triethylamine gives the corresponding 5-aminotriazole (Equation (45)) <80HCA1, 83H(20)1495>.

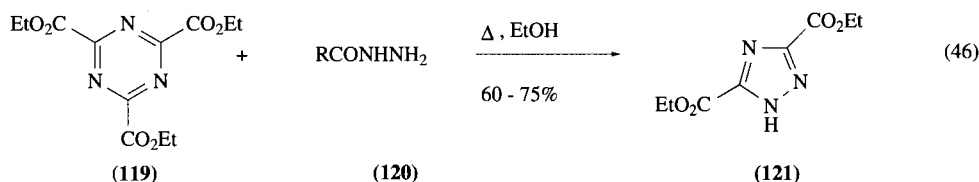


Sugar 1-hydrazones are in equilibrium with the corresponding glycosyl hydrazine and will react with electrophiles to form triazolynyl sugars (Scheme 21) <83JHC1447>. Variation of the electrophile can provide a range of substituted triazoles.

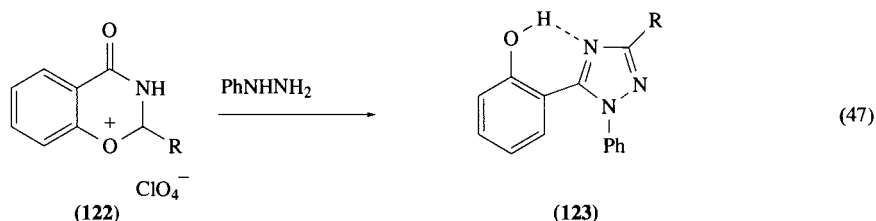
Treatment of the *s*-triazine (**119**) with hydrazide (**120**) in EtOH gave the 3,5-diethylcarboxylate (**121**) (Equation (46)) <84JOU811, 85CHE593>.



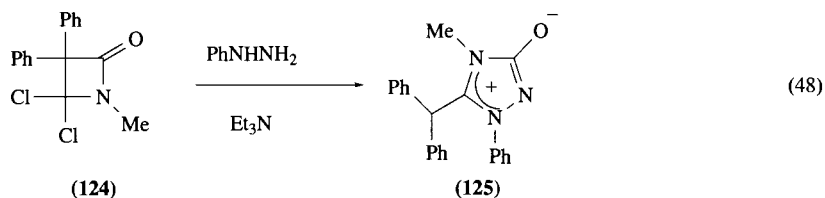
Scheme 21



The oxonium salt (**122**) reacts with phenylhydrazine to give the 1-phenyltriazole (**123**), the x-ray structure of which shows intramolecular hydrogen bonding between the phenol hydrogen and N(4) (Equation (47)) <89CHE94>.



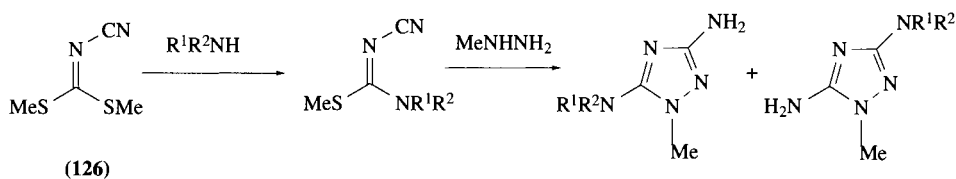
The azetidinone (**124**) reacts with phenylhydrazine to give the mesoionic triazole (**125**) (Equation (48)) <83TL1035>.



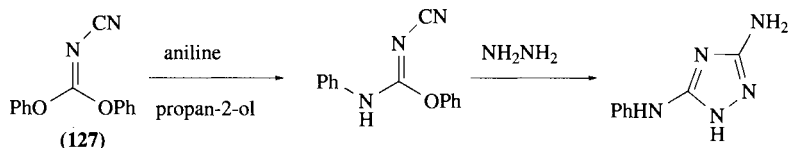
Dimethyl *N*-cyanoisothiourea (**126**) can undergo sequential nucleophilic substitution by an amine followed by methylhydrazine to give the corresponding *N*¹-methyltriazole. A number of closely related reactions are known (Scheme 22) <82JHC1157, 83CB1547, 84H(21)580, 87JHC1189, 88JOC3120>.

A similar sequence of reactions occurs with diphenyl cyanocarbonimidate (**127**). Sequential reaction of (**127**) with aniline and hydrazine gave 3-amino-5-phenylaminotriazole (Scheme 23) <82JHC1205, 87JHC275>. With amino acids as the first nucleophile, more complex triazoles can be formed <93T165>.

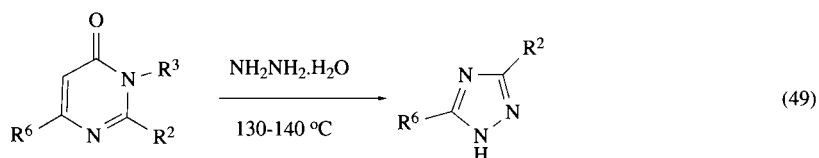
4-Pyrimidones react with hydrazine hydrate at 130–140°C to give the triazole (Equation (49)) <83H(20)1243>.



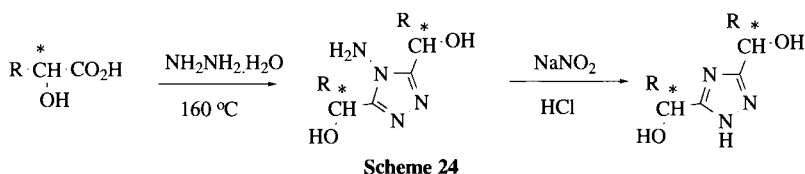
Scheme 22



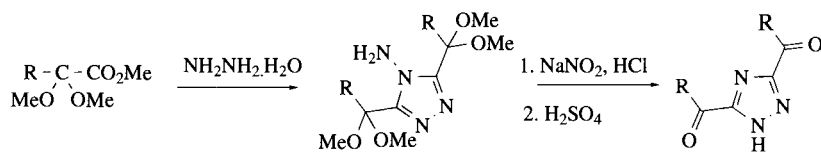
Scheme 23



Hydrazine hydrate reacts with α -hydroxyacids to give the *N*-aminodihydrotriazole which is diazotised with sodium nitrite in HCl to the 3,5-disubstituted triazole enantiomer (Scheme 24) <87H(26)989>. These triazoles were converted to macrocyclic derivatives (see Section 4.02.12.3). The ketals of α -oxoesters undergo the same series of reactions to give, after hydrolysis, the 3,5-dicarbonyl derivatives (Scheme 25) <92S398>.

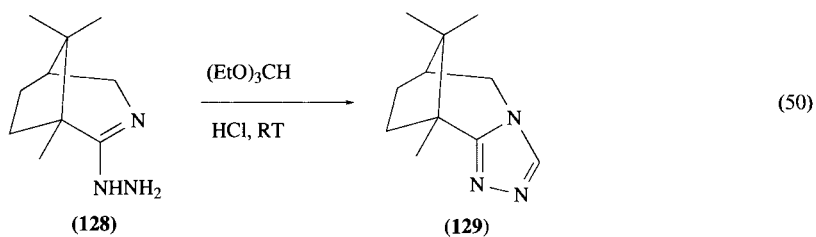


Scheme 24

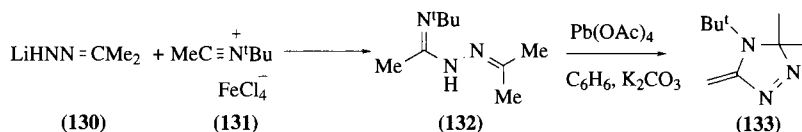


Scheme 25

The iminohydrazine (128) reacts with ethyl orthoformate to give the triazoloazepine (129) (Equation (50)) <86H(24)907>.

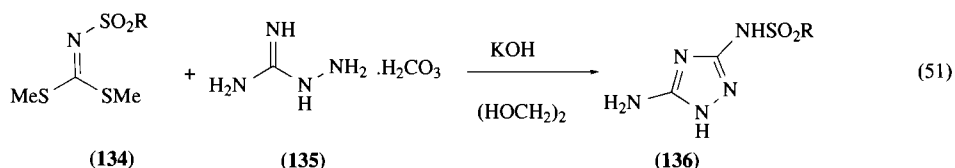


The lithiated hydrazone (**130**) reacts with the salt (**131**) to give the amidrazone (**132**) in 35% yield. Oxidation of (**132**) with lead tetraacetate gives the 3,4-dihydrotriazole (**133**) (Scheme 26) <86CC1721>.

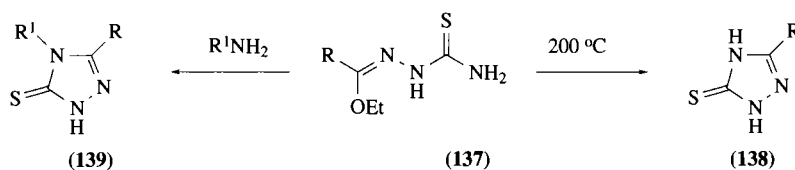


Scheme 26

Nucleophilic addition of aminoguanidine (**135**) to *N*-sulfonylcarbonyldithioimides (**134**) in ethylene glycol at 170°C gives 3-sulfonylamino-5-aminotriazoles (**136**) (Equation (51)) (91S220).

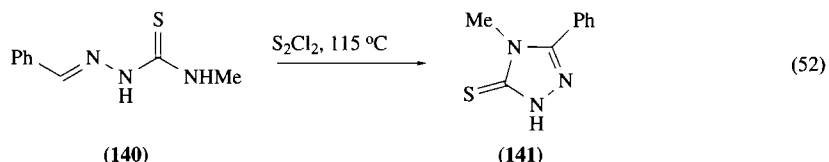


Heating the thiosemicarbazone (**137**) at 200°C gave the triazoline-5-thione (**138**) as a minor product but treating it with an amine gave the triazoline-5-thione (**139**), where R and R' can be widely varied (Scheme 27) ^[84JHC1689].

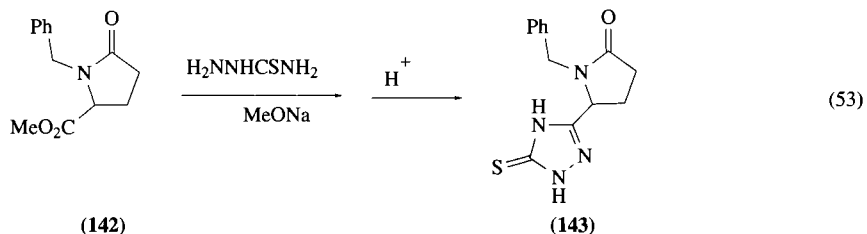


Scheme 27

The thiosemicarbazone (**140**) reacts with S_2Cl_2 at 115°C to give the triazoline-5-thione (**141**) (Equation (52)) ^[86JHC881].

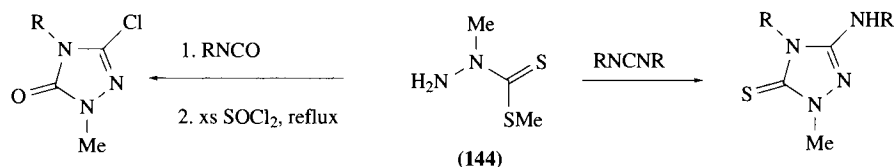


Thiosemicarbazide reacts with the ester (**142**) in the presence of sodium methoxide to give the triazoline-5-thione (**143**) (Equation (53)) ^[89JHC1723]. The same product can be obtained by reacting the hydrazide of (**142**) with the substituted thioisocyanate under basic conditions.

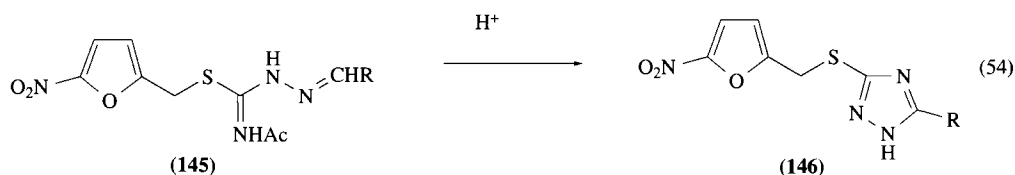


Carbodiimides react with (144) to give triazoline-5-thiones, while with isocyanates the triazolinones are formed after ring closure of the initial product by heating in excess SOCl_2 (Scheme 28) ^[89S923].

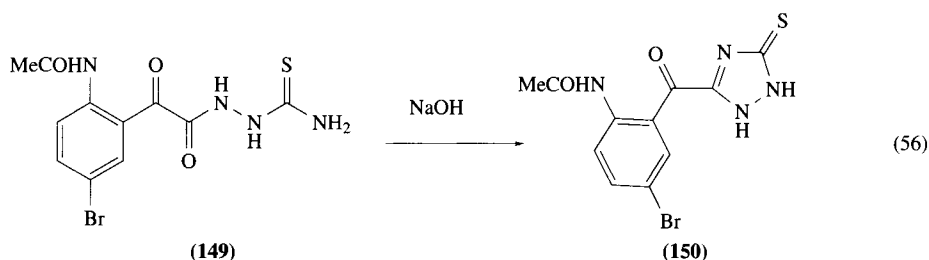
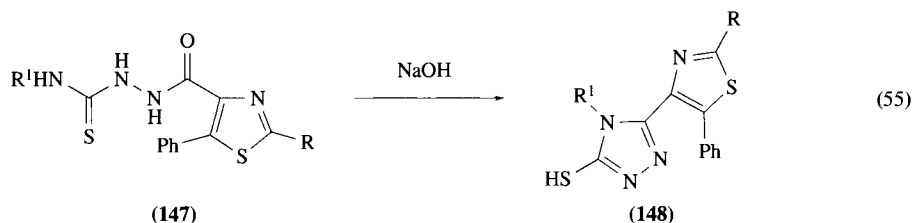
The isothiosemicarbazone (**145**) is converted under acidic conditions to the triazole (**146**) (Equation (54)) ^{<88CHE573>}.



Scheme 28

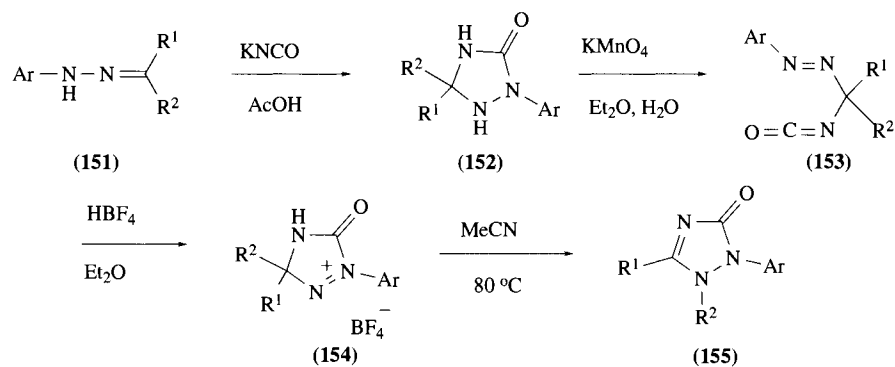


The thiosemicarbazide (**147**) cyclises to the triazole (**148**) on treatment with sodium hydroxide (Equation (55)) <92BAU534> and (**149**) undergoes a similar reaction to give (**150**) (Equation (56)) <90JOU737>.

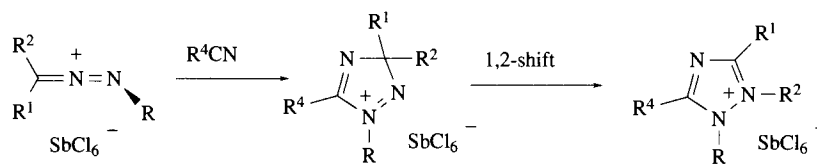


Aryl hydrazones (**151**) react with potassium isocyanate in acetic acid to give the 5,5-disubstituted triazolidone (**152**). Oxidation of (**152**) with permanganate gave the α -(aryloxy)alkyl isocyanate (**153**) which cyclised with HBF_4 to give the triazolium fluoroborate (**154**). This underwent a 1,2-rearrangement in acetonitrile to give the triazolinone (**155**) (Scheme 29) <90S803>. Where R^1 , R^2 form part of a ring system, ring expansion occurs in the final step <90S808, 90S1048>.

Diazaallene salts react with isocyanates to give triazoles, a 1,2-shift occurring in the process



Scheme 29

$$\begin{array}{c} \text{Me} \\ \diagup \\ \text{C} = \text{N} = \text{N} \text{---} \text{Ar} \\ \diagdown \\ \text{Me} \end{array} + \text{Bu}^t - \text{N} = \text{C} = \text{O} \xrightarrow[0 - 25^\circ \text{C}]{\text{CH}_2\text{Cl}_2} \begin{array}{c} \text{Bu}^t \quad \text{Me} \\ \diagdown \quad \diagup \\ \text{N} = \text{C} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{N}^+ - \text{N} - \text{Me} \\ | \\ \text{Ar} \end{array} \text{SbCl}_6^- \quad (57)$$


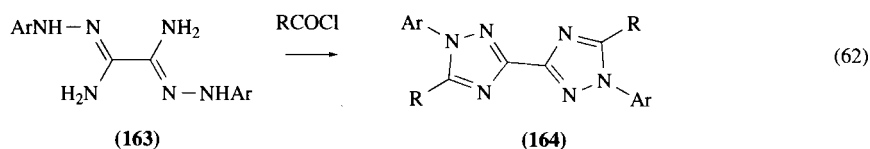
Scheme 30

$$\begin{array}{c}
 \text{R}^1 \\
 \diagdown \\
 \text{C}=\text{N}-\text{N}=\text{C}(\text{NH}_2)(\text{NMe}_2) \\
 \diagup \\
 \text{R}^2
 \end{array}
 +
 \begin{array}{c}
 \text{CN} \\
 \diagup \\
 \text{EtOCH}=\text{C} \\
 \diagdown \\
 \text{CO}_2\text{Et}
 \end{array}
 \xrightarrow{\text{C}_6\text{H}_6, \text{rt}}
 \begin{array}{c}
 \text{N} \\
 \diagdown \quad \diagup \\
 \text{C}=\text{N}-\text{N}=\text{C}(\text{NMe}_2) \\
 \diagup \quad \diagdown \\
 \text{N}
 \end{array}
 \begin{array}{c}
 \text{R}^1 \\
 \diagdown \\
 \text{C} \\
 \diagup \\
 \text{R}^2
 \end{array}
 \begin{array}{c}
 \text{N} \\
 \diagdown \quad \diagup \\
 \text{C}=\text{N}-\text{N}=\text{C}(\text{NMe}_2) \\
 \diagup \quad \diagdown \\
 \text{N}
 \end{array}
 \quad (59)$$

(159) $\xrightarrow[\text{AlCl}_3, 100-110\text{ }^\circ\text{C}]{(\text{NC})_2\text{CHCO}_2\text{R}}$ (160)

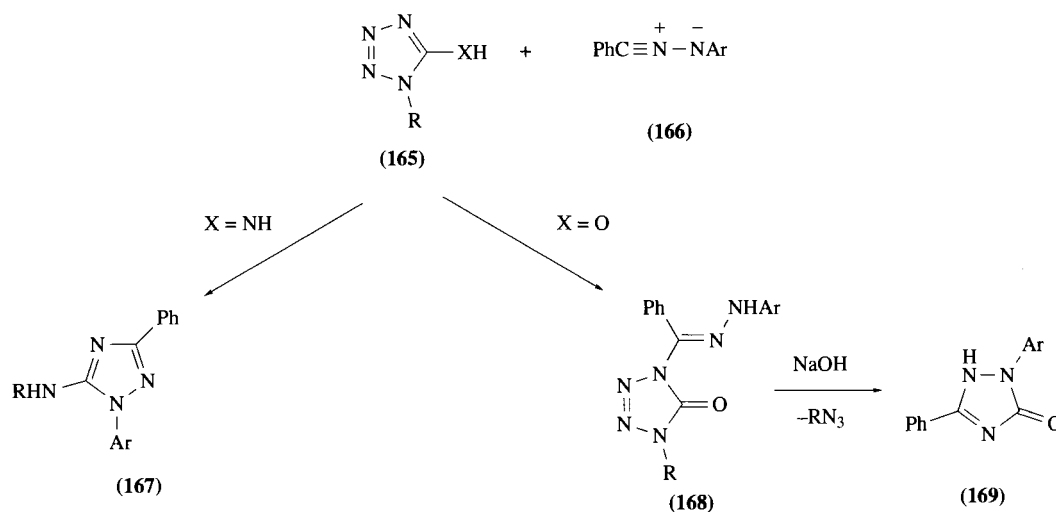
$$\begin{array}{ccc}
 \begin{array}{c} \text{F}_3\text{C} \\ \diagdown \\ \text{C}=\text{N} \\ \diagup \\ \text{H}_2\text{N} \end{array} & \xrightarrow{\Delta} & \begin{array}{c} \text{NH}_4^+ \\ | \\ \text{N}^- \end{array} \\
 \diagdown & & \diagup \\
 \text{N} & & \text{C}=\text{CF}_3 \\
 \diagup & & \diagdown \\
 \text{H}_2\text{N} & & \text{F}_3\text{C} \\
 \text{(161)} & & \text{(162)}
 \end{array}
 \quad (61)$$

1,1'-Disubstituted 3,3'-bitriazoles (**164**) have been prepared by acylation of bis-amidrazones (**163**) (Equation (62)) <93T2761>.



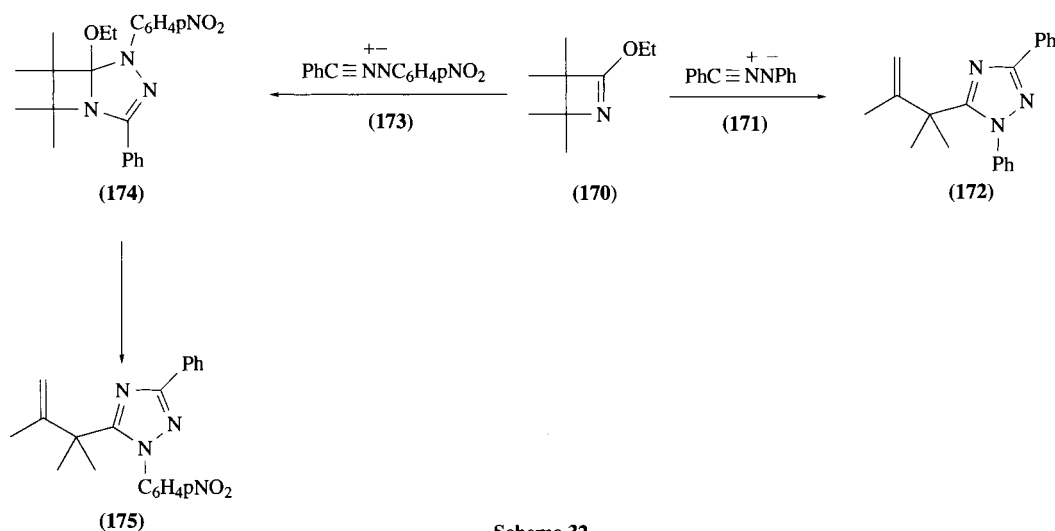
4.02.9.3 Methods Employing Nitrilimines

1,3-Dipolar additions have been extensively used for the synthesis of triazoles. The nitrilimine (**166**) reacts with the tetrazole (**165**, X = NH) to give the triazole (**167**). The reaction of (**166**) with the tetrazole (**165**, X = O) gives the tetrazole (**168**), which on treatment with base gives the triazolinone (**169**) (Scheme 31) <93JCR(S)306>.



Scheme 31

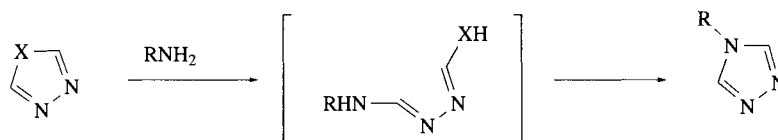
The azacyclobutene (**170**) reacts with the nitrilimine (**171**) to give the triazole (**172**). With the nitrilimine (**173**), the 1,3-cycloaddition product (**174**) can be isolated, but the ring opens on heating in 1,4-dichlorobenzene to give (**175**) (Scheme 32) <93T4383>.



Scheme 32

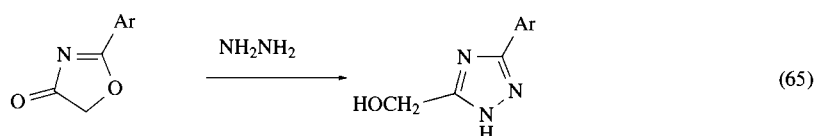
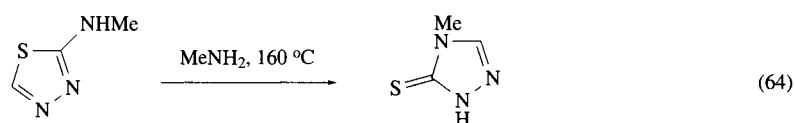
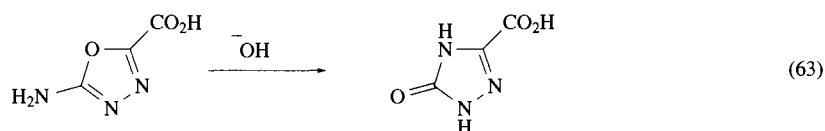
4.02.10 SYNTHESIS OF TRIAZOLES BY TRANSFORMATION OF OTHER HETEROCYCLIC SYSTEMS

The conversion of a nontriazole ring system into a triazole most commonly involves the substitution of a nitrogen for another heteroatom in a five-membered ring. The process usually involves nucleophilic ring opening of the heterocycle followed by ring closure and loss of the other atom. Such reactions thus often involve the same intermediates as those described in the reactions of acyclic systems (Scheme 33).

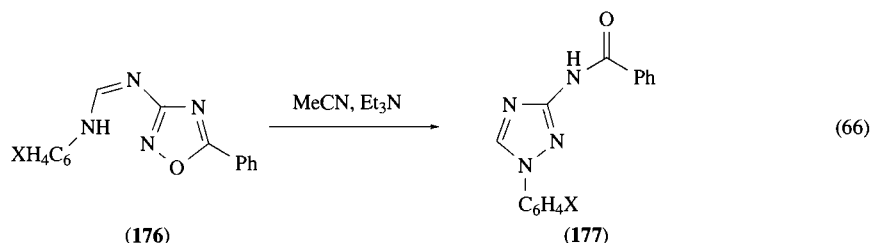


Scheme 33

Little new material in this area has appeared since it was reviewed by Polya in 1984 <84CHEC-I(5)733>, and only a few typical examples will be illustrated (Equation (63) <73KGS1345>, Equation (64) <57CB202>, and Equation (65) <70JCS(C)1515>). For a more extensive examination of this area reference should be made to the review in CHEC-I <84CHEC-I(5)733>.

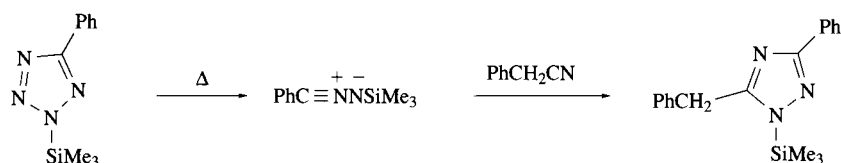


The kinetics of the rearrangement of the oxadiazole (176) to the triazole (177) have been investigated (Equation (66)) <94T7315>.

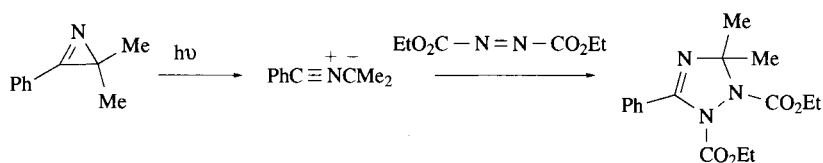


Reactions involving the formation of nitrilimines or related compounds from ring systems are also well documented. Again, these reactions frequently have common intermediates with the acyclic reactions described in Section 4.02.9.3. These intermediates may self-condense or react with reagents to give triazoles. Some examples are given in Schemes 34 and 35 and a more exhaustive description is given by Polya <84CHEC-I(5)733>.

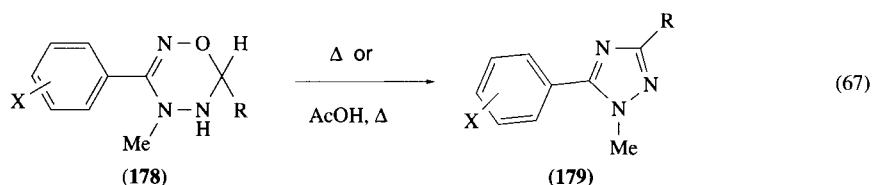
The oxatriazine (178) rearranges thermally or under acidic conditions to give triazole (179) (Equation (67)) <93H(36)455>.



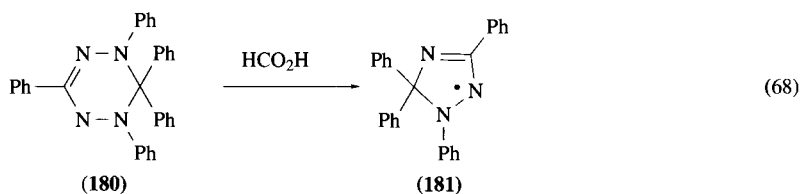
Scheme 34



Scheme 35

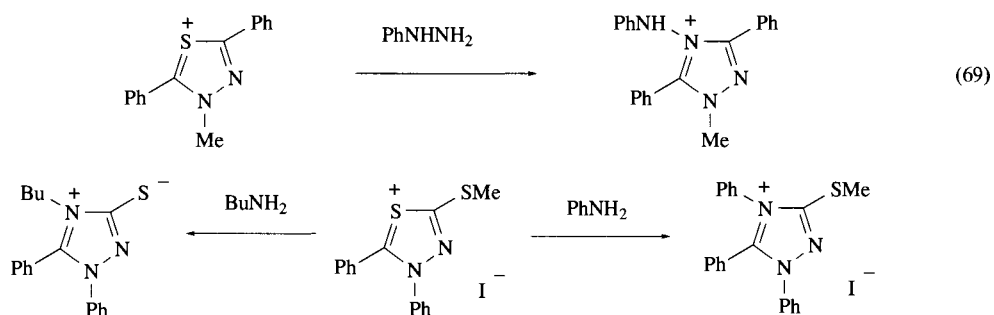


Treatment of the tetrazine (180) with formic acid gives the stable radical (181) (Equation (68)) <89AG(E)491>.



4.02.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUND AND CRITICAL COMPARISON OF METHODS

Triazolium salts can be prepared from thiazolium salts by treatment with amines (Equation (69)) <74ZOR377>. Methylthiothiazolium salts react similarly (Scheme 36) <73IJC753>.



Scheme 36

The method of choice for the synthesis of triazoles depends largely on the substitution pattern required. Acyclic compounds are usually the preferred substrates and the hydrazines are readily available and cheap. For 3-aminotriazoles, dimethyl *N*-cyanoisothiourea or diphenyl cyanocarbonimidates, although more expensive, are valuable precursors since the 5-substituent can be varied widely. 1,3-Dipolar addition using nitrilimines has been extensively used and again can be

valuable for a specific substitution pattern. Manipulation of substituents or the introduction of substituents via triazole anions is also useful in transforming readily available triazoles into derivatives that are more difficult to prepare directly. A detailed discussion of the synthesis of 1-substituted triazoles is available <94H(37)1951>.

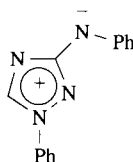
4.02.12 IMPORTANT COMPOUNDS AND APPLICATIONS

The interest in triazoles largely derives from their biological effects in both medicine <83MI 402-01, 84MI 402-01, 91MI 402-01> and agriculture, but there is also an interest in 3-nitrotriazole and its derivatives as explosives <83JST(102)391, 87MI 402-01>. In many cases the biological properties of triazoles are also found in related heterocycles but the triazoles are often the most potent derivatives <84MI 402-01, 89MI 402-02>. There has also been a considerable interest in triazoles as ligands in organometallic compounds and as functional groups on macrocyclic rings for selective complexation of ions.

4.02.12.1 Analytical and Synthetic Applications

4.02.12.1.1 Analytical uses

Triazoles have been used extensively in analytical chemistry. Nitron (**182**) has been used for the determination of boron, rhenium, and tungsten. Nitron has been bonded to a polymer and used for the removal of nitrate from water <79MI 402-01>. Other triazoles have been used for the spectrophotometric assay of cobalt, rhodium, and platinum <68MI 402-01, 72ZAK2209>. Hydroxyphenylazotriazoles form brilliant lakes with a number of metal ions <73AJC1585>. 5-¹⁴C-3-Diazotriazole couples only to tryptophane below pH 6.8 and can be used for the specific determination of tryptophane in proteins <84MI 402-02>.



(182)

4.02.12.1.2 Synthetic uses

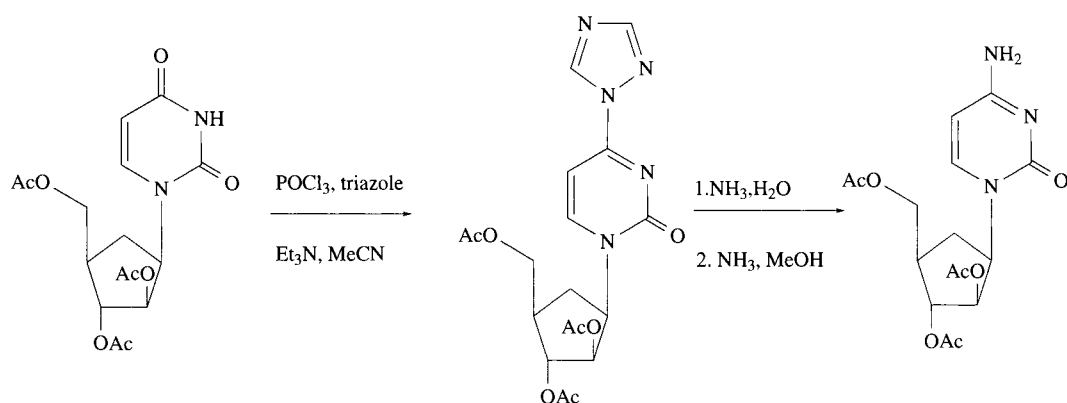
Halotriazoles can act as halogenating agents and *N*-acyltriazoles can act as acyl transfer reagents. Triazole can be used for the synthesis of peptide bonds and is superior to imidazole in that less racemization is observed. It can also be used to transfer the *t*-butyloxycarbonyl (*t*-Boc) protecting group to the nitrogen of amino acids. For details see Polya <84CHEC-I(5)733, p. 786>.

Divakar and Reese <82JCS(P1)1171> used triazole as a reagent having good nucleophilic and leaving-group properties for both the conversion of uridine into cytosine and for conversion of the corresponding arabinose derivatives (Scheme 37). This reaction has found further use in the conversion of other nucleotide and nucleoside derivatives <91S283, 91S947, 93ACS889>. In an interesting modification, the triazole ring has been constructed from the amine group of an adenine derivative and displaced by other nucleophiles, as illustrated in Scheme 38 <94JA9331>.

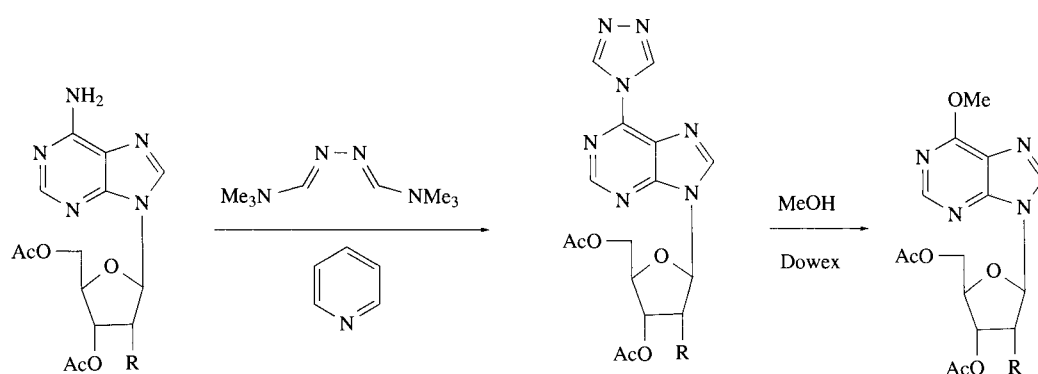
Other examples of triazole as a leaving group are known <93JHC333>. PTAD has been used as a protecting group for dienes (see Section 4.02.6.3).

4.02.12.2 Biological Uses

3-Aminotriazole has been used as a herbicide and defoliant and also as a histidine analogue. It is reported to inhibit intracellular catalase <93MI 402-01> and to block certain ethanol-induced behav-



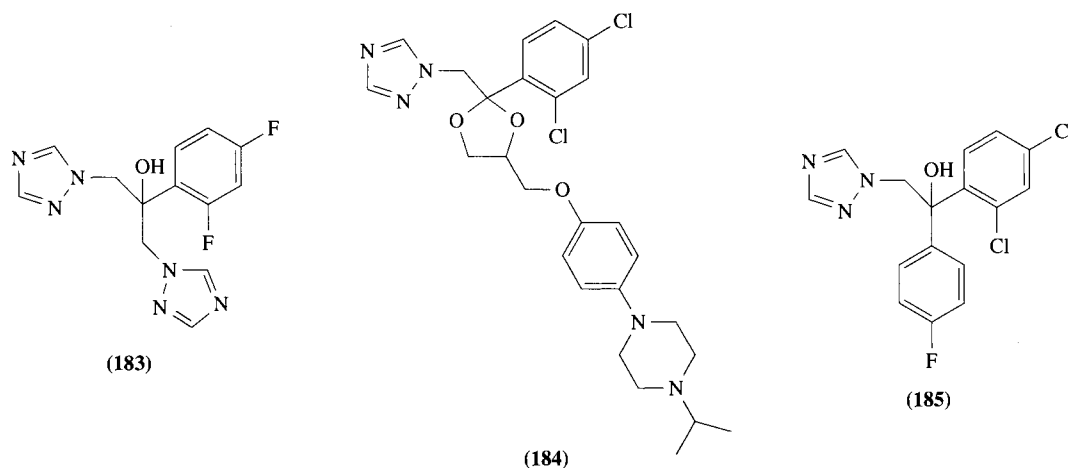
Scheme 37



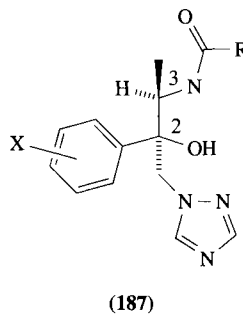
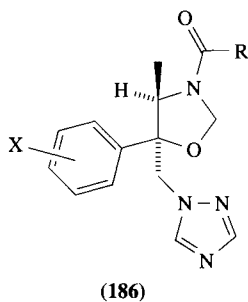
Scheme 38

journal effects <93BP1873>. 3-Nitrotriazole and derivatives have found use as radiosensitizers of hypoxic cancer cells <89CPB1951, 90T3211, 92CL915>. Simple 5-oxo- and 5-thio-3-aryltriazole derivatives have anticonvulsant activity <90JMC2772>. A precursor of paclobutrazol, an agrochemical, crystallizes from the racemic mixture as pure crystals of one enantiomer <90JPC3223>.

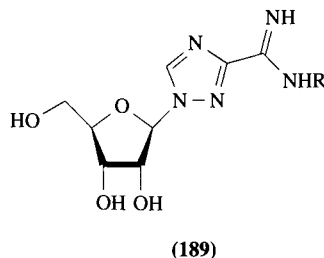
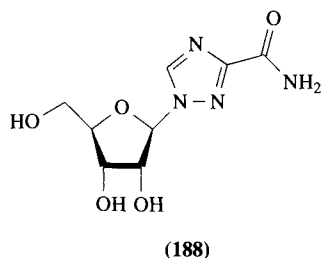
A variety of compounds related to fluconazole (**183**) <93JHC1405> have been prepared as potential antifungal agents, including terconazole (**184**) <83JMC611> and ICI 153,066 (**185**). These compounds appear to inhibit the biosynthesis of ergosterol, the major steroid in fungal membranes. The P-450 dependent 14- α -desmethylation of 24-methyldihydrolanosterol to ergosterol is blocked and 14- α -methylsteroids accumulate and the fungal cell membranes are disrupted (see <89JMC2231, 92EJM495, 92MI 402-01>). Fluconazole causes second bronchial arch anomalies in mice <93MI 402-02>.



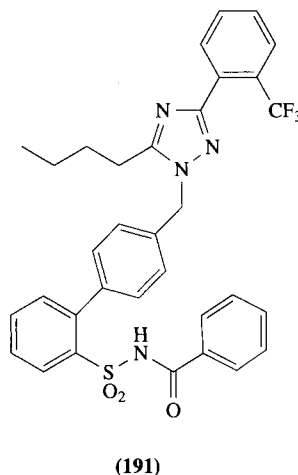
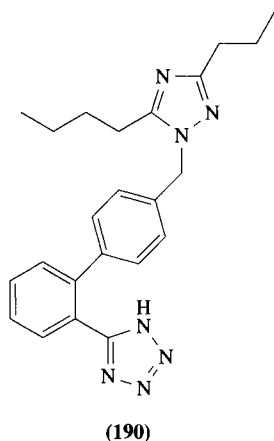
A number of compounds which control *Candida albicans* infections in mice have been prepared which contain 4,5-dihydrooxazole rings. It has been shown that only certain enantiomers are highly active (e.g., **186**, 4(R), 5(R)) <91TL7545>. The dihydrooxazole ring is not necessary if the substituents have the correct absolute stereochemistry (e.g., **187**, 2(R), 3(R)) <90CPB1258, 90CPB2476, 91BCJ2877, 91CPB2241, 91CPB2581, 91TL7545, 93CPB1035, 93CPB1043, 94BCJ1427>.



Ribavirin (**188**) is a broad spectrum antiviral agent consisting of a 3-amidotriazole as the *N*-glycoside of ribose. It is active against both RNA and DNA viruses and is used in an aerosol for lower respiratory tract viral disease. It is also used in the treatment of influenza, Lassa fever and Hantaan virus. A number of 3-sulfonamide derivatives have been prepared but these were devoid of antiviral or antitumor activity <88JHC1857>. A number of amidine and guanidine derivatives have been prepared (e.g., **189**, R = H.HCl, Me, CN), some of the guanidine derivatives also exhibiting broad spectrum antiviral activity <89JMC1447, 92JMC3231>.



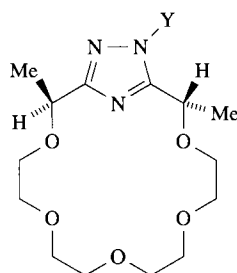
A number of triazole derivatives are angiotensin II receptor antagonists <93JMC101, 93JMC591, 93JMC2172, 94JHC2808, 94JMC4464>. Proceedings of a symposium on this subject have appeared <94BMC1>. The compounds act at the AT₁ receptor to mediate the action of angiotensin II to increase blood pressure. Examples of the type of compound involved are illustrated by SC-50560 (**190**) and L-159,913 (**191**).



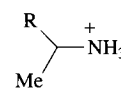
Some substituted 3-thiomethyltriazole derivatives show antithyroid activity <92EJM359> and some *N*-1-methylcarboxylates mimic the action of penicillins <92EJM193>. An A_{2a} adenosine receptor antagonist containing a triazole ring has been described <94BMC2539>.

4.02.12.3 Molecular Recognition

Triazoles have been incorporated into macrocyclic frameworks to participate in molecular recognition processes <85JOC3065>. The macrocycle (**192**) was synthesized as an enantiomer and can discriminate between enantiomers of specific ammonium salts (e.g., (**193**) R = naphth, Ph) <87H(26)989, 91JOC4193, 92T9545>. Other similar macrocycles have been prepared, some containing two triazole rings, and transport of ions through a liquid medium has been demonstrated <87JHC1085, 91JHC773, 94SI091, 94TA1291, 94TL7669>.



(**192**) Y = H, CH₂CO₂cholesteryl, n-dodecyl



(**193**)

4.02.12.4 In Inorganic Complexes

Triazole and various triazole derivatives have found extensive use as ligands in complexes of metals. 4,4'-Bitriazole (btr) forms the iron complex Fe(NCS)₂(btr)₂·H₂O which shows a high spin-low spin transition around 150 K <87JA5272>. A variety of other complexes have been reported <91IC3167>. The physical properties of complexes of 3-pyrazinyltriazoles with ruthenium <88AX(C)56, 91IC48> and 3,5-dipyridinyltriazoles with osmium <91IC641> and ruthenium <89AX(C)381, 91IC3263> have been reported. A variety of copper complexes containing triazole derivatives have been prepared <86CC1430, 89AX(C)601, 92IC198, 92JCS(D)3145, 93JCS(D)1371, 93JCS(D)2163>. Cadmium <90JCSR355>, mercury <93JOM(450)41>, and molybdenum <93JOM(453)211> complexes have been prepared, one molybdenum compound having bis-(*N*-1-triazole)boron as a ligand.

4.02.12.5 Other Uses

As discussed in CHEC-I <84CHEC-I(5)733, p. 788>, triazole has been used in dyes, photographic chemicals, and in the formation of polymers. Work in these areas continues and numerous papers have been published. Both oligopeptides <90H(31)1629> and photochromic polymers <92MI 402-02> containing the triazole group have been reported.

4.03

1,2,3-Oxadiazoles

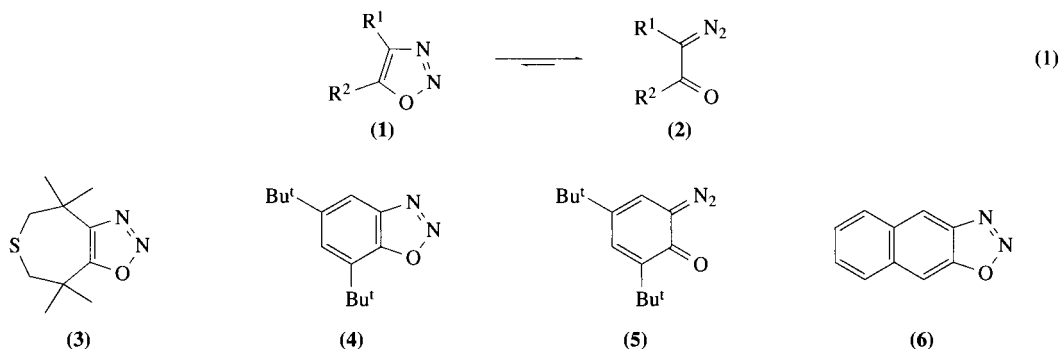
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University of Liverpool, UK

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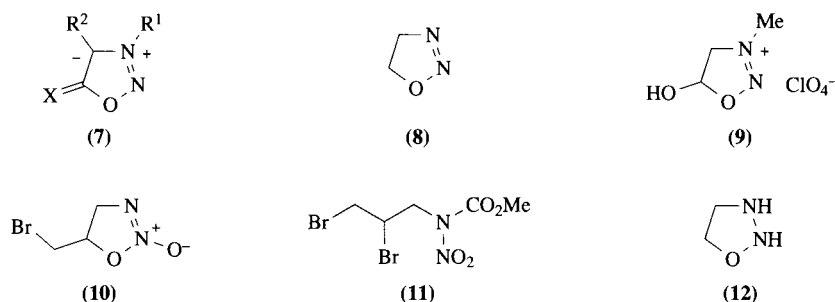
4.03.1 INTRODUCTION

With a few exceptions simple 1,2,3-oxadiazoles (**1**) are not isolable because they are less stable than their open tautomers (**2**) (Equation (1)). The sterically protected 1,2,3-oxadiazole (**3**) is the only known oxadiazole bearing alkyl substituents. It exists in the cyclic form in the crystalline state but as the diazoketone in chloroform solution <80TH 403-01>. 1,2,3-Benzoxadiazole has been detected in a matrix at 15 K <84AG(E)509>; this and some substituted 1,2,3-benzoxadiazoles have been shown to exist in equilibrium with their open-chain tautomers <91JST(247)135>. The position of the equilibrium is strongly dependent upon solvent and substituent effects; the most stable of the

compounds investigated was 5,7-di-*t*-butyl-1,2,3-benzoxadiazole (**4**), which is at least 1.5 kcal mol⁻¹ more stable than its tautomer (**5**) in the vapor phase. Naphth[2,3-*d*]-1,2,3-oxadiazole (**6**) is stable in the solid state at -15 °C in the absence of light <91AG(E)1476>. There are several examples in the older literature, and one in the more recent literature <84C387> of compounds that have been incorrectly formulated as 1,2,3-oxadiazoles. These examples, and the evidence against the 1,2,3-oxadiazole structures, have been summarized in a dissertation <94TH 403-01>.



The 1,2,3-oxadiazole ring system is well represented by the mesoionic sydnones (**7**; X = O) and sydnone imines (**7**; X = NR³). 4,5-Dihydro-1,2,3-oxadiazole (**8**) has been postulated as an intermediate in the metabolism of some (2-hydroxyethyl)nitrosamines and (2-haloethyl)nitrosoureas <94JOC3301> and one derivative, the salt (**9**), has been isolated as a crystalline solid <88JA5946>. 4,5-Dihydro-1,2,3-oxadiazoles could, in principle, be products of the dipolar cycloaddition of diazoalkanes to carbonyl compounds. It has not proved possible to detect them directly in such reactions <B-84MI 403-01> although dihydro-1,2,3-oxadiazole structures are occasionally proposed in the literature <82KGS679, 93T6053>. The *N*-oxide (**10**) has been isolated from the reaction of the nitramine (**11**) with potassium hydroxide <83IZV667>. Stable derivatives of the 1,2,3-oxadiazoline ring system (**12**) are unknown.



The preparation and reactions of 1,2,3-oxadiazoles have been reviewed by Meier and Hanold <94HOU(E8c)397>. 1,2,3-Oxadiazoles were described by Clapp in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)365>. The chemistry of sydnones is described in two other reviews <82T2965, 91MI 403-01>. For this chapter the literature published between 1982 and mid-1995 has been surveyed.

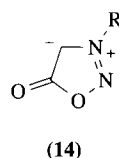
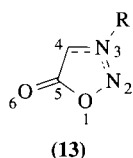
4.03.2 THEORETICAL METHODS

The geometry and energy of 1,2,3-oxadiazole have been calculated by an *ab initio* method <85AG(E)713>. The calculations indicate that the heterocycle is unlikely to be isolated as a discrete species, even in a matrix at low temperature, because there is a low energy barrier to ring opening to diazoacetaldehyde (Section 4.03.4). The same conclusion is reached on the basis of MNDO calculations, which also predict the relative stability of substituted 1,2,3-benzoxadiazoles and the isomeric diazocyclohexadienones <91JST(247)135>. Other calculations on 1,2,3-oxadiazole relate to its predicted dipole moment ($\mu = 3.70$ D) <74JCS(P2)420> and to its aromaticity <90JPR885, 93QSAR146>. The geometry and energy of 4,5-dihydro-1,2,3-oxadiazole (**8**) have also been calculated by *ab initio*

methods <94JOC3301>. The molecule (**8**) is predicted to be unstable, its most favorable mode of decomposition being a retro 1,3-dipolar addition to diazomethane and formaldehyde. This is in accord with the lack of examples of the forward reaction (Section 4.03.1).

During the period covered by this chapter there have been several further theoretical studies of the structure and properties of sydnones. Semiempirical MNDO calculations have been carried out on sydnone (**7**; $R^1, R^2 = H, X = O$) <87CB275> and on several sydnones for which x-ray crystal structures are available <85CCA15, 87CB275, 93JPC8193, 95JCS(P2)253>. The MINDO/3 method has been used to calculate the geometry and electron distribution in sydnone <82JOC786, 87CB275>. AM1 and a variety of *ab initio* calculations have also been performed on sydnones <86JST(136)261, 87CB275, 90IJQ153, 93JPC8193, 95JCS(P2)253>.

None of the calculations accurately reproduces the bond lengths in the sydnone ring; the best correlation with experimental data is obtained from *ab initio* calculations at the 3-21G level on 3-(4-tolyl)sydnone <95JCS(P2)253>. However, the semiempirical and *ab initio* calculations all provide the same overall picture of the bond lengths and bond order in sydnones. The substituents on the sydnone ring have very little effect on the bond lengths in the ring. Sydnones are best regarded as azomethine imines bearing a conjugative electron-withdrawing group (the carbonyl group) at the carbon terminus, C-4 <87CB275>. The bond from C-5 to the exocyclic oxygen is essentially a double bond, bonds O-1 to N-2, O-1 to C-5, and C-4 to C-5 are approximately single bonds and bonds N-2 to N-3 and N-3 to C-4 are partial double bonds, as shown in (**13**). Sydnones are not delocalized "aromatic" ring systems, although the most stable conjugate acid, which has a proton on the exocyclic oxygen atom, can be regarded as aromatic <85CCA15>.



A selection of calculations of net atomic charges is given in Table 1. The values show that different substituents have very little effect on the electron distribution. The semiempirical methods all show that C-4 is negatively charged, N-2 is approximately neutral, and N-3 bears a small positive charge. In contrast the *ab initio* calculations indicate that N-3 is negatively charged. These calculations are based on the Mullikan population analysis and may be unreliable for heteronuclear systems; other *ab initio* calculations, based on the Lowdin method, are more in accord with the semiempirical results <95JCS(P2)253>. Thus, the resonance structure (**14**) appears to be the best single representation. The calculated dipole moments (between 5.57 and 7.85 D for sydnone <87CB275> and between 7.40 and 9.48 D for 3-(4-tolyl)sydnone <95JCS(P2)253>) are consistent with the high values obtained by experiment.

Table 1 Calculated net atomic charges in sydnones.

<i>R</i> in (13)	Method	O-1	N-2	N-3	C-4	C-5	O-6	Ref.
H	MNDO	-0.14	-0.03	-0.01	-0.24	0.33	-0.26	87CB275
H	MINDO/3	-0.38	0.07	0.34	-0.40	0.79	-0.56	87CB275
Ph	MNDO	-0.15	-0.03	0.02	-0.25	0.33	-0.31	85CCA15
4-Me·C ₆ H ₄	MNDO	-0.15	-0.03	0.02	-0.25	0.33	-0.32	95JCS(P2)253
4-Me·C ₆ H ₄	AM1	-0.18	0.04	0.05	-0.39	0.32	-0.28	95JCS(P2)253
4-Me·C ₆ H ₄	<i>ab initio</i> ^a	-0.51	0.11	-0.73	-0.01	0.82	-0.63	95JCS(P2)253
4-EtO·C ₆ H ₄	MNDO	-0.15	-0.04	0.03	-0.25	0.34	-0.32	93JPC8193
4-EtO·C ₆ H ₄	AM1	-0.18	0.04	0.06	-0.39	0.32	-0.28	93JPC8193
4-EtO·C ₆ H ₄	<i>ab initio</i> ^a	-0.51	0.14	-0.75	-0.02	0.81	-0.64	93JPC8193

^a3-21G basis functions.

Calculations of the frontier orbital energies and coefficients for sydnone and for some substituted sydnones have also been carried out <87CB275>. The values for sydnone, calculated by the MINDO/3 method, are shown in Figure 1. The HOMO is a pure π -orbital with large coefficients on N-2 and C-4 <93JPC8193>. The values are not substantially different when other methods of calculation are used, and they are not greatly affected by substituents at N-3. The calculated HOMO-LUMO separation is consistent with the first ionization energy of 3-methylsydnone (8.9 eV) obtained experimentally by PE spectroscopy. The main significance of the calculations is that they lead to

the prediction that 1,3-dipolar cycloaddition of sydnones to electron-deficient alkenes (acrylonitrile, methyl acrylate, etc.) should be controlled by the HOMO of the sydnone and the LUMO of the dipolarophile (Figure 1). This is in contrast to earlier predictions that the reaction is controlled by the LUMO of the sydnone <82JOC786>.

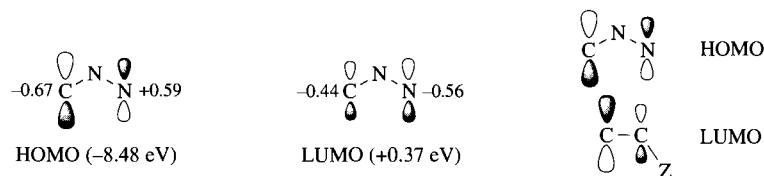
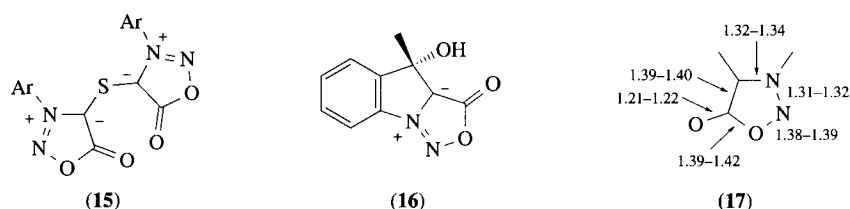


Figure 1 Frontier orbital energies and coefficients for sydnone, calculated by the MINDO/3 method, and the predicted dominant frontier orbital interaction with an electron-deficient alkene.

4.03.3 EXPERIMENTAL STRUCTURAL METHODS

4.03.3.1 X-ray Crystal Structures

The crystal structure of 4,5-dihydro-5-hydroxy-3-methyloxadiazolium perchlorate (**9**) has been obtained. This confirms that it has a cyclic structure and not an alternative (*N*-nitroso aldehyde) structure <88JA5949>. Crystal structure data have also been obtained for several sydnones in addition to those described earlier <84CHEC-1(6)365>. These include the following 3-substituted sydnones: 3-(4-tolyl)-<84AX(C)1226>, 3-(4-ethoxyphenyl)- <84AX(C)1226, 93JPC8193>, 3-(4-isopropoxyphenyl)-<85AX(C)1776>, 3-(4-benzyloxyphenyl)- <85AX(C)1776>, 3-cyclohexyl- <91MI 403-01>, 3-(3-pyridyl)-<91MI 403-01>, 4-acetyl-3-(4-tolyl)- <87AX(C)1122>, and 4-acetyl-3-phenylsydnone oxime <87AX(C)1122>. The structures of three sulfides (**15**) <89AX(C)471> and of the fused sydnone (**16**) <92AX(C)377> have also been reported; the bond lengths in (**16**) are not significantly different from those of other sydnones. Some of the x-ray data have been collated <95JCS(P2)253>. In these structures the sydnone ring is near-planar and the bond lengths (in Å) lie in the range illustrated in structure (**17**). The structures differ in the degree of twist between the 3-substituent and the heterocyclic ring: the twist angle ranges from 2.0° to 78.6° with different 3-aryl substituents <93JPC8193>.

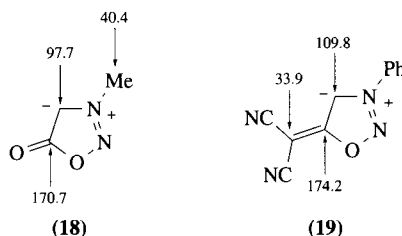


4.03.3.2 NMR Spectra

The ^{13}C NMR spectra of naphthoxadiazole (**6**) are consistent with its formulation as a 2,3-disubstituted naphthalene rather than as an *o*-quinone diazide; for example, the lowest field ^{13}C NMR signal is at δ 148.7 <91AG(E)1476>.

The ^1H , ^{13}C , ^{14}N , and ^{17}O NMR spectra of 3-methylsydnone have been recorded in order to provide a complete set of chemical shift values for all the atoms in the molecule <83BCJ2198>. The signal for H-4 is at δ 6.89 and that for the 3-methyl hydrogens at δ 4.31, in accord with earlier measurements. The ^{13}C chemical shifts are shown in (**18**). The ^{14}N chemical shift for N-3 is at 252.1 ppm (relative to NH_4^+) but N-2 appears as a very broad signal. Two signals in the ^{17}O spectrum appear at 234 and 389 ppm (relative to external D_2O). The signal at 234 ppm was assigned to the ring oxygen atom and that at 389 ppm to the exocyclic oxygen atom. The assignments of these signals were reversed in a later, more extensive, study by ^{17}O NMR spectroscopy in which specifically labeled sydnones were used <88HCA241>. ^{17}O spectra were also recorded for 3-phenylsydnone (O-1 388 ppm, exocyclic O 232 ppm) and for several related compounds, including the dicyano compound

(19) (339 ppm). The values for the sydnones are interpreted in terms of a highly polarized bond to the exocyclic oxygen atom. The ^{13}C chemical shifts of (19) have also been recorded (in d_6 DMSO) $\langle 84\text{CL1045} \rangle$ and are shown on the structure. Other ^{13}C spectra of sydnones have been reported $\langle 85\text{MI 403-01} \rangle$.



4.03.3.3 Mass Spectra

A molecular ion is seen in the electron impact mass spectrum of compound (6) but the base peak is that resulting from the loss of nitrogen [$M - 28$] $\langle 91\text{AG(E)1476} \rangle$. The electron impact mass spectra of sydnones show the loss of NO and CO, either consecutively or simultaneously $\langle 84\text{CHEC-I(6)365} \rangle$. A study of the CI mass spectra of protonated sydnones, with methane as the reagent gas, shows that HNO and CO are the fragments lost $\langle 89\text{H(29)185} \rangle$. The electron impact mass spectrum of compound (19) shows an intense molecular ion which loses NO and then HCN $\langle 85\text{JCS(P1)2439} \rangle$.

4.03.3.4 UV, PE, and IR Spectra

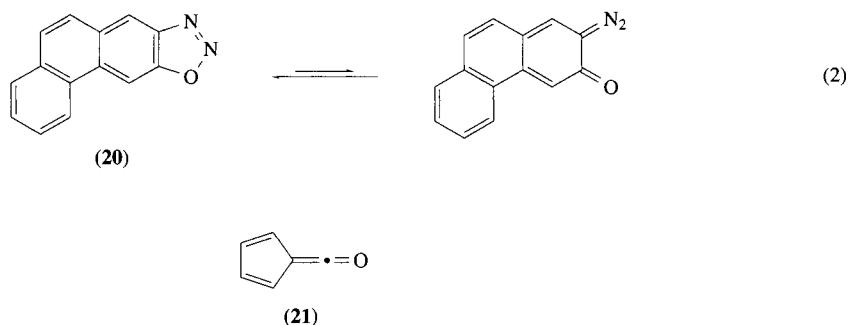
IR, UV absorption, and UV photoelectron spectroscopy have proved to be very useful in studying the equilibria between 1,2,3-benzoxadiazoles and *o*-quinone diazides. The IR spectrum of (6) shows absorptions at 1626, 1611, 1464, and 1457 cm^{-1} whereas the isomeric quinone diazide shows strong absorptions at 2090 and 1718 cm^{-1} $\langle 91\text{AG(E)1476} \rangle$. Similar spectra are observed for 1,2,3-benzoxadiazoles and *o*-benzoquinone diazides in argon matrices $\langle 91\text{JST(247)135} \rangle$. The UV absorption spectrum of 1,2,3-benzoxadiazole in an argon matrix shows maxima at 201, 243, and 289 nm; the spectrum in hexane shows maxima at 203 (ϵ 11000), 244 (4500) and 295 (2200) nm $\langle 84\text{AG(E)509, 91JST(247)135} \rangle$. Naphthoxadiazole (6) has a similar spectrum in heptane, the maxima being shifted to longer wavelengths compared with the spectrum of benzoxadiazole $\langle 91\text{AG(E)1476} \rangle$. From the PE spectrum of 1,2,3-benzoxadiazole the vertical ionization energies are 9.45 eV ($^2A'$ (π)), 9.95 ($^2A''$ (π)), 11.20 ($^2A'$ (σ_N)) and 12.37 eV ($^2A''$ (π)).

Carbonyl stretching frequencies of sydnones occur over a wide range, from 1720 to 1790 cm^{-1} . 3-Phenylsydnone has an IR absorption frequency for the exocyclic carbonyl group of 1757 cm^{-1} ; values for other 3-arylsydnones obey a modified Hammett equation $\langle 95\text{MI 403-01} \rangle$. Sydnones show a single maximum in the UV spectrum close to 300 nm.

4.03.4 THERMODYNAMIC ASPECTS

1,2,3-Oxadiazole (1; $\text{R}^1 = \text{R}^2 = \text{H}$) is calculated to be 8.9 kcal mol^{-1} less stable than its open chain tautomer (2) $\langle 85\text{AG(E)713} \rangle$. On the other hand, 1,2,3-benzoxadiazole is about 1 kcal mol^{-1} more stable than 2-diazocyclohexadienone $\langle 91\text{JST(247)135} \rangle$. The position of the equilibrium is markedly affected by substituents. The benzoxadiazole (4) is more stable than its tautomer (5) by about 1.5 kcal mol^{-1} but tetrafluorobenzoxadiazole is substantially less stable than the corresponding diazocarbonyl isomer. The open-chain forms are also favoured by polar solvents and by hydrogen bonding. In the naphthalene series, the stabilization of the fused oxadiazole (6) relative to its open chain tautomer can be ascribed to partial bond fixation in the naphthalene system, which disfavors

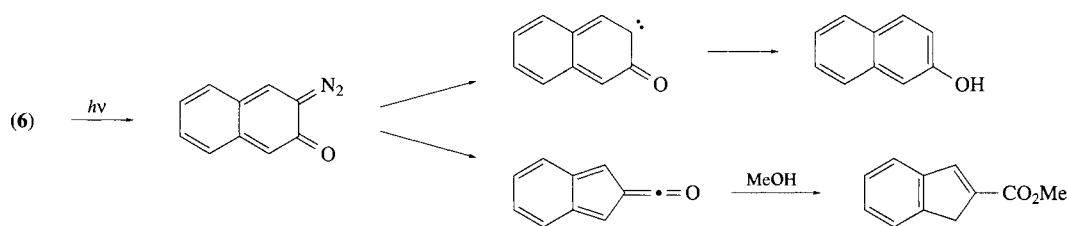
the diazoketone form. Similarly, phenanthro-1,2,3-oxadiazole (**20**) appears from NMR data to be more stable in solution than its valence tautomer (Equation (2)) <94TH 403-02>.



4.03.5 REACTIVITY OF CONJUGATED SYSTEMS

4.03.5.1 Benz-1,2,3-oxadiazoles and Naphth[2,3-*d*]-1,2,3-oxadiazole

Benzoxadiazole is cleaved to 2-diazocyclohexadienone by IR irradiation. The ketene (**21**) is then formed by the loss of nitrogen and (concerted) Wolff rearrangement <91JST(247)135>. Naphth[2,3-*d*]-1,2,3-oxadiazole (**6**), when irradiated in a mixture of hexane and methanol at 0–5°C, gives 2-naphthol and methyl indene-2-carboxylate. These products can also be accounted for by opening to the diazocarbonyl tautomer followed by the loss of nitrogen (Scheme 1) <94CB551>.



Scheme 1

4.03.5.2 Sydnone

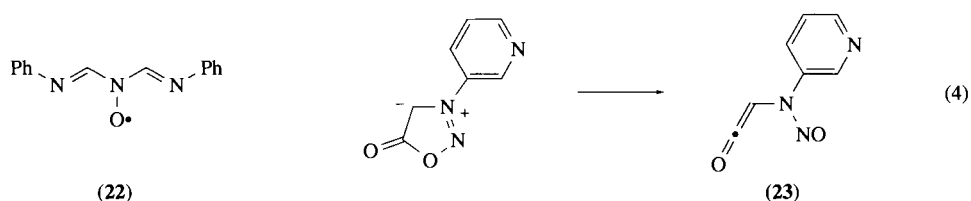
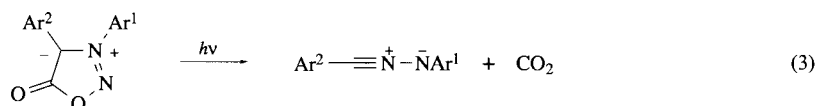
The chemistry of the 1,2,3-oxadiazole ring system is confined almost entirely to the mesoionic sydnones and related compounds. Sydnones are sensitive to hydrolysis, especially in basic media where they are rapidly cleaved. Nevertheless a range of useful reactions of sydnones, involving both ring cleavage and substitution with retention of the ring system, is known. Many of the publications that have appeared in the period 1982–1995 represent modifications or extensions to known reactions of sydnones. The subjects covered include the following.

Substituents can be introduced into the 4-position of sydnones by conventional electrophilic substitution but there are also several examples of electrophilic substitution following metallation at C-4 <95H(41)1525>. Standard transformations of functional groups at C-4 of sydnones have also been extensively investigated. In particular, these reactions have been used to synthesize sydnones bearing a variety of heterocyclic substituents at the 4-position <92MI 403-01>. Sydnones can act as 1,3-dipoles and there are some useful synthetic applications of their dipolar cycloaddition reactions.

In the following sections the emphasis is on work published during the period covered by this chapter but earlier work is mentioned where appropriate. The earlier work is described in more detail in other reviews <82T2965, 84CHEC-I(6)365, 94HOU(E8c)397>.

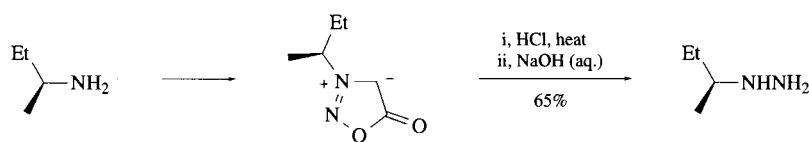
4.03.5.2.1 Unimolecular ring cleavage

Sydneses are cleaved by UV irradiation but the products depend upon the nature of the substituents. 3,4-Diarylsydneses lose carbon dioxide on irradiation and give transient nitrile imines (Equation (3)). These intermediates have been generated by flash photolysis of diarylsydneses and have been intercepted by dipolarophiles <87MI 403-01, 89JPR789>. The nitrile imines have also been intercepted by internal dipolarophiles <86HCA927>. Nitrile imines have not been detected from 3-arylsydneses unsubstituted at C-4 but the radical species (22) was detected by ESR from the photolysis of 3-phenylsydnone <91MI 403-02>. Some sydneses are known to develop a color when irradiated by UV light and the ketene (23) has been identified as the blue species formed from 3-(3-pyridyl)sydnone (Equation (4)) <94MI 403-01>.

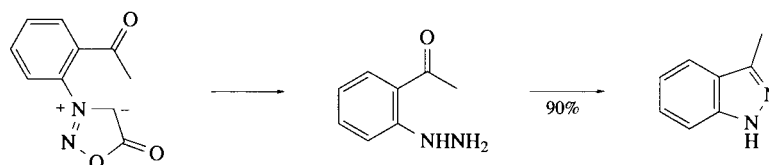


4.03.5.2.2 Acid-catalyzed ring cleavage

The acid-catalyzed cleavage of sydneses is useful for the preparation of hydrazines. Primary amines can be converted into the corresponding hydrazines by way of sydneses as intermediates. The method is exemplified by the conversion of (*S*)-2-butylamine into (*S*)-2-butylhydrazine shown in Scheme 2 <76CJC2639>. Preparations of 3-pyridylhydrazines <88JHC1055> and arylhydrazines <94MI 403-02> have also been reported. When the aryl group bears a suitable *ortho* substituent the reaction can lead to the formation of heterocycles <88JHC1817, 92HCA1931>; an example is shown in Scheme 3.



Scheme 2

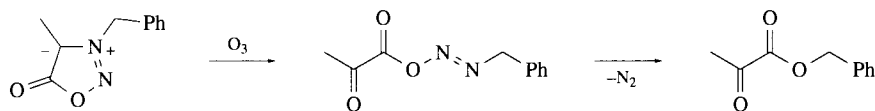


Scheme 3

4.03.5.2.3 Oxidative ring cleavage

4-Phenyl-3-benzylsydnone is cleaved by reaction with oxygen in the dark and gives a mixture of products including benzaldehyde, benzoic acid, and benzyl benzoate <83JOC1444>. Mechanisms have

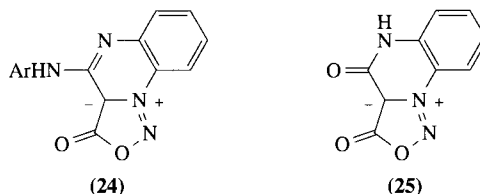
been suggested for the reaction involving radical intermediates. 4-Methylsydnones are oxidized by ozone to pyruvate esters (Scheme 4) <84JA3701>. Oxidative cleavage by Cytochrome P-450 has also been reported <86JA5584>.



Scheme 4

4.03.5.2.4 Electrophilic substitution at C-4

Electrophiles can be introduced directly into sydnones unsubstituted at C-4 and there are many examples quoted in earlier reviews. There have been further studies of the Vilsmeier–Haack formylation <83MI 403-01> and of the halogenation <85MI 403-02> of 4-unsubstituted sydnones. Halogenation reactions were performed in 10% sulfuric acid using *N*-halosuccinimides in suspension. In these conditions 4-chloro-, 4-bromo-, and 4-iodosydnones can be obtained in good yield. The position of electrophilic substitution of 3-arylsydnones depends upon the nature of the aryl group. Thus, for example, 3-(2-aminophenyl)sydnone is brominated in the benzene ring *para* to the amino group <94JHC1631> whereas the sydnone ring is brominated in preference to a pyrazolyl ring <83CJC154>. Intramolecular electrophilic substitution at C-4 can provide a route to fused sydnones; compounds (24) <91S745> and (25) <94H(38)2023> have been synthesized in this way.



Electrophiles can also be introduced at C-4 by way of organometallic intermediates. These reactions are described in Section 4.03.7.

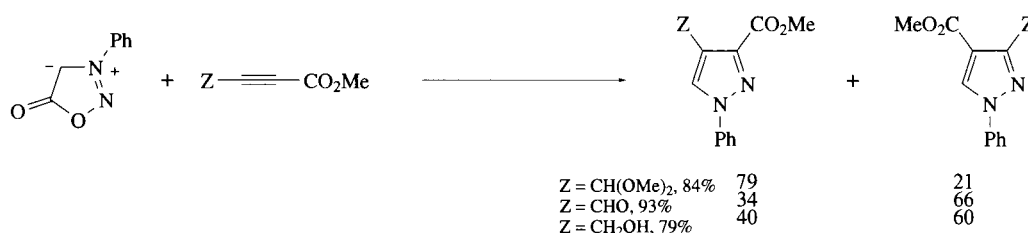
4.03.5.2.5 Nucleophilic attack at hydrogen (deprotonation)

Metallation reactions at C-4 of sydnones have been reviewed <95H(41)1525>. Typical conditions for 3-arylsydnones involve reaction of the sydnone with butyllithium at -50°C <86BCJ483>; methylmagnesium bromide has also been used as the base <92MI 403-02>. These reactions are invariably used as a means of effecting electrophilic substitution at C-4 as described in Section 4.03.7.

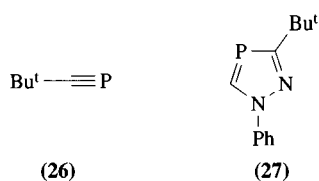
4.03.5.2.6 1,3-Dipolar cycloaddition reactions

Sydnones can be regarded as cyclic azomethine imines and as such, they undergo thermal cycloaddition reactions with a range of dipolarophiles <B-84MI 403-02>. On photolysis 3,4-diarylsydnones lose carbon dioxide and give nitrile imines, which can also be intercepted by dipolarophiles (Section 4.03.5.2.1). Thermal reactions with acetylenic dipolarophiles lead to the formation of pyrazoles by spontaneous loss of carbon dioxide from the cycloadducts. One disadvantage of the reaction as a preparative method is that the reactions are rarely completely regioselective with unsymmetrical alkynes. This is illustrated by the reactions of 3-phenylsydnone with acetylenic esters (Scheme 5) <89H(29)967>. Benzenesulfonylacetylenes show greater regioselectivity, in favour of the

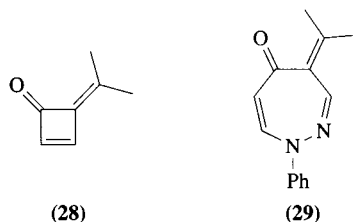
4-benzenesulfonylpyrazoles <85JCS(P1)2621>. The phosphalkyne (**26**) also adds to 3-phenylsydnone regioselectively to give the heterocycle (**27**) in high yield <87CB1809>.



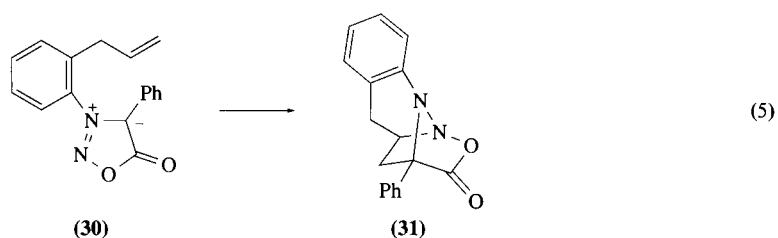
Scheme 5



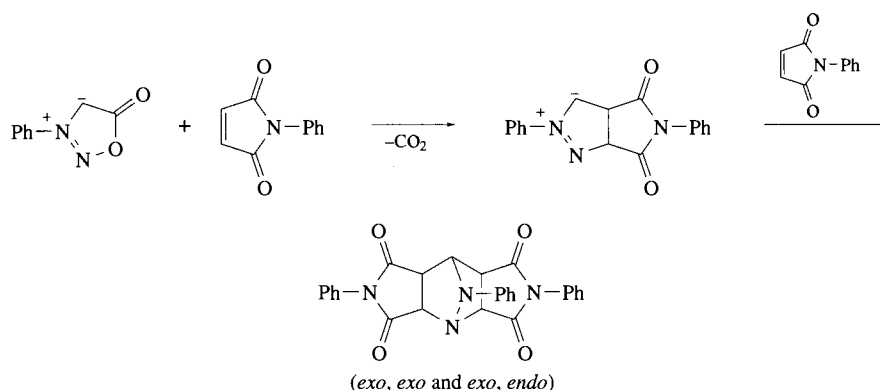
With monosubstituted alkenes bearing conjugative electron-withdrawing groups, the regioselectivity of the addition is preferentially that predicted by the frontier orbital analysis shown in Figure 1; that is, with the carbon bearing the electron-withdrawing substituent Z next to nitrogen. Unfortunately this analysis does not extend to disubstituted alkenes. Thus, the cyclobutenone (**28**) adds to 3-phenylsydnone to give the diazepin-5-one (**29**); other sydnone also show regioselectivity that favours this isomer over the alternative diazepin-4-one <87CB275>.



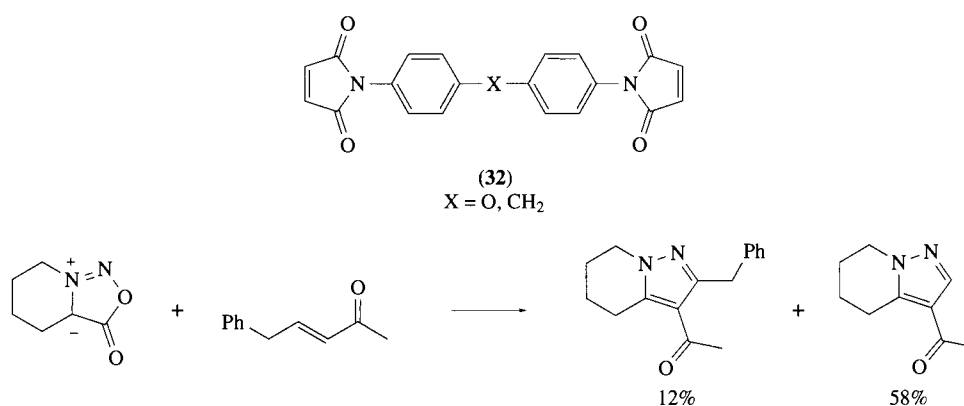
The addition to alkenes normally leads to unstable adducts that lose carbon dioxide under the reaction conditions. The intramolecular cycloaddition of the sydnone (**30**) takes place at room temperature, however (Equation (5)) and the cycloadduct (**31**) has been characterized <86HCA927>. The unstable species formed by the loss of carbon dioxide are also azomethine ylides. It is therefore possible for a second 1,3-dipolar addition to take place, as illustrated in Scheme 6 for the reaction of 3-phenylsydnone with *N*-phenylmaleimide <86TL317, 92JA8414>. This 2 : 1 addition has been used as the basis of a synthesis of polyimides. Imides of the type (**32**) were used as the dipolarophiles and their reaction with 3-phenylsydnone gave linear polymers <87MM726>.



The final products derived from 1 : 1 addition of sydnone to alkenes are usually pyrazoles or dihydropyrazoles. The pyrazoles are formed by oxidation of intermediate dihydropyrazoles. An unusual example of aromatization by elimination of an alkane (toluene) in preference to hydrogen is illustrated in Scheme 7 <89TL4625>.



Scheme 6



Scheme 7

4.03.6 REACTIVITY OF NONCONJUGATED RINGS

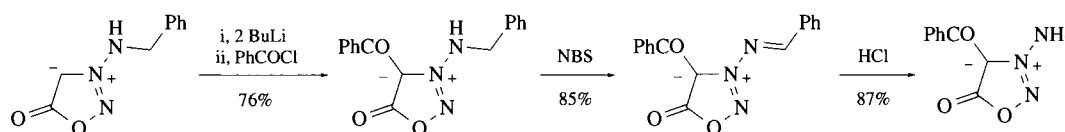
The known chemistry is limited to 4,5-dihydro-3-methyl-1,2,3-oxadiazolinium salts, which have been studied in order to elucidate the mechanism of action of (β -hydroxyethyl)nitrosamines as alkylating agents <94DIS(B)4671, 94JOC3301>. The cation undergoes attack by nucleophiles at the methyl group (resulting in methylation of the nucleophile) or at C-5, which leads to opening of the ring.

4.03.7 . REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4.03.7.1 Reactivity of Substituents Attached to C-4

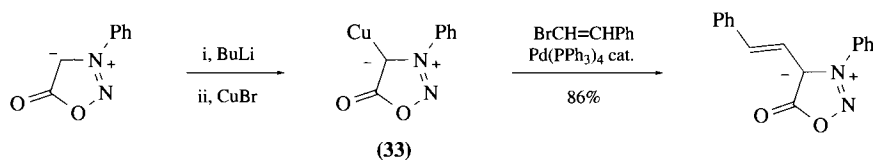
4.03.7.1.1 Reactions of C-4 metallated species

A variety of electrophiles can be introduced into the 4-position of 3-arylsydnone by way of 4-lithio intermediates <84CHEC-I(6)365>. The method has been used to introduce several sulfur, selenium, and tellurium electrophiles <86BCJ483, 86BCJ487> and to introduce formyl and acetyl substituents <92MI 403-02>. 3-Amino-4-benzoylsydnone, the first example of a sydnone with a primary amino substituent at N-3, was prepared by using this method to introduce the benzoyl group (Scheme 8) <88H(27)1697>.

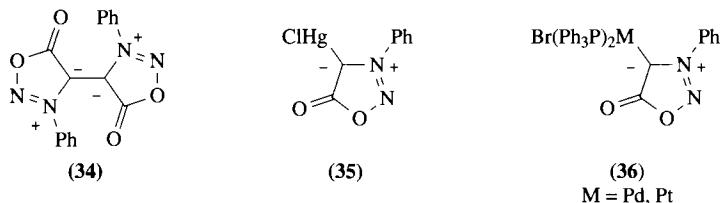


Scheme 8

Other organometallic species have been used to introduce vinyl and aryl substituents at C-4, 4-lithio-3-phenylsydnone reacted with copper(I) bromide to give a thermally stable copper species (33). This underwent palladium(0) catalyzed coupling to iodobenzenes and to vinyl bromides (Scheme 9) <88JOM(352)C34>. Reaction of the lithio intermediate with copper(II) chloride gave the dimer (34) <88JOM(352)C34>. The chloromercurio species (35) has been used in Heck-type coupling reactions with vinyl halides and the sydnone (36) bearing palladium and platinum substituents have been generated from 4-bromo-3-phenylsydnone and $M(PPh_3)_4$ at room temperature <89JOM(379)195>.



Scheme 9



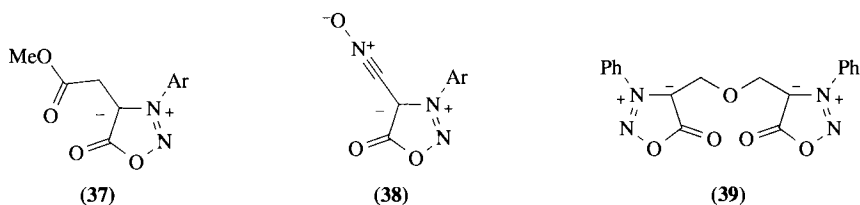
4.03.7.1.2 Replacement of C-4 substituents by hydrogen

A substituent at C-4 can be used as a temporary blocking group to allow reaction to take place at another site in a sydnone. For example, 4-acetyl-3-phenylsydnone was nitrated in the benzene ring (at the *meta* position) and the acetyl substituent was then removed by reaction with barium hydroxide <94CJC1610>. Formyl groups <93MI 403-01> and bromoacetyl groups <94MI 403-03> have similarly been removed under basic conditions.

The 4-bromo substituent of 4-bromo-3-arylsydnone has been replaced by hydrogen using either sodium dithionite <86SC461> or sodium sulfite <89SC2249>.

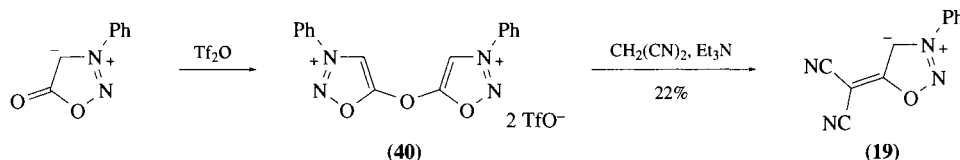
4.03.7.1.3 Other reactions

Standard functional group transformations of 4-formylsydnone include reduction <84MI 403-03>, Claisen-Schmidt condensation with acetophenone <93MI 403-01> and condensation with nitroalkanes <94MI 403-04>. 4-Acetyl-3-arylsydnone is converted into the methyl esters (37) by reaction with thallium(III) nitrate and methanol <84MI 403-03>. 4-Aryl-3-formylsydnone can be converted into their oximes in the normal way and the oximes have been used to prepare several other functionalized sydnone. Dehydration gives the corresponding nitriles <86MI 403-01>. The nitrile oxides (38) have been generated from the corresponding hydroximoyl chlorides <88MI 403-01>. 4-Hydroxymethyl-3-phenylsydnone is converted into the ether (39) by reaction with sulfuric acid <93CJC796>. Several sydnone bearing five-membered heterocyclic substituents at C-4 (thiazolyl, 1,2,4-oxadiazolyl, etc.) have been prepared by standard procedures <83BCJ3535, 84BCJ1362, 86MI 403-02, 89MI 403-01>.

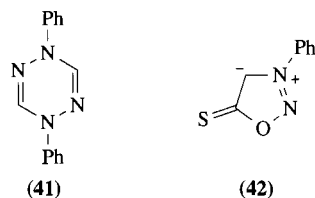


4.03.7.2 Reactivity at C-5

3-Phenylsydnone reacts with triflic anhydride to give the salt **(40)** <84CL1045>. The air-stable sydnone ylide **(19)** can be produced from this salt by reaction with malononitrile (Scheme 10) <85JCS(P1)2439, 95JCS(P1)1989>. 1,4-Dihydro-1,4-diphenyl-1,2,4,5-tetrazine **(41)** is formed in quantitative yield when 3-phenylsydnone is heated with Lawesson's reagent. The thione **(42)** is probably an intermediate since this gives the same product with Lawesson's reagent <88BCJ2977>.



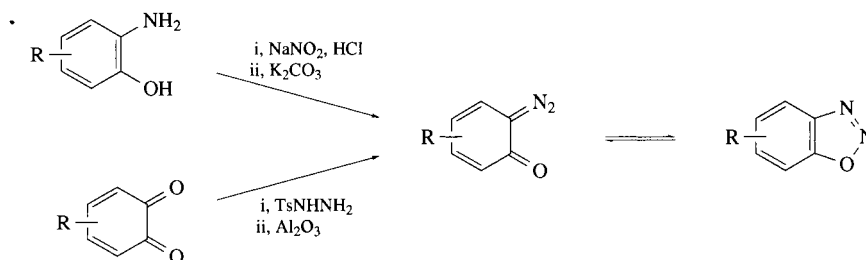
Scheme 10



4.03.8 RING SYNTHESSES

4.03.8.1 Benz-1,2,3-oxadiazoles and Naphth[2,3-*d*]-1,2,3-oxadiazole

Routes to benzoxadiazoles are based on approaches to the tautomeric 6-diazo-2,4-cyclohexadienones (Scheme 11) <91JST(247)135>. The appropriate 2-aminophenol hydrochloride is diazotized using either sodium nitrite or isoamyl nitrite and the diazonium chloride is then carefully neutralized with sodium carbonate or potassium carbonate. An alternative approach is from the monotosylhydrazide of the appropriate *o*-benzoquinone. Naphthoxadiazole **(6)** was prepared, in a manner analogous to the first route of Scheme 11, from 3-amino-2-naphthol <91AG(E)1476>. A slightly modified preparation is described in a later paper; the method was applied to the synthesis of [9a-¹³C]naphth[2,3-*d*]-1,2,3-oxadiazole from 3-amino-[2-¹³C]-2-naphthol <92MI 403-03>.

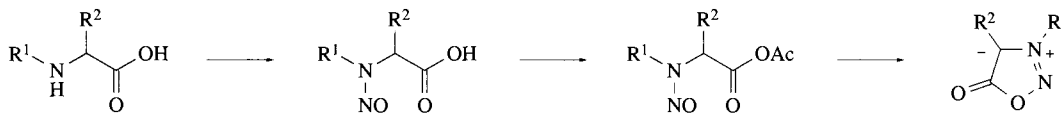


Scheme 11

4.03.8.2 Sydnone

The standard route to sydnones (Scheme 12) remains as the only general entry to this class of compounds. The nitrosation step has been carried out under neutral conditions, using isoamyl

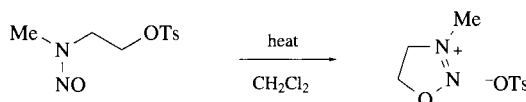
nitrite as the nitrosating agent. This allows functionalized 3-arylsydnonones to be prepared in good yield <88S1011>. The cyclization step is aided by ultrasonic irradiation and 3-arylsydnonones have been isolated in high yield from these reactions <87MI 403-02, 94MI 403-05>.



Scheme 12

4.03.8.3 4,5-Dihydro-1,2,3-Oxadiazoles

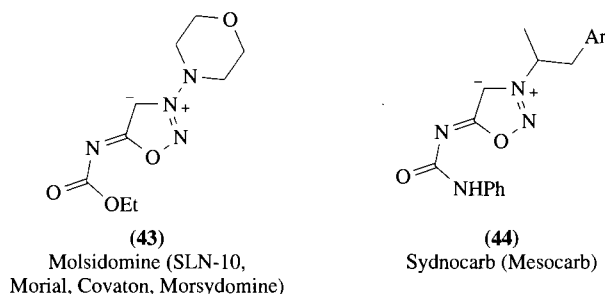
Methods of preparation of the few known compounds of this type were outlined in Section 4.03.1. The preparation of 4,5-dihydro-3-methyl-1,2,3-oxadiazolium tosylate is shown in Scheme 13 <94JOC3301>. Analogues bearing a 5-alkoxy substituent can be prepared by the cyclization of 2,2-dialkoxy-*N*-methyl-*N*-nitrosoethylamines <94DIS(B)4671>.



Scheme 13

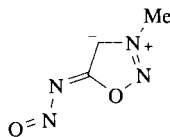
4.03.9 IMPORTANT COMPOUNDS AND APPLICATIONS

1,2,3-Oxadiazole derivatives have a wide range of biological activities. The two most important and widely studied derivatives are the sydnonimines Molsidomine (**43**) and Sydnocarb (**44**). Molsidomine has a long-term effect in vasodilation and thus reduces the work of the heart in cases of ischaemic heart disease. In combination with the β -blocker propranolol, molsidomine has been shown to be highly effective for the treatment of portal hypotension <96MI 403-01>. Molsidomine is also an effective treatment for angina <85MI 403-03>. The pharmacological activity of this drug is believed to be related to the formation of a metabolite, *N*-morpholino-*N*-nitrosoaminoacetonitrile, which acts as a nitric oxide donor <95BJP1371>. Molsidomine has also been used in the treatment of congestive heart disease <95MI 403-02>. Sydnocarb acts on the central nervous system and has been used as a psychostimulant <87MI 403-03> and an antidepressive.

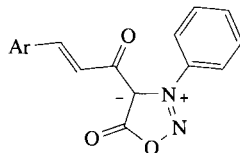


The nitrosoimine derivative RE 2047 (**45**) in combination with pentoxifylline demonstrates potent antithrombotic activity <95AP(328)71>. Other sydnonones with pharmacological activity include derivatives of the general formulas (**46**) and (**47**). These agents were shown to have antiinflammatory, analgesic, and antipyretic activity <95JPS263>. 3-Arylsydnonones have been intensively studied because

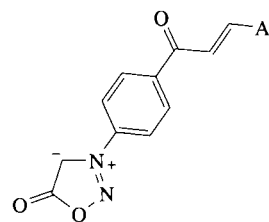
of their CNS activity. In addition, agents in this class possess good antimicrobial activity <94JCR(S)502>.



(45) RE 2047

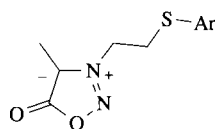


(46)



(47)

The 3-arylthioethylsydnone (**48**) (TTMS) has been investigated as a P450 inactivator. Metabolism of this derivative results in *N*-alkylation and deactivation of the P450 catalytic site <88BJ(22)4805>. As a result of this metabolic pathway TTMS acts as a potent inhibitor of ferrochelatase.



(48) TTMS
Ar = 2,4,6-Me₃C₆H₂

Many other sydnone derivatives have been tested for antioxidant activity <95JPP623>, antitumour activity <94MI 403-06>, antifungal activity <95IJC(B)346>, and analgesic activity <95EJM641>.

The use of sydnone derivatives for the synthesis of polyimides is referred to in Section 4.03.5.2.6. 3-Methylsydnone has been used as a polar, water-miscible solvent for electrolytes <84CL1477>.

ACKNOWLEDGEMENT

The authors thank Professor Zeller of the University of Tübingen for advice and for unpublished information on the 1,2,3-oxadiazole ring system.

4.04

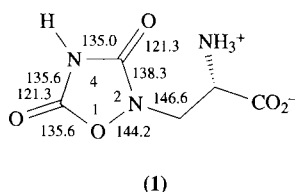
1,2,4-Oxadiazoles

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Universität Konstanz Germany

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4.04.1 LITERATURE ON 1,2,4-OXADIAZOLES

The chemistry of 1,2,4-oxadiazoles has been repeatedly reviewed <61MI 404-01, 62MI 404-01, 65FCF807, 76AHC(20)65, 84CHEC-I(6)378, 94HOU(E8c)409>. Eloy's review from 1965 contains a list of about 420 1,2,4-oxadiazoles containing melting and boiling points, vapor pressures, and heats of vaporization. In 1993/94, our knowledge on 1,2,4-oxadiazoles grew at an annual rate of about 200 publications. More than 60% of these publications concerned biological activities of 1,2,4-oxadiazoles, especially of quisqualic acid (**1**), the only naturally occurring 1,2,4-oxadiazole known hitherto.



4.04.2 THEORETICAL METHODS

Many quantum mechanical calculations for 1,2,4-oxadiazoles have been published <67TCA342, 86JST(136)215, 90IJQ153, 90JPR885>. Proton affinities and pK_a -values of amino substituted 1,2,4-oxadiazoles have been calculated <89KGS508>. INDO calculations on 3-phenyl-1,2,4-oxadiazole and its 5-methyl analogue suggest that nucleophilic attack should occur on C(3) and C(5) <88JCS(P2)117>. In connection with pharmacological structure-activity relationships, electrostatic maps of the surroundings of several 1,2,4-oxadiazoles have been calculated <91JMC140, 91JMC1086>.

According to CNDO/2 calculations the ring of 4,5-dihydro-1,2,4-oxadiazoles is planar and, in contrast to the 1,2,4-oxadiazole ring, is quite polar <77JOC1555>. In the first excited singlet state the dipole moments of the 4,5-dihydro heterocycles increase dramatically, again in contrast to those of 1,2,4-oxadiazoles. In agreement with absorption and fluorescence spectra, a 3-phenyl group donates electrons into the oxadiazoline ring in the ground state but attracts electrons in the first excited state. On the other hand, a 3-phenyl group attracts electrons from the oxadiazole ring in both the ground and the excited state.

4.04.3 EXPERIMENTAL STRUCTURAL METHODS

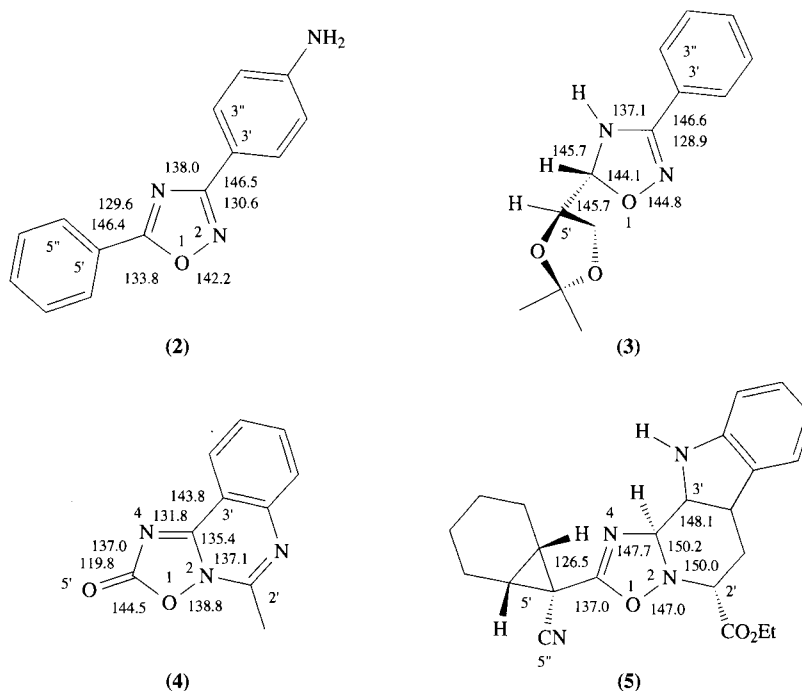
4.04.3.1 X-ray Diffraction

More than forty x-ray diffraction analyzes for 1,2,4-oxadiazoles and a 1,2,4-oxadiazolium salt <86JMC1540> have been reported and data for compounds (**1**)–(**5**) are presented as representative.

Selected bond angles and dihedral angles for (**1**) are O(1)–N(2)–C(3) = 107.1°, N(2)–C(3)–N(4) = 106.1°, C(3)–N(4)–C(5) = 111.8°, N(4)–C(5)–O(1) = 107.7°, C(5)–O(1)–N(2) = 106.5°, O(1)–N(2)–C(2') = 111.6°, C(3)–N(2)–C(2') = 121.6°, N(2)–C(3)–O(3') = 123.9°, N(4)–C(3)–O(3') = 130.0°, N(4)–C(5)–O(5') = 130.7°, O(1)–C(5)–O(5') = 121.6°, O(1)–N(2)–C(3)–N(4) = 8.3°, N(2)–C(3)–N(4)–C(5) = –4.5°, C(3)–N(4)–C(5)–O(1) = –1.4°, N(4)–C(5)–O(1)–N(2) = 6.5°, C(5)–O(1)–N(2)–C(3) = –9.2°, C(2')–N(2)–O(1)–C(5) = –37° <88MI 404-01>. The ring is essentially planar. The geometry around N(2) is pyramidal.

Selected bond angles and dihedral angles for (**2**) are O(1)–N(2)–C(3) = 103.37(5)°, N(2)–C(3)–N(4) = 114.23(7)°, C(3)–N(4)–C(5) = 102.76(7)°, N(4)–C(5)–O(1) = 113.69(6)°, C(5)–O(1)–N(2) = 105.95(5)°, O(1)–C(5)–C(5') = 119.08(7)°, N(2)–C(3)–C(3') = 123.60(7)°, N(4)–C(3)–N(3') = 122.17(7)°, N(4)–C(5)–C(5') = 127.22(8)°, C(3')–C(3')–C(3)–N(4) = –3.8(2)°, C(5')–C(5')–C(5)–N(4) = 3.7(3)°, C(5')–C(5')–C(5)–O(1) = 177.3(2)° <78AX(B)3390, 94AX(C)807>. The oxadiazole ring is planar. The bond lengths have been interpreted as consistent with the heterocycle having some aromatic character.

Selected bond angles and dihedral angles for (**3**) are O(1)–N(2)–C(3) = 106.0(2)°, N(2)–C(3)–N(4) = 114.3(2)°, C(3)–N(4)–C(5) = 106.6(2)°, N(4)–C(5)–O(1) = 102.4(2)°, C(5)–O(1)–N(2) = 108.5(2)°, O(1)–C(5)–C(5') = 111.3(2)°, N(2)–C(3)–C(3') = 122.4(2)°, N(4)–C(3)–N(3') = 123.2(2)°, N(4)–C(5)–C(5') = 112.4(2)° <90H(31)233>. The dihedral angle



between the mean square planes of the phenyl ring and the central ring is 21.7° ; the torsional angle between the two heterocycles was found to be 70.9° . The oxadiazole ring is planar. The bond length of $137.1(3)$ pm for $\text{C}(3)\text{—N}(4)$ indicates a partial double bond character. In 4,5-dihydro-3,4-diphenyl-1,2,4-oxadiazol-5-one, $\text{N}(4)$ is sp^2 hybridized with its lone pair orthogonal to the plane of the heterocycle $\langle 87\text{AX}(\text{C})1587 \rangle$. The bonds $\text{N}(4)\text{—C}(3)$ ($136.9(3)$ pm) and $\text{N}(4)\text{—C}(5)$ ($136.3(3)$ pm) show considerable double bond character.

Selected bond angles for **(4)** are $\text{O}(1)\text{—N}(2)\text{—C}(3) = 108.4^\circ$, $\text{N}(2)\text{—C}(3)\text{—N}(4) = 112.9^\circ$, $\text{C}(3)\text{—N}(4)\text{—C}(5) = 105.8^\circ$, $\text{N}(4)\text{—C}(5)\text{—O}(1) = 110.0^\circ$, $\text{O}(1)\text{—N}(2)\text{—C}(2') = 124.3^\circ$, $\text{C}(3)\text{—N}(2)\text{—C}(2') = 127.4^\circ$, $\text{N}(2)\text{—C}(3)\text{—C}(3') = 115.6^\circ$, $\text{N}(4)\text{—C}(3)\text{—C}(3') = 131.6^\circ$, $\text{N}(4)\text{—C}(5)\text{—O}(5') = 132.2^\circ$, $\text{O}(1)\text{—C}(5)\text{—O}(5') = 117.9^\circ$ $\langle 76\text{TL}3615 \rangle$. According to the bond angles reported the ring must be planar.

Selected bond angles and dihedral angles for **(5)** are $\text{O}(1)\text{—N}(2)\text{—C}(3) = 99.4(1)^\circ$, $\text{N}(2)\text{—C}(3)\text{—N}(4) = 105.9(1)^\circ$, $\text{C}(3)\text{—N}(4)\text{—C}(5) = 103.7(1)^\circ$, $\text{N}(4)\text{—C}(5)\text{—O}(1) = 117.8(2)^\circ$, $\text{C}(5)\text{—O}(1)\text{—N}(2) = 104.7(1)^\circ$, $\text{O}(1)\text{—N}(2)\text{—C}(2') = 105.6(1)^\circ$, $\text{C}(3)\text{—N}(2)\text{—C}(2') = 110.4(1)^\circ$, $\text{N}(2)\text{—C}(3)\text{—C}(3') = 110.0(1)^\circ$, $\text{N}(4)\text{—C}(3)\text{—C}(3') = 116.0(1)^\circ$, $\text{N}(4)\text{—C}(5)\text{—C}(5') = 128.1(2)^\circ$, $\text{O}(1)\text{—C}(5)\text{—C}(5') = 114.0(1)^\circ$, $\text{O}(1)\text{—N}(2)\text{—C}(3)\text{—N}(4) = -28.2^\circ$, $\text{N}(2)\text{—C}(3)\text{—N}(4)\text{—C}(5) = 20.6^\circ$, $\text{N}(4)\text{—C}(5)\text{—O}(1)\text{—N}(2) = -15.6^\circ$, $\text{C}(5)\text{—O}(1)\text{—N}(2)\text{—C}(3) = 25.7^\circ$, $\text{C}(5)\text{—O}(1)\text{—N}(2)\text{—C}(2') = -88.7^\circ$, $\text{N}(4)\text{—C}(5)\text{—C}(5')\text{—C}(5'') = -151.2^\circ$, $\text{C}(5)\text{—N}(4)\text{—C}(3)\text{—C}(3') = 142.9^\circ$, $\text{N}(2)\text{—O}(1)\text{—C}(5)\text{—C}(5') = 161.3^\circ$ $\langle 88\text{MI} 404\text{-}02 \rangle$. The oxadiazoline ring is nonplanar.

4.04.3.2 NMR Spectra

The ^1H NMR shifts (ppm relative to TMS as internal standard) shown in Figure 1 were calculated from the reported shifts (neat compounds?) relative to benzene as external reference under the assumption that internal TMS is shifted 7.26 ppm highfield from external benzene $\langle 64\text{HCA}942 \rangle$. The shifts for phenyl are the centers of complex signals.

For 3-phenyl-1,2,4-oxadiazole the $\text{H}(5)$ shift in CCl_4 is 8.70 ppm $\langle 89\text{MI} 404\text{-}01 \rangle$. Resonances (dimethylsulfoxide- d_6) for $\text{H}(5)$ of 4-unsubstituted 4,5-dihydro-1,2,4-oxadiazoles appear at 5.15–7.22 ppm $\langle 73\text{BSF}2996 \rangle$. Anisotropy effects of 4-aryl substituents of 4,5-dihydro-1,2,4-oxadiazoles cause high-field shifts of the signals for $\text{H}(5)$ to 1.5–1.7 ppm (CDCl_3) $\langle 90\text{G}679 \rangle$. Shifts (CDCl_3) for $\text{H}(5)$ of 2,5-dihydro-1,2,4-oxadiazoles have been found at 5.73–5.96 ppm $\langle 91\text{LA}603 \rangle$.

1,2,4-Oxadiazoles

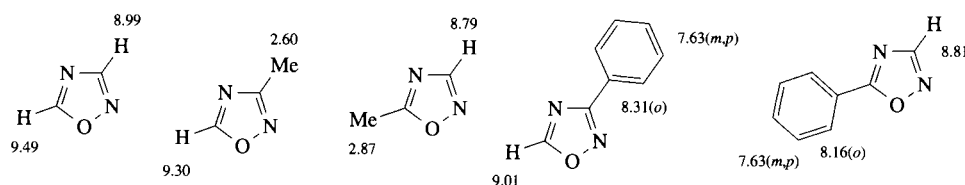


Figure 1 ^1H NMR shifts (ppm relative to TMS as internal standard) for some 1,2,4-oxadiazoles. Source: <64HCA942>.

Typical ranges of ^{13}C NMR shifts (ppm) are shown in Figure 2 <89H(29)1957, 89MI 404-01, 91CL1221, 93CB109>. For a few 1,2,4-oxadiazoles, 4,5-dihydro-1,2,4-oxadiazoles, and 1,2,4-oxadiazolidines ^{15}N NMR resonances have been reported <84BSB559, 87JCS(P1)2593, 91CB2065>.

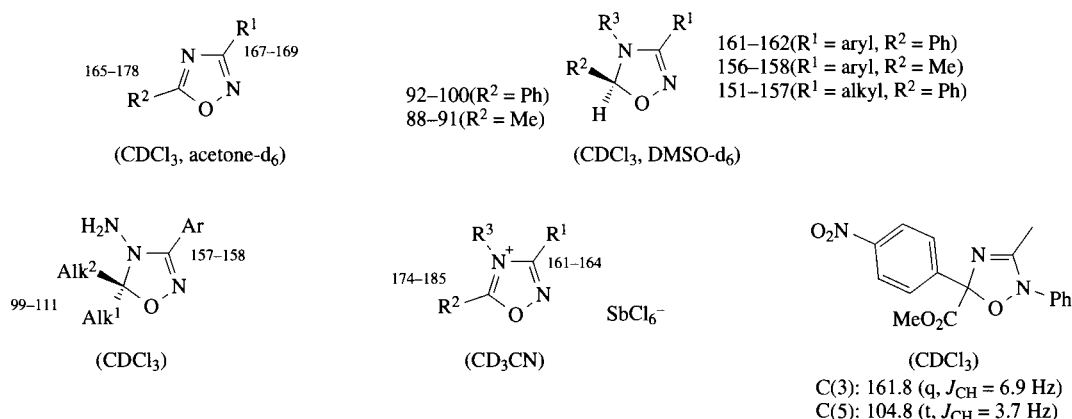
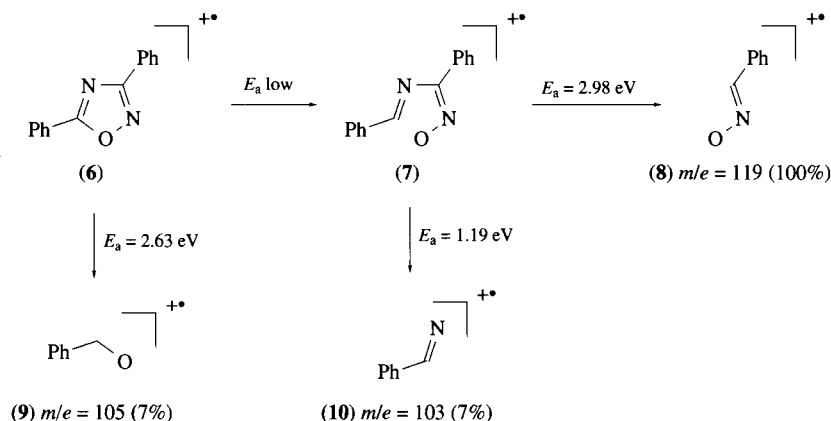


Figure 2 ^{13}C NMR shifts (ppm) for some 1,2,4-oxadiazoles. Source: <89H(29)1957, 89MI 404-01, 91CL1221, 93CB109>.

4.04.3.3 Mass Spectra

The main electron-impact induced cleavage of the oxadiazole (6) is a stepwise 1,3-dipolar cycloreversion (Scheme 1) <76OMS(11)217>. The process with the lowest activation energy E_a is the cleavage of the C—O bond (and not the N—O bond as in isoxazoles). The formation of the open-chain molecular ion (7) excludes the formation of (9) (Scheme 1). The intermediate (7) fragments in a way such that the positive charge is retained in the dominant fragment (8). This suppresses the formation of (10), even though E_a for (7) $\rightarrow$ (10) is smaller than E_a for (7) $\rightarrow$ (8).



Scheme 1

4,5-Dihydro-1,2,4-oxadiazoles (**12**) fragment along paths (a), (b), and (c) (Scheme 2). The weak N—O bond (ca. 220 kJ mol⁻¹) makes cleavages (a) and (b) most probable ^{<68JHC61>}.



4.04.3.4 UV Spectra

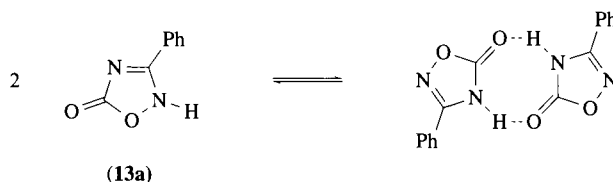
3,5-Dimethyl-1,2,4-oxadiazole has no UV absorption above 200 nm. For 3-phenyl-1,2,4-oxadiazole $\lambda_{\text{max}} = 238$ nm ($\epsilon = 14000$), for the 5-phenyl isomer $\lambda_{\text{max}} = 250$ nm ($\epsilon = 16100$), and for 3,5-diphenyl-1,2,4-oxadiazole $\lambda_{\text{max}} = 245$ nm ($\epsilon = 37200$) (ether) have been reported ^{<64HCA942>}. 3-Ethyl-5-phenyl-1,2,4-oxadiazole has $\lambda_{\text{max}}(\text{CHCl}_3 \text{ or } 2\text{-propanol}) = 284$ nm, while for the fluorescence $\lambda_{\text{fl, max}}(\text{CHCl}_3) = 310$ nm has been observed ^{<77JOC1555>}. Hypochromism with increase in con-

centration of some 1,2,4-oxadiazoles has been interpreted as self-association of the heterocycles in sandwich orientation with their dipole moments opposed <68SA(A)1975>.

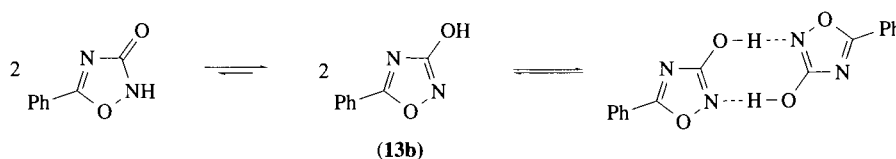
For a number of 5-ethyl-3-aryl-4,5-dihydro-1,2,4-oxadiazoles absorptions with $\lambda_{\max}(\text{CHCl}_3)$ 283–291 nm and fluorescences with $\lambda_{\max}(\text{CHCl}_3)$ 407–427 nm were found <77JOC1555>.

4.04.3.5 IR Spectra

1,2,4-Oxadiazoles show IR absorptions at 1590–1560 (C=N), 1470–1430, 1390–1360, 1070–1030, 915–885, and 750–710 cm^{-1} <59CR(249)1096>. Detailed analyzes exist for the IR spectra of the parent 1,2,4-oxadiazole and some of its methyl derivatives <67SA(A)2647>. For 3,4,5-trisubstituted 1,2,4-oxadiazolium salts strong absorptions around 1600 cm^{-1} were observed (in CH_2Cl_2) <93CB109>. 4,5-Dihydro-1,2,4-oxadiazole-5-ones and -5-thiones, for example (13a), seem to exist in the N(2)—H form <76BSB35>. In CHCl_3 5–10% of the NH form of the oxadiazole (13b) may coexist with the OH form. Both (13a) and (13b) form monomer–dimer equilibria in solution (Schemes 3 and 4) <65T1681>. Some typical IR spectra (wave numbers, KBr) for saturated 1,2,4-oxadiazoles are shown in Figure 3 <61AP(294)765, 64G478, 72CR(C)567>.



Scheme 3



Scheme 4

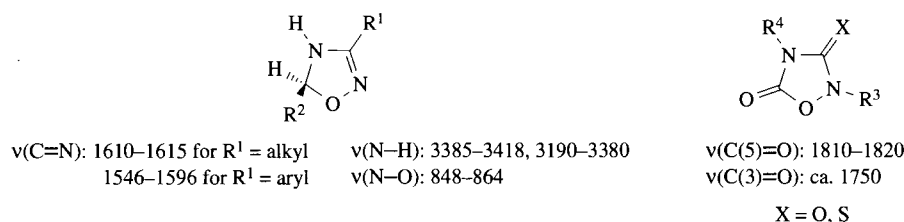


Figure 3 Typical IR spectra (wave numbers, KBr) for saturated 1,2,4-oxadiazoles. Source: <61AP(294)765, 64G478, 72CR(C)567>.

For 4,5-dihydro-1,2,4-oxadiazoles in CCl_4 one unsymmetrical band or two bands for NH are observed <71JST(7)381>.

4.04.3.6 Miscellaneous

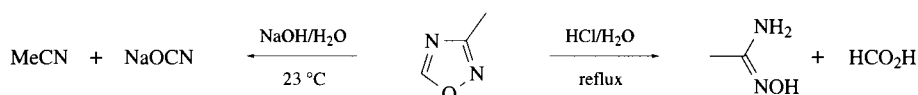
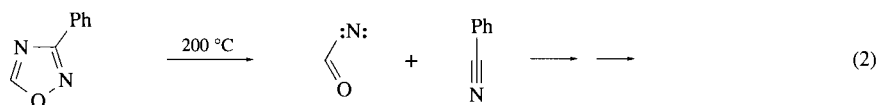
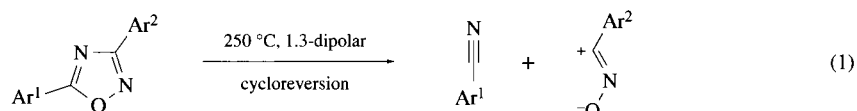
The hydrogen bonding acceptor ability ($\log K_{\beta}$) for 3,5-diphenyl-1,2,4-oxadiazole has been determined <89JCS(P2)1355>. An aromaticity index indicates low aromaticity of the parent 1,2,4-oxadiazole <85T1409>.

The microwave spectrum of 1,2,4-oxadiazole has been reported <67NAT1301>.

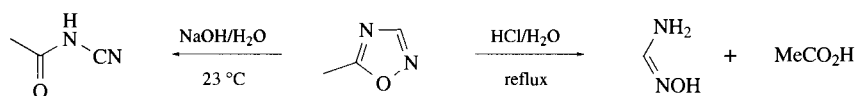
4.04.4 THERMODYNAMIC ASPECTS

Many 1,2,4-oxadiazoles are volatile compounds, distilling with the vapors of water and organic solvents [64HCA838, 65FCF807]. Depending on their molecular weight 1,2,4-oxadiazoles are liquids or solids with a "pleasant odor"; for example, 3,5-dimethyl-1,2,4-oxadiazole has a boiling point of 124°C, is very soluble in water and organic solvents, and is volatile with ether vapors [62HCA441]. The heat of fusion of a 1,2,4-oxadiazole (methazole) has been determined [90MI 404-01]. Dipole moments and Kerr constants of certain oxadiazoles seem to indicate some ability of the ring oxygen atom to donate π electrons into the ring [92KGS540].

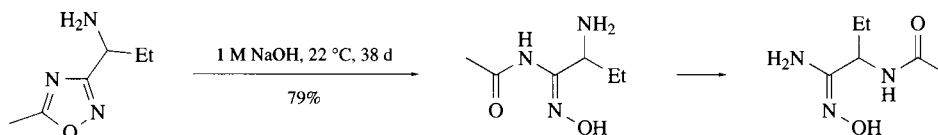
Disubstituted 1,2,4-oxadiazoles are thermally quite stable. For instance, the 3,5-diphenyl derivative can be distilled quickly (b.p. 296°C) without decomposition [1884CB1685]. However, heating 3,5-diaryl-1,2,4-oxadiazoles for some time at 250°C at atmospheric pressure causes decomposition, which is believed to start with a 1,3-dipolar cycloreversion to arynitrile oxide and arynitrile (Equation (1)). 3,5-Bis(perfluoroalkyl)-1,2,4-oxadiazoles are especially stable thermally, oxidatively, and hydrolytically [65JOC3734]. Mono and unsubstituted 1,2,4-oxadiazoles are thermally and hydrolytically markedly less stable, for example, 3-phenyl-1,2,4-oxadiazole decomposes slowly at room temperature ("within a decade") and rapidly at 200°C to cyanuric acid, benzonitrile, etc. (Equation (2)) [66JHC470]. While 3,5-dialkyl or 3,5-diaryl substituted 1,2,4-oxadiazoles survive boiling in aqueous sodium hydroxide or hydrochloric acid, monosubstituted oxadiazoles [64HCA838] and certain amines [73JCS(P)47] are readily hydrolyzed under basic or acidic conditions (Schemes 5–7).



Scheme 5



Scheme 6



Scheme 7

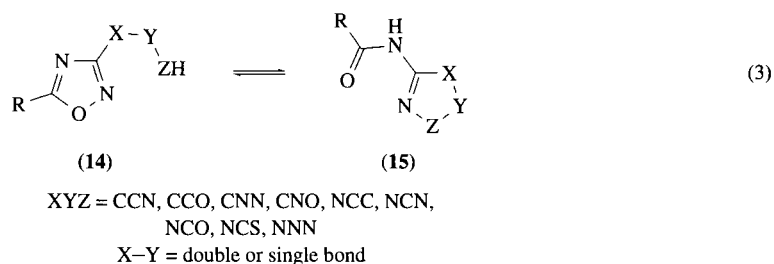
The unsubstituted 1,2,4-oxadiazole is an extremely volatile liquid (b.p. 87°C), and is very soluble in water and organic solvents. The compound decomposes at ambient temperature. However, a complex with CdCl_2 can be stored. Mild heating decomposes the complex into its components [62HCA446].

4.04.5 REACTIVITY OF FULLY CONJUGATED 1,2,4-OXADIAZOLES

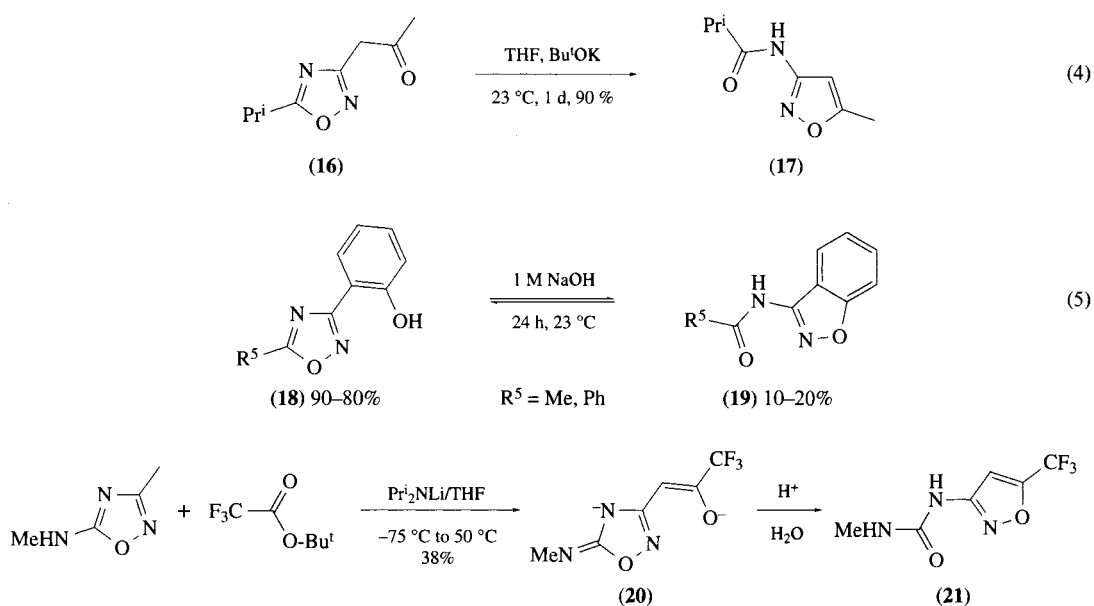
4.04.5.1 Unimolecular Thermal and Photochemical Reactions

4.04.5.1.1 Thermal ring transformations

1,2,4-Oxadiazoles (**14**) (and other 1-oxa-2-azoles, too) undergo intramolecular nucleophilic displacement of O(1) of the general type (**14**) $\rightarrow$ (**15**) (Equation (3)) $\langle 81\text{AHC}(29)141, 86\text{JST}(136)215, 93\text{AHC}(56)49, 94\text{H}(37)2051 \rangle$ by the attack on N(2) by oxygen, sulfur, nitrogen, and carbon nucleophiles Z forming the third atom of a side chain in the 3-position of the heterocycle. If the nucleophile Z is the second or the fourth atom of the side-chain, ring transformation does not take place. However, a ring transformation has been reported, where the attacking nucleophile is the first atom of the side chain $\langle 78\text{JA}4208 \rangle$.

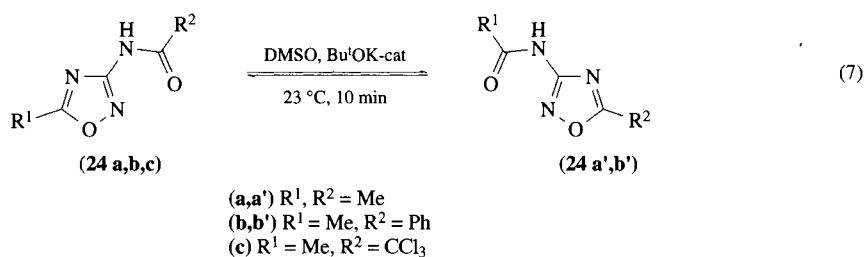
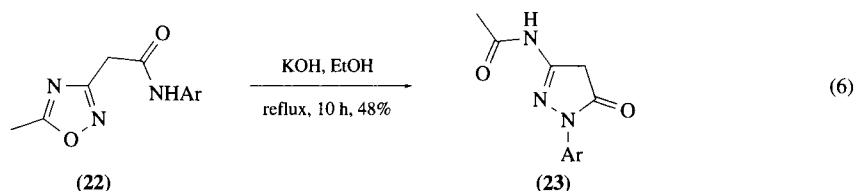


The driving force behind the ring transformations of 1,2,4-oxadiazoles seems to be the transformation of an isoamide into a more stable amide function. Ring transformations of 1,2,4-oxadiazoles are faster than the corresponding transformations of 1,2-oxazoles. Electron-withdrawing substituents R and strongly nucleophilic groups Z facilitate the transformation. According to AM1 and MNDO calculations the ring transformations are concerted S_N2 processes or pass over bicyclic intermediates. For example, the acetonide compound (**16**) rearranges irreversibly to (**17**) at room temperature in the presence of a strong base (Equation (4)) $\langle 83\text{M}373 \rangle$. Similar transformations have also been carried out under acidic conditions $\langle 81\text{T}1415 \rangle$. Occasionally, the reverse reaction—formation of a 3-acetonide-1,2,4-oxadiazole from a 3-acylamino-1,2-oxazole—has been observed $\langle 82\text{M}731 \rangle$. The transformation (**18**) $\rightarrow$ (**19**) is an equilibrium process lying on the side of the oxadiazoles (Equation (5)) $\langle 29\text{JPR}232 \rangle$. The ring transformation (**20**) $\rightarrow$ (**21**) has been described in a patent (Scheme 8) $\langle 89\text{JAP}(K)0109978 \rangle$.

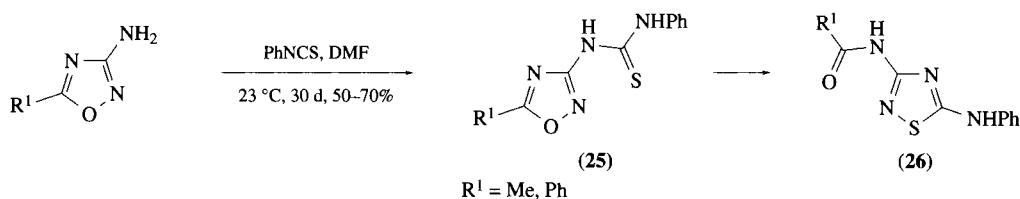


Scheme 8

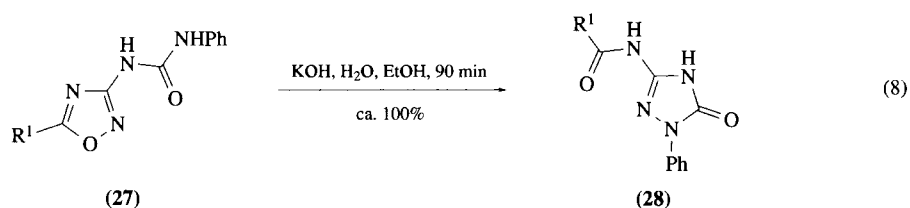
When heated in ethanolic KOH the acetamide (**22**) gives (**23**) (Equation (6)) <84JOC5247>. While (**24a**, **b**, **a'**, **b'**) form equilibria on heating, the amide (**24c**) could not be rearranged (Equation (7)). For the base-catalyzed degenerate rearrangement of (**24a**) in DMSO at 112 °C, a barrier to activation $\Delta G^\ddagger = 82 \pm 2 \text{ kJ mol}^{-1}$ has been measured <75JHC1327>, while for the uncatalyzed rearrangement (DMSO- d_6 , 40–70 °C) the higher value $\Delta G^\ddagger = 113 \text{ kJ mol}^{-1}$ was found <91H(32)1547>.



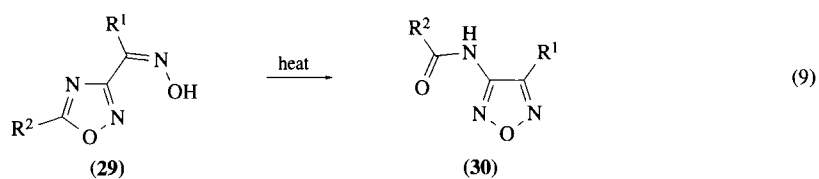
Thioureas (**25**) rearrange spontaneously at room temperature to thiadiazoles (**26**) (Scheme 9) <77JCS(P1)1616>. In contrast, the corresponding ureas (**27**) require refluxing in aqueous potassium hydroxide in order to be transformed into the triazolones (**28**) (Equation (8)) <90JCS(P2)1289>.



Scheme 9

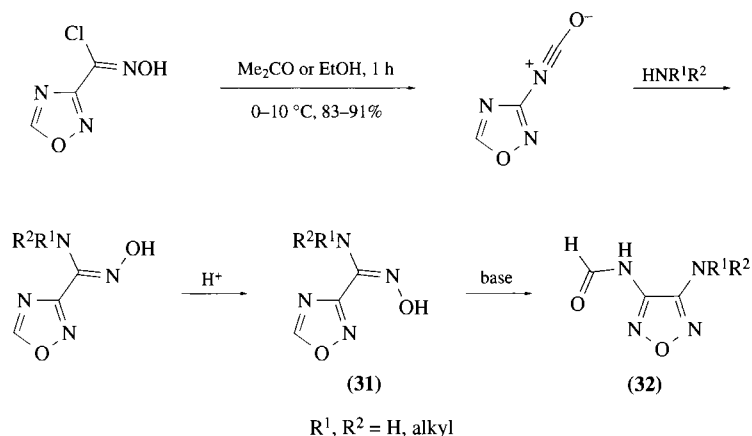


Oximes (**29**) and (**31**) with OH *cis* with respect to the oxadiazole ring rearrange to furazanes (**30**) and (**32**) (oximes (**29**) with $R^1 = \text{N}_3$ do not) (Equation (9) and Scheme 10) <90KGS1443, 93AHC(56)49, 94H(37)2051>.



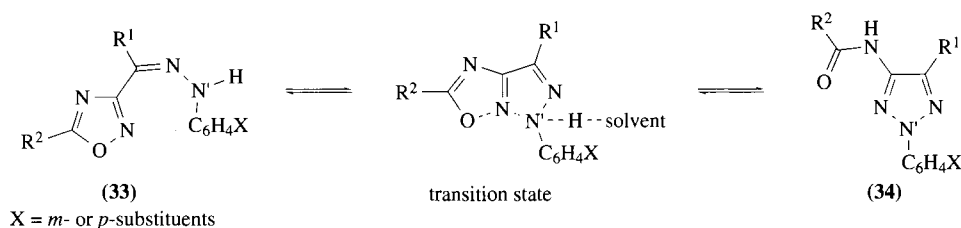
$R^1 = \text{Ph}; R^2 = \text{aryl, alkyl}$

Hydrazones (**33**) rearrange to 1,2,3-triazoles (**34**) from a geometry in which the oxadiazole and N' are *cis* oriented with respect to each other (Scheme 11) <81JHC723>. Electron-donating as well as



Scheme 10

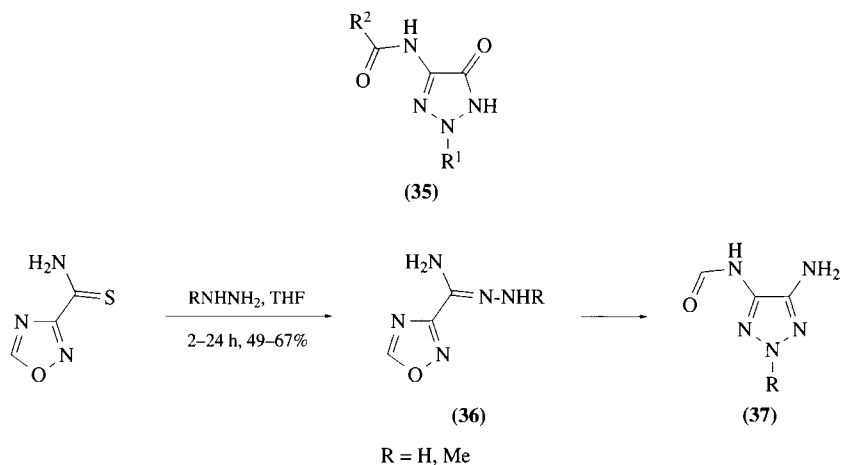
electron-withdrawing substituents X increase the rate of the rearrangement. Electron-repellent substituents increase the nucleophilic strength of the nitrogen atom N' but retard the breaking of the N'—H bond in the transition state.



Scheme 11

Electron-withdrawing substituents reduce the nucleophilic strength of N' but favor N'—H breaking. Ring transformations of hydrazones (33) are catalyzed by Cu^{II}-acetate (93JCS(P1)2491).

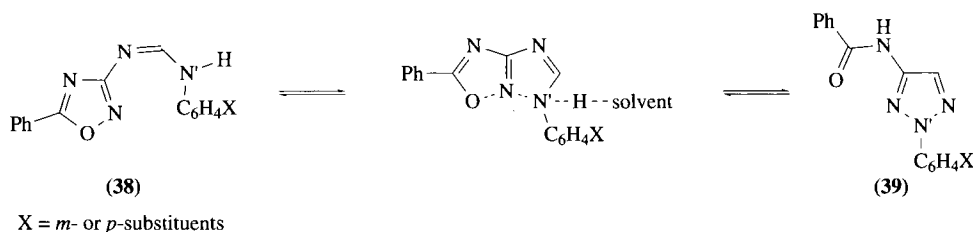
N',N'-Disubstituted hydrazones rearrange smoothly to furnish 1,2,3-triazolium salts, hydrazides give triazolones (35), and amidrazones (36) afford (37) (Scheme 12) (91KGS822, 92KGS969).



Scheme 12

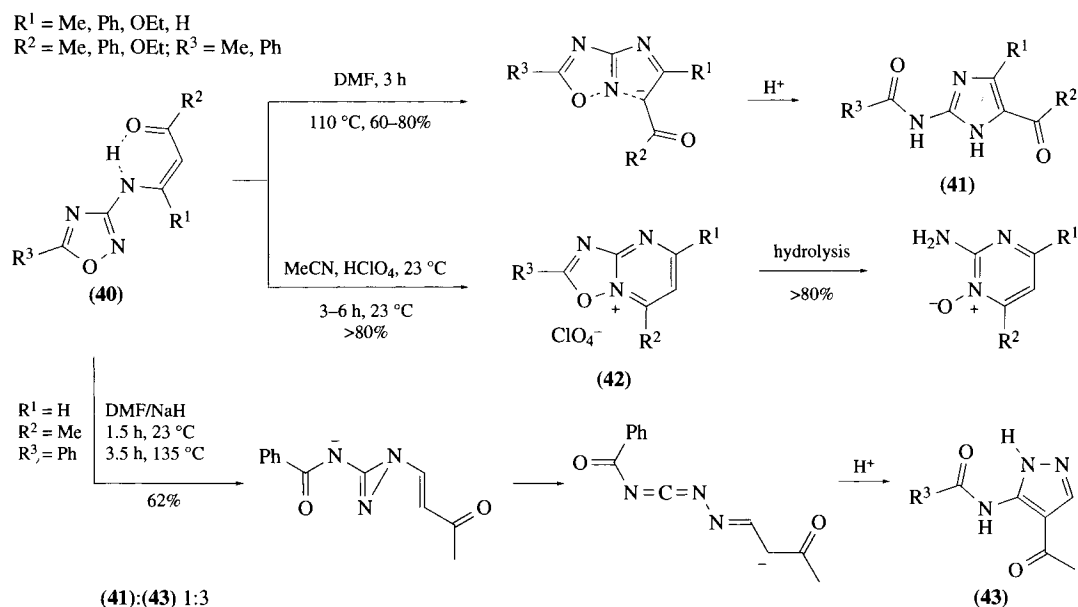
Formamidines (38) rearrange to 1,2,4-triazoles (39) (Scheme 13) (94T7315). Under neutral conditions the rate of the rearrangement increases with increasing ability of the solvent to support the

breaking of the N'—H bond in the transition state. Added base enhances the rate of the rearrangement by abstracting the proton from N' <93JCS(P2)1339>.



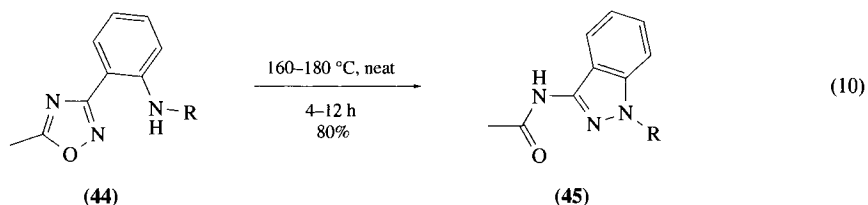
Scheme 13

Enaminoesters and enaminketones, for example (40), rearrange to imidazoles (41) or oxadiazolium salts (42) (Scheme 14) <74T3859>. For R¹ = H mixtures of imidazoles and pyrazoles, for example (43), have been obtained <78JA4208>. The formation of (43) is an example of a ring transformation, where the attacking nucleophile is the first atom of the side-chain in the 3-position of the oxadiazole (Scheme 14).



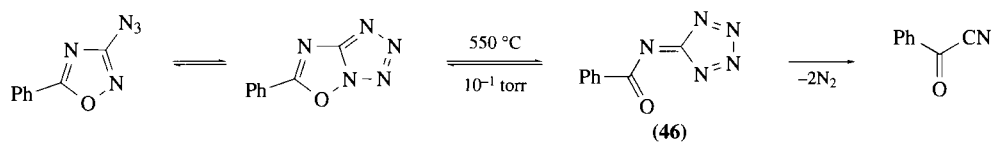
Scheme 14

Rearrangements of 3-(*o*-aminophenyl)-1,2,4-oxadiazoles (44) or their *N*-acyl derivatives (R = acyl) to indazoles (45) require drastic conditions (Equation (10)) <82JCS(P1)759, 90ACH795>, for related reactions see also <82H(19)339, 83T823>.

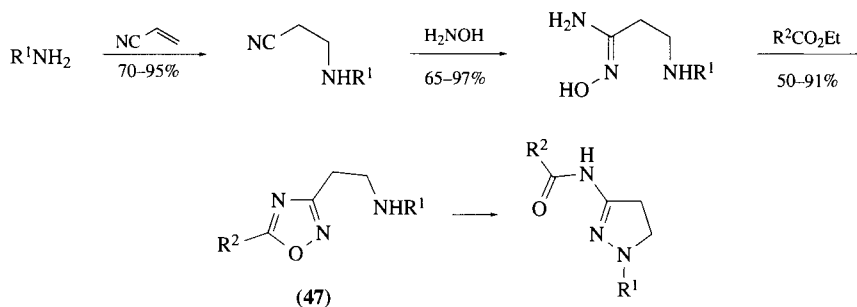


Ring transformation of oxadiazoles with an azide group in the 3-position furnishes pentaazfulvene intermediates, such as (46), which decompose to nitrogen and an acyl cyanide (Scheme 15) <82TL121>.

The belief that ring transformations of 1,2,4-oxadiazoles require an vinyl substituent in the 3-position had to be abandoned when it was found that compounds like (47) with saturated side chains undergo smooth ring transformation to 4,5-dihydropyrazoles (Scheme 16) <79JCR(S)64, 79JCR(M)801>.

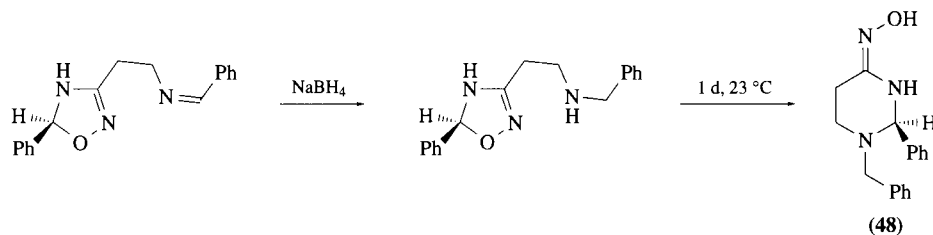


Scheme 15



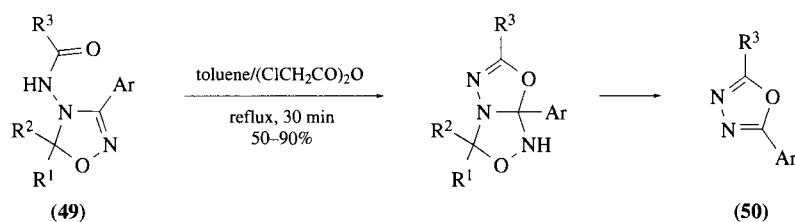
Scheme 16

It is noteworthy that 4,5-dihydro-1,2,4-oxadiazoles with a nucleophilic β -aminoethyl substituent in the 3-position undergo ring transformation to cyclic amide oximes (48) by nucleophilic attack on C(5) (Scheme 17) <92JCS(P1)3069>.

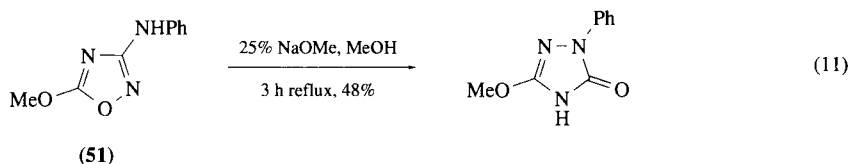


Scheme 17

A ring transformation (49) $\rightarrow$ (50) has been described (Scheme 18) <91JHC1229>. 3-Arylamino-5-methoxy-1,2,4-oxadiazoles (51) rearrange in the presence of sodium methoxide to triazolones (Equation (11)) <82JOC1969>.



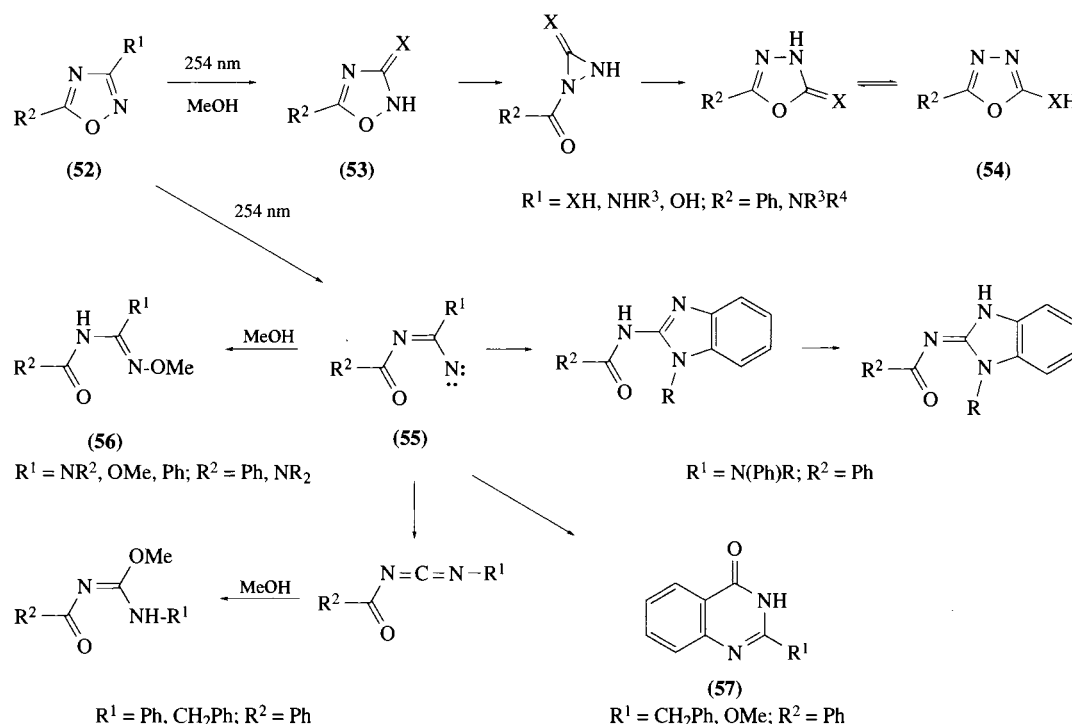
Scheme 18



4.04.5.1.2 Photochemical reactions

UV irradiation of 3-amino-1,2,4-oxadiazoles (52) ($R^1 = \text{NHR}$) leads to 1,3,4-oxadiazoles (54) and/or to open-chain compounds like (56) (Scheme 19) <88JCS(P1)1313>. A ring-contraction-ring-

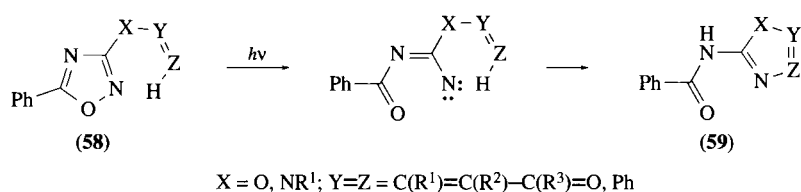
expansion mechanism via tautomeric forms (**53**) accounts for the formation of (**54**) <88JHC931, 91JCS(P2)187>.



Scheme 19

For $R^2 = Ph$ the 5-phenyloxadiazole chromophore of (**52**) is excited, the O—N bond breaks, and the intermeditate nitrene (**55**) is either intercepted by a nucleophilic solvent like methanol (R^1 , $R^2 = Ph$) or closes the ring (from a triplet state <91JCS(P2)187>) to a quinazolinone (**57**) (Scheme 19) <68TL2421>. Further reaction paths of (**55**) are also shown in Scheme 19.

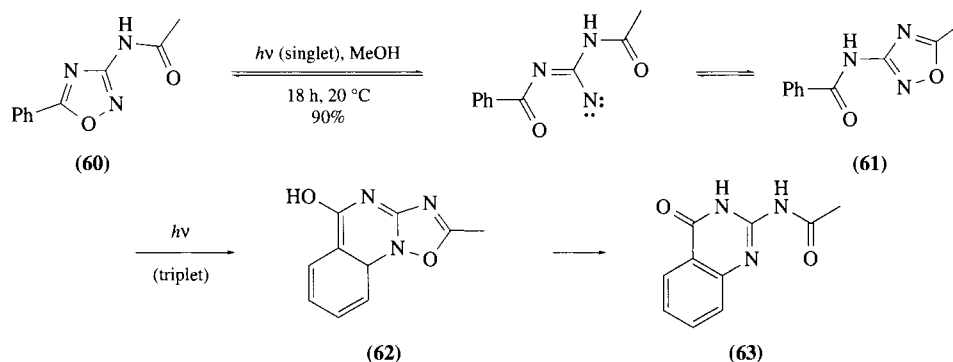
Oxadiazoles (**58**) not only undergo thermally but also photochemically induced “azole to azole interconversions” (isoheterocyclic reactions) to (**59**) (Scheme 20) <89H(29)1301, 91JCS(P2)187>. For instance, photolysis of the 3-acetamino-1,2,4-oxadiazole (**60**) involves excitation of the 5-phenyl substituted oxadiazole chromophore into a singlet state followed by N—O bond rupture and formation of the new oxadiazole (**61**) (Scheme 21). Excitation of the enolized benzoylamido chromophore of (**61**) into a triplet state is followed by electrocyclic ring closure to (**62**), which rearranges to (**63**). Thermally, (**61**) is rearranged to (**60**) without producing any (**63**) (Scheme 21) (cf. <90JHC861>).



Scheme 20

4.04.5.2 Electrophilic Attack at Nitrogen

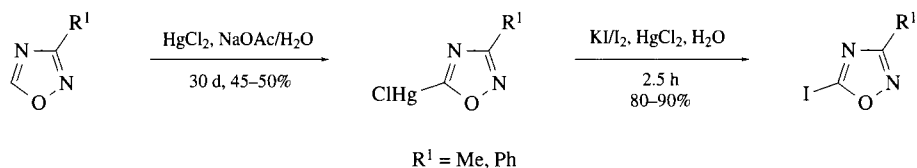
3-Aryl-5-methyl-1,2,4-oxadiazoles serve as monodentate ligands for a number of transition metal complexes <85SA(A)1433>.



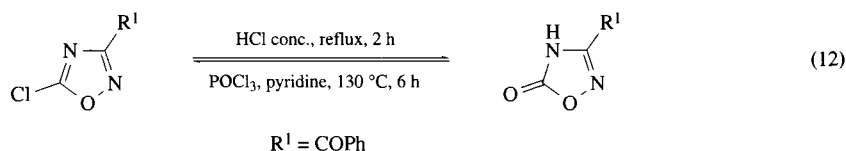
Scheme 21

4.04.5.3 Electrophilic Attack at Carbon

1,2,4-Oxadiazoles are rather inert against electrophilic attack (halogenation, nitration, Friedel-Crafts alkylation, acylation). The 3,5-diphenyl compound can be heated in concentrated sulfuric acid and can be crystallized from fuming nitric acid without change. Nitration of 3-phenyl-1,2,4-oxadiazole gives the *m*-nitrophenyl derivative (63G1196). However, electrophilic mercuration of 5-unsubstituted oxadiazoles is possible. 5-Halooxadiazoles are prepared from the 5-mercurio compounds (Scheme 22) (64HCA838). However, only the 5-iodo derivatives are obtained in good yields. Hydrolysis of the 5-chlorooxadiazoles gives 5-oxo compounds, which can be converted back into the 5-chloro derivatives with POCl_3 in hot pyridine (Equation (12)) (73JHC357).

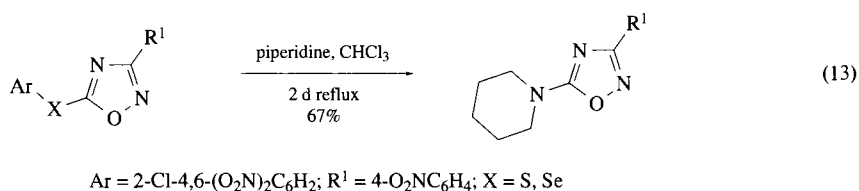


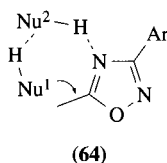
Scheme 22



4.04.5.4 Nucleophilic Attack at Carbon

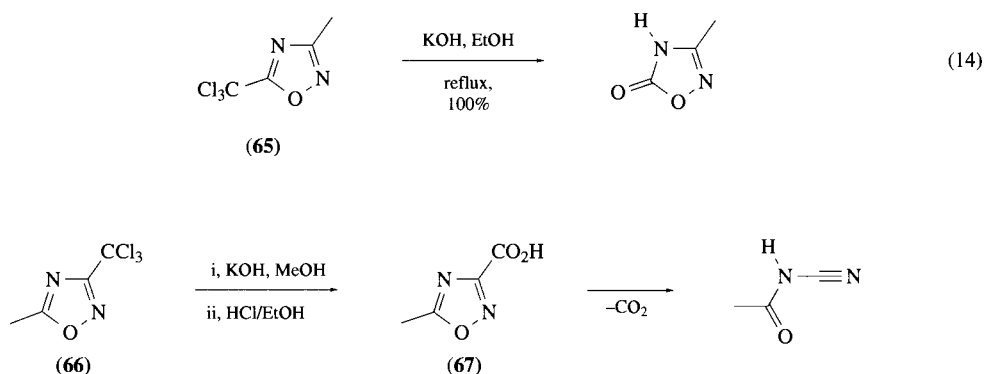
1,2,4-Oxadiazoles are prone to nucleophilic attack (see Section 4.04.4 for discussion of hydrolysis). Nucleophilic displacements of leaving groups in the 5-position of the 1,2,4-oxadiazole ring are important in such an attack. For example, the 5-chloro compounds react with amines and ammonia to afford 5-amino compounds (67BSF1219). With thiourea the 5-thioxo compounds are formed (92JMC3691). Other useful leaving groups in the 5-position are bromo, iodo, alkoxy, arylthio, arylseleno (Equation (13)) (87JCS(P1)607), trinitromethyl, amino, amido (61AC(R)130), and especially Cl_3C (64HCA838) substituents. Attack of protic nucleophiles $\text{Nu}-\text{H}$ on C(5) is assisted by hydrogen bonding of the solvent or $\text{Nu}-\text{H}$ to N(4), as in (64) (88JCS(P2)117).





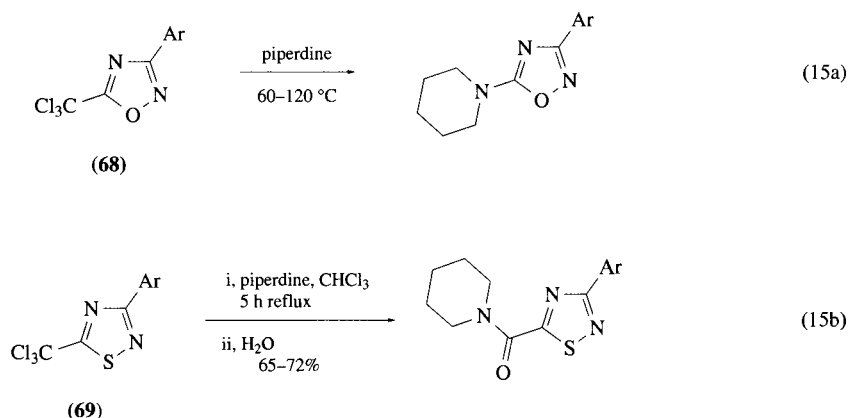
On the other hand, 3-chloro-1,2,4-oxadiazoles have been reported to be rather stable in aqueous NaOH and hot water. Only after heating for several days with potassium methoxide in methanol was the 3-methoxy compound isolated <B-71MI 404-01>.

While the 5-trichloromethyl group of (65) furnishes the 5-oxo compound when treated with KOH (Equation (14)), the 3-trichloromethyl isomer (66) gives the carboxylic acid (67), which quickly rearranges to acetyl cyanamides with loss of CO₂ (Scheme 23) <64HCA838>.



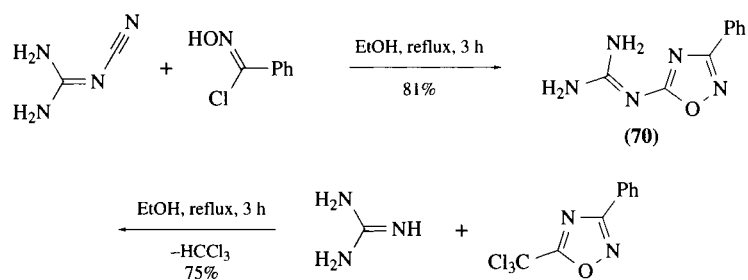
Scheme 23

The extraordinary activation of the 5-Cl₃C group is further demonstrated by comparison of (68) with the thio analogues (69). The whole Cl₃C group of (68) is displaced by piperidine (Equation (15a)) <73CPB1641>, while under similar conditions only one chlorine atom is displaced in the thiadiazoles (69) (Equation (15b)) <86PS(26)151>.



5-Trichloromethyl-1,2,4-oxadiazoles have been converted into 5-guanidino compounds, such as (70) <87JCS(P1)1005>, which can alternatively be prepared by cycloaddition of benzonitrile oxide to the nitrile group of cyanoguanidine (Scheme 24) <92JMC3691>. Hydrolysis of (70) afforded the 5-oxo compound. Similarly, displacement of the 5-trichloromethyl group by ammonia, primary and secondary amines, or by hydrazines furnished 5-amino-1,2,4-oxadiazoles <66HCA1430, 73CPB1641, 81JHC37>.

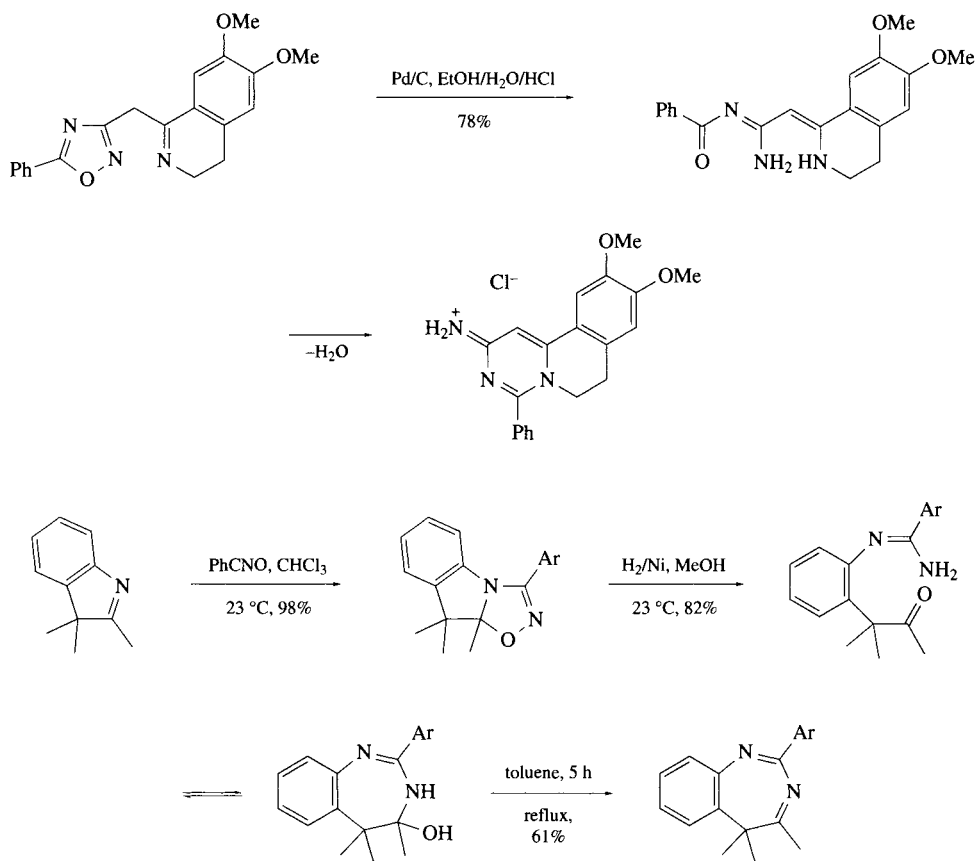
5-Trifluoromethyl-1,2,4-oxadiazoles are hydrolyzed to amidoximes when treated at ambient temperature with ammonia in ethanol/water <91KGS827>.



Scheme 24

4.04.5.5 Reductions of 1,2,4-Oxadiazoles

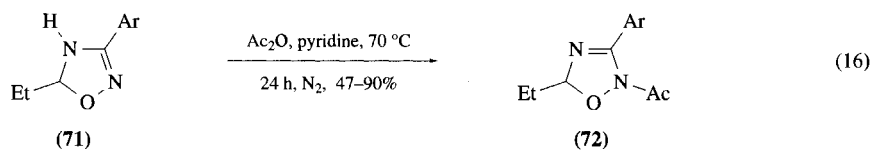
3,5-Disubstituted 1,2,4-oxadiazoles have been reduced with LiAlH₄ to *N*-substituted amidoximes <63CI(M)1238>. Catalytic hydrogenation of 1,2,4-oxadiazoles starts with breaking of the N—O bond (Scheme 25) <76CPB1197, 87CB1039, 90T7865, 93CB1835>.



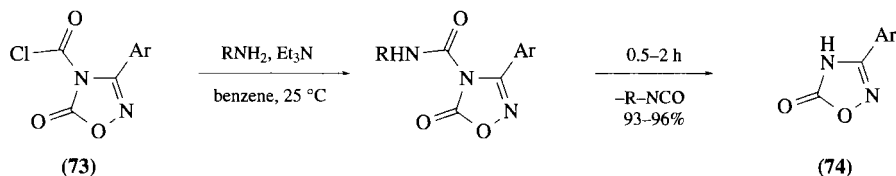
Scheme 25

4.04.6 REACTIVITY OF NONCONJUGATED 1,2,4-OXADIAZOLES

Acetylation of compound (71) with acetic anhydride in pyridine produces the N(2)-acetylated compound (72) (x-ray analyzes) (Equation (16)). With potassium hydride in 1,2-dimethoxyethane, mixtures of the N(2)-(72) and the N(4)-acetylated heterocycles are obtained <91LA603>.



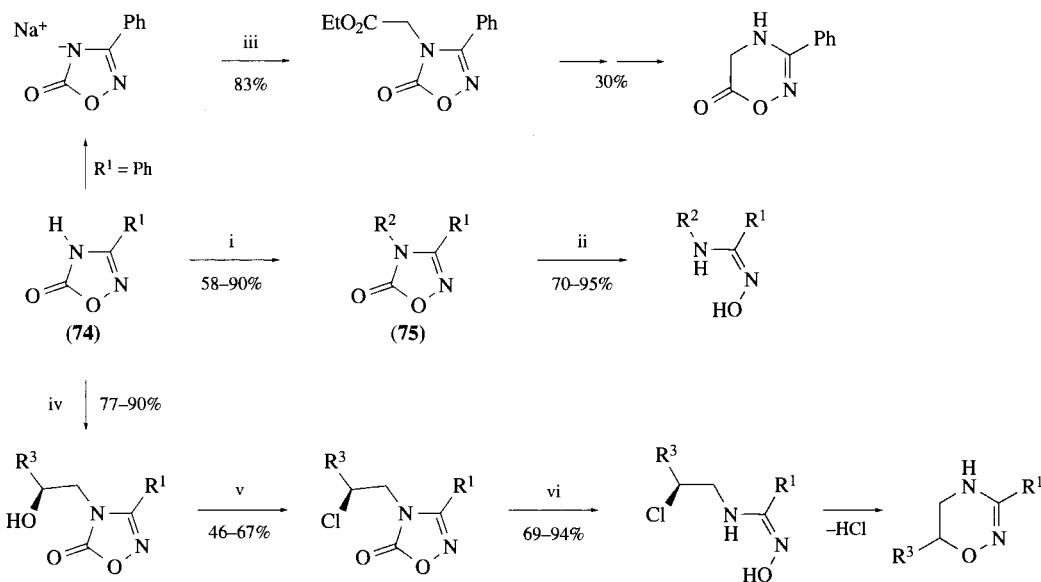
4,5-Dihydro-1,2,4-oxadiazol-5-ones (**74**) cannot be *N*-acylated by either chlorocarbonyl isocyanate or trichloroacetyl chloride. However, preparation of 4-chlorocarbonyl compounds (**73**) can be achieved by cycloaddition of stable nitrile oxides to the C=N double bond of chlorocarbonyl isocyanate <88S994, 90ZOR339>. Compounds (**73**) decompose with ammonia, primary amines, or primary amides to isocyanates and (**74**) (Scheme 26).



Ar = 2,4,6-Me₃C₆H₂, 2,3,5,6-Me₄C₆H; R = H, Ph, PhCO

Scheme 26

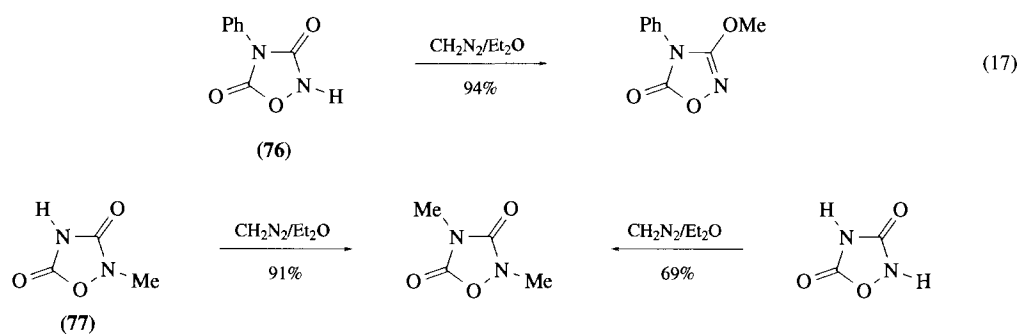
Methylation of oxadiazoles (**74**) with diazomethane gives mixtures of *O*- and *N*-methyl products (Scheme 27) <65T1681, 81JCS(P1)1703>. Likewise, alkylation of the silver salts of (**74**) affords mixtures of *O*- and *N*-alkyl products <64HCA838> while the sodium salt furnishes the thermodynamically preferred *N*-alkyl compound with ethyl chloroacetate <84CB2999>. *N*-Alkylation can be achieved with alkyl halides in acetone in the presence of K₂CO₃ or in dimethylformamide with sodium ethanolate <87JCS(P1)2163, 93H(36)1027>. *N*- as well as *O*-methylation with diazomethane has been reported for 1,2,4-oxadiazolidine-3,5-diones (**76**), (**77**) (Equation (17) and Scheme 28) <69AP(302)691>. The 5-imino compound (**78**) is alkylated with alkyl halides in the presence of a strong base to 4-alkyl derivatives <64FRPM2023>.



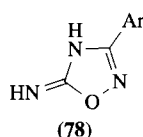
R³ = H, methyl; R¹ = alkyl, aryl; R² = alkyl, allyl, benzyl; X = Cl, Br, I

i, R²X, K₂CO₃/acetone/MeOH, 6 h reflux; ii, 5% NaOH, 30 min reflux; iii, ClCH₂CO₂Et, DMF, KI, 8 h, 100 °C
iv, R³-CH₂-CH₂-O, 40% NaOH, 1,4-dioxane, 7 h, 120 °C; v, Cl₂SO, reflux, 1 h; vi, 10% NaOH/EtOH, 1 h, reflux

Scheme 27

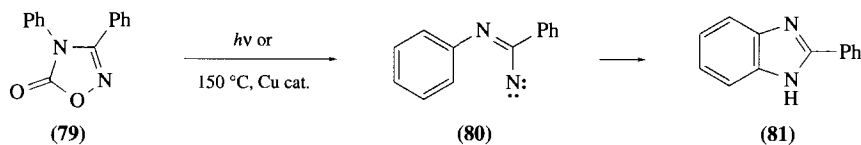


Scheme 28



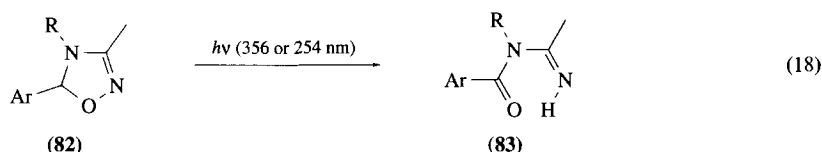
In contrast to (74), compounds (75) are easily hydrolyzed to amidoximes. *N*(4)-Alkylation of oxadiazolones (74) by oxiranes has been used for a synthesis of oxadiazines <75CB1911>.

Photolysis as well as thermolysis (150°C, copper-catalyzed) of (79) results in quantitative loss of CO₂ (Scheme 29). The 1,3-dipole (80) cyclizes to the benzimidazole (81) or is intercepted by dipolarophiles like benzonitrile or by an alcohol (Scheme 29) <68TL325>. Other oxadiazolones of type (79) fragment to CO₂, a nitrile, a nitrene, and a carbene finally leading to a host of products <79JCS(P1)483>.



Scheme 29

In 4,5-dihydro-1,2,4-oxadiazoles (82) the N—O bond breaks on irradiation to give *N*-acylamidines (83) (Equation (18)) <70JHC151, 88T4917>. Therefore, oxadiazolines (82) are sensitive to diffuse daylight. For R = *t*-butyl, elimination of RH occurs in preference to ring cleavage.

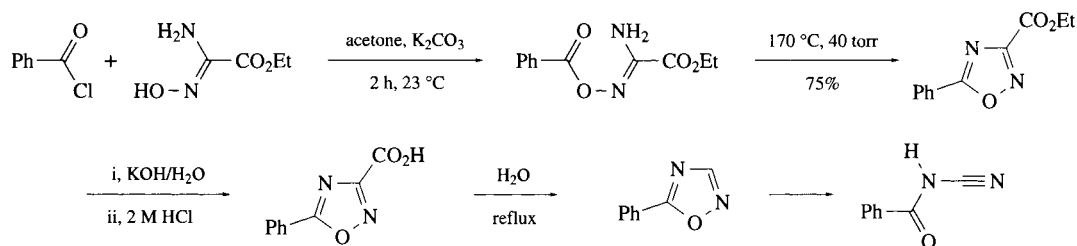


4.04.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBONS

The amino group of 3-amino-1,2,4-oxadiazoles shows little nucleophilic character. For example, addition to phenyl isothiocyanate to give 3-(phenylthioureido) compounds requires heating of the components without solvent at 120–130°C or the use of polar aprotic solvents (DMSO, DMF) and long reaction times (30 days at 23°C) <77JCS(P1)1616>. 3-(Thioureido)-1,2,4-oxadiazoles undergo fast ring transformations to thiadiazoles (see Section 4.04.5.1.1).

Methylation of 3-amino-1,2,4-oxadiazoles with iodomethane in dimethyl formamide affords the 2-methyl-3-amino-1,2,4-oxadiazolium iodides <86JMC1540>. On the other hand, in contrast to a 5-amino group, a 3-amino group can be diazotized with nitrous acid to give the 3-hydroxy compounds in moderate yields <69BSB47>. 3-Enaminoesters are obtained from 3-amino-1,2,4-oxadiazoles and β-ketoesters on refluxing in toluene for 100 h <74T3859>. A 3-(monofluoroamino)-1,2,4-oxadiazole has been prepared by fluorination of the 3-amino group with caesium fluoroxysulfate <91T7447>.

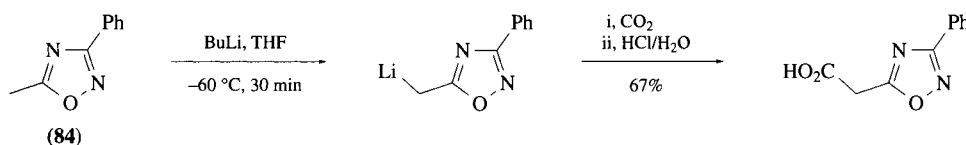
Ethyl 1,2,4-oxadiazole-3-carboxylates are saponified with ethanolic KOH to stable potassium salts <63G482>. The free acids decarboxylate to acylcyanamides (Scheme 30).



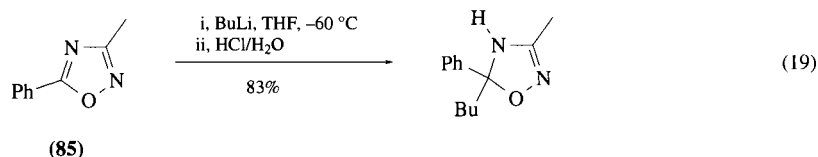
Scheme 30

Curtius rearrangement of the appropriate carboxylic azides has been used to prepare 3-, and 5-amino-1,2,4-oxadiazoles <66JCS(C)1522>.

The 5-methyl-3-phenyl-1,2,4-oxadiazole (**84**) is deprotonated by bases to an anion, which adds to the carbonyl group of ketones or of CO₂ (Scheme 31) <89JCS(P1)2047>. In contrast, the methyl group of (**85**) is not lithiated by butyllithium. Instead, the reagent adds to the 4,5-bond (Equation (19)) <70CJC2006>.

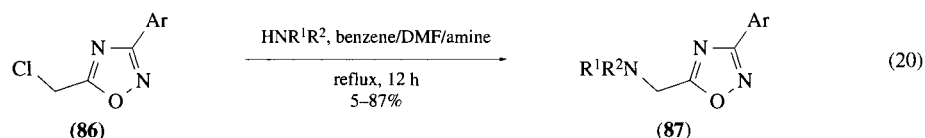


Scheme 31



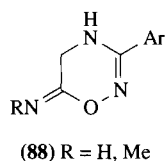
While 5-[2-(dialkylamino)ethyl]-1,2,4-oxadiazoles are stable in dilute acid, they are slowly hydrolyzed in boiling 0.1 M NaOH, as a result of α -deprotonation of the 5-substituent <89PHA494>.

In contrast to a 3-halomethyl group, the halogen atom of a 5-halomethyl group is readily displaced by nucleophiles. For instance, reaction of (**86**) with primary or secondary amines gives amines (**87**) (Equation (20)) <61MI 404-02, 72JHC435>.

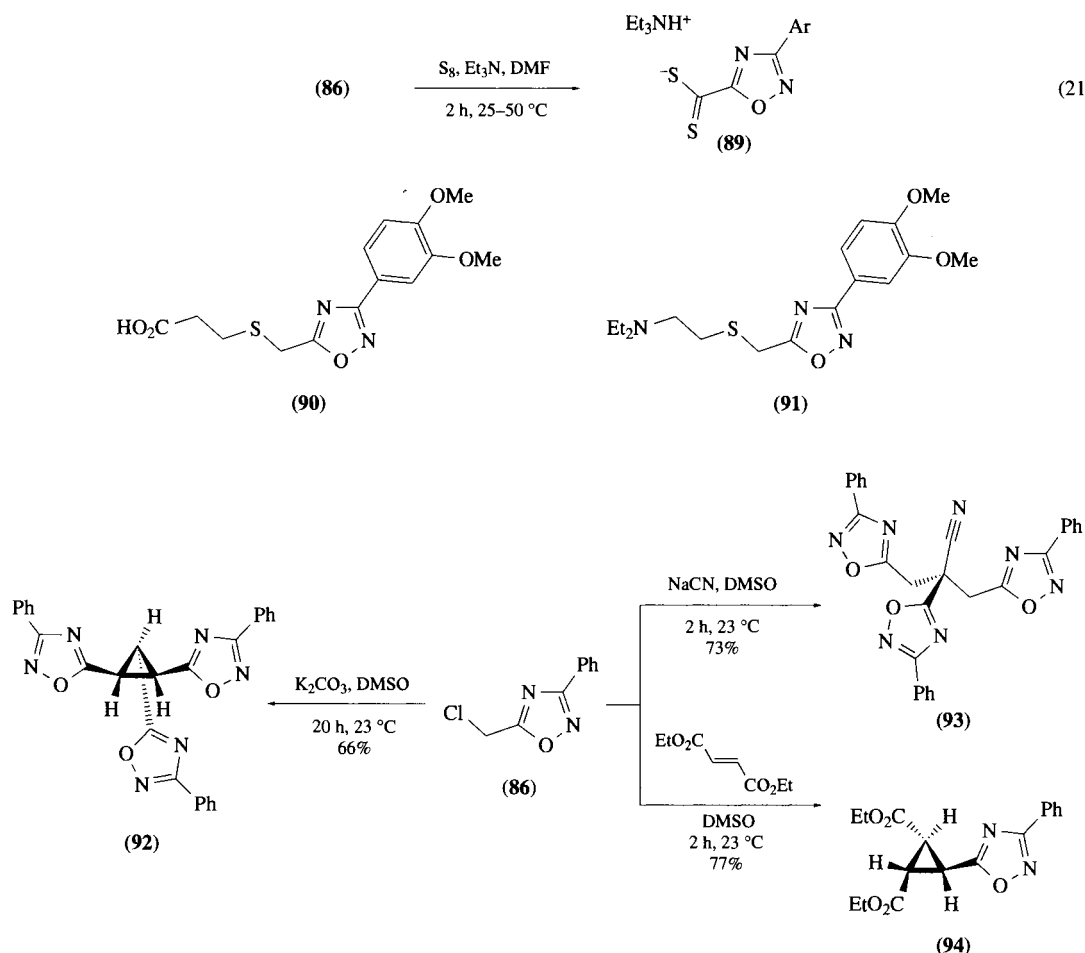


R¹, R² = alkyl, aryl; Ar = 5-nitrofuryl-2, Ph

However, with liquid ammonia or anhydrous methylamine 1,2,4-oxadiazines (**88**) are formed. 5-(Chloromethyl)-1,2,4-oxadiazoles (e.g., (**86**)) react with urotropin to form salts, which are hydrolyzed with hydrochloric acid to 5-(aminomethyl) compounds (the Delepine reaction). Alternatively, 5-(aminomethyl)-1,2,4-oxadiazoles have been prepared by condensation of amidoximes with α -amino acids <72JHC435>.

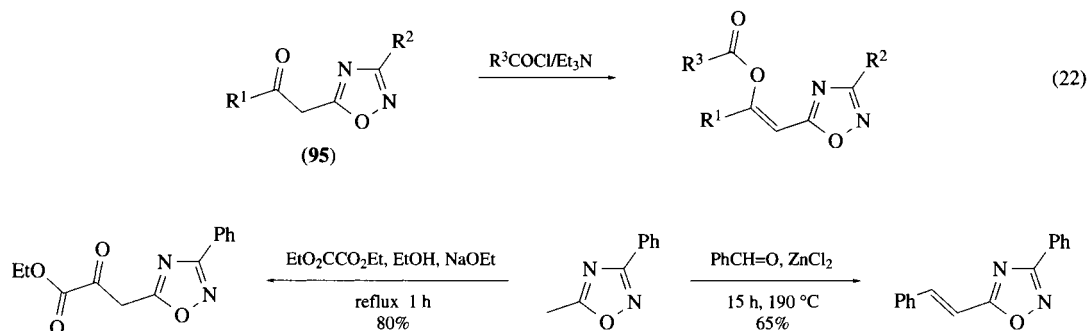


With sulfur and triethylamine in dimethylformamide, compounds (**86**) give (**89**) (Equation (21)) <89JPR243>. With thiols or K_2S , sulfides are produced (e.g., (**90**) and (**91**)), which show spasmolytic activity *in vitro* <86MI 404-01>. Smooth S_N2 -displacements of chlorine occur with phenol, thiophenol, SCN^- , and thiourea in dimethylsulfoxide. However, with K_2CO_3 or sodium cyanide, (**86**) (Ar = Ph) affords the trimers (**92**) or (**93**) (Scheme 32). With electron-deficient *trans* alkenes, stereoselective formation of cyclopropanes (**94**) was observed (Scheme 32). No reactions occur with maleates <66HCA412>.



Scheme 32

5-(Acylmethyl)-1,2,4-oxadiazoles (**95**) are easily acylated to vinyl esters (Equation (22)) <87H(26)1015>. 1,2,4-Oxadiazoles carrying a 5-substituent CH_2R undergo aldol condensations (Scheme 33) <88MI 404-02>.



Scheme 33

4.04.8 RING SYNTHESSES OF 1,2,4-OXADIAZOLES

There are five general methods known for the preparation of 1,2,4-oxadiazoles:

(i) condensation of amidoximes with derivatives of carboxylic acid furnishes *O*-acylamidoximes, which are thermally cyclized to 1,2,4-oxadiazoles, a method first used by Tiemann and Krüger <1884CB1685>;

(ii) Beckmann and Sandel found that *N*-acylamide oximes cyclize faster than *O*-acylamidoximes <1897LA(296)279>;

(iii) 1,3-dipolar cycloaddition of nitrile oxides to nitriles affording 1,2,4-oxadiazoles has been introduced by Leandri <56MI 404-01>;

(iv) electrocyclic ring closure of nitrenoids $N-CR^3=N-CR^5=O$ gives 1,2,4-oxadiazoles by $N-O$ bond formation <67JA5958, 74CL247, 76S268>; and

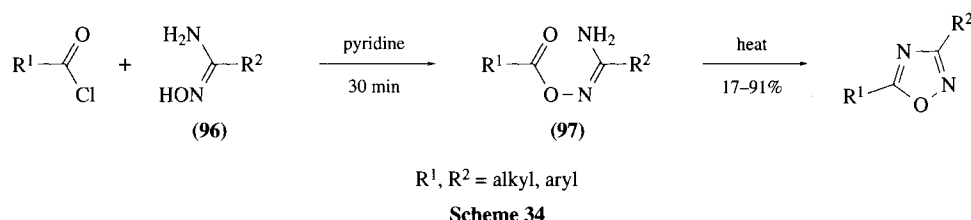
(v) 4,5-dihydro-1,2,4-oxadiazoles are readily oxidized to 1,2,4-oxadiazoles <1889CB2412>.

4.04.8.1 Formation of 1,2,4-Oxadiazoles

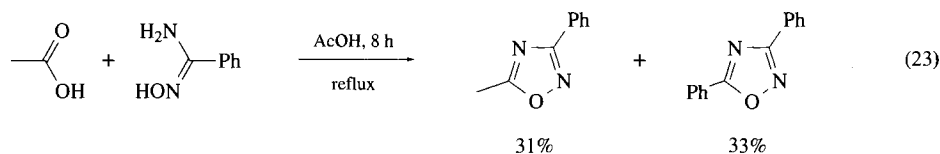
4.04.8.1.1 1,2,4-Oxadiazoles by cyclization of *O*-acylamidoximes

Most widely used for synthesizing 1,2,4-oxadiazoles is the cyclization of *O*-acylamidoximes (**97**) by heating them at their melting points or in a high boiling solvent <65CB144, 82CPB336, 87H(26)1015, 92JMC457, 92JMC3691, 93BSF86>, with phosphorus pentoxide or phosphorus oxychloride <65JOC3734, 88IC3100>, or with acetic anhydride. If the weakly nucleophilic amide group of (**97**) is converted into the more nucleophilic amide anion (NaH), cyclization occurs under mild conditions (0°C). No oxadiazoles are obtained by treating *O*-tosylamidoximes with NaH. Instead Beckmann (Tiemann) rearrangement to cyanamides takes place <89MI 404-02>. Occasionally, Tiemann rearrangements are also side reactions of thermal cyclizations of *O*-acylamidoximes <65JOC4359, 69JPR661, 92IZV1863>. The mechanisms for the cyclizations of (**97**) have been studied <80JCS(P2)1792, 85CCC2722>.

In a modern version, the *O*-acylamidoxime (**97**) is prepared *in situ* from an amidoxime (**96**) and an acyl chloride in pyridine (Scheme 34) <89JHC125>.

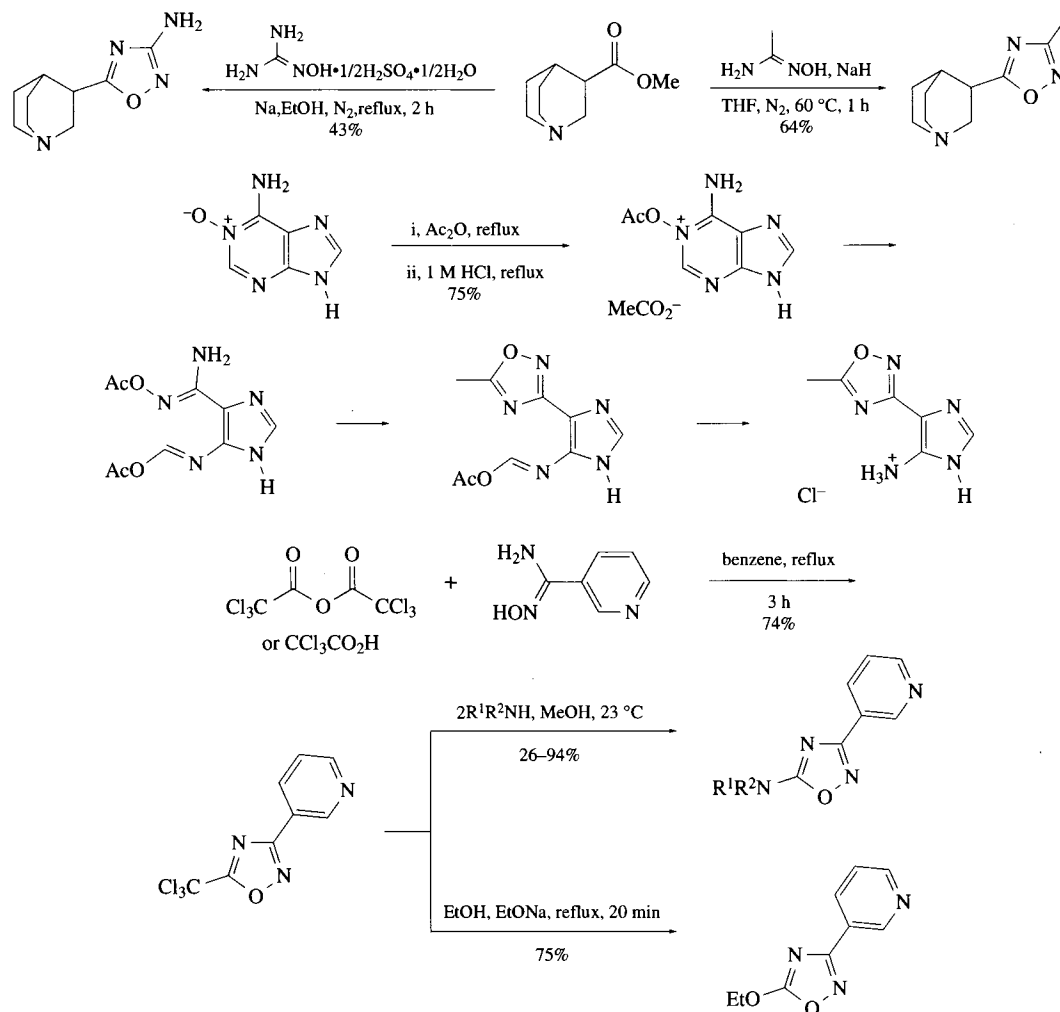


O-Acylation of (**96**) has been achieved with an acid and dicyclohexylcarbodiimide as condensing agent <72JHC435, 75JHC1327>. However, heating amidoximes (**96**) with carboxylic acids alone gives mixtures of compounds containing oxadiazoles (Equation (23)) <64BSB518, 89BSB203>.



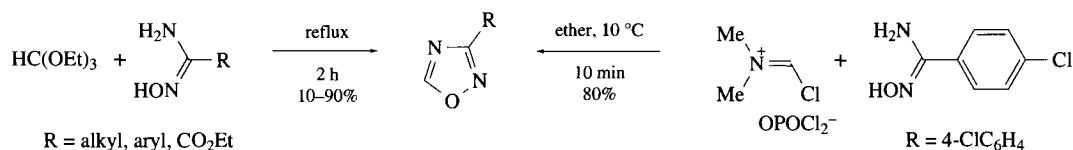
Amidoximes (**96**) have also been acylated with carboxylic anhydrides <1884CB1685, 84JHC1193, 89JCS(P1)1889, 94KGS534>, carboxylic esters <75JOC2481, 91JMC687, 94JMC758>, benzotrichlorides <1884CB1685, 90T1659>, carboxamides <77HCA237>, nitriles <90T3941, 94IZV118>, *N,N*-dialkylcarboxamide dialkylacetals <82JHC1397, 94KGS534>, alkoxyimidoyl compounds <63CB1049>, ketene <63BSB91>, and others <82SC457, 88KGS1457>. A number of examples are given in Scheme 35 <60JA1148, 73CPB1641, 90JMC1128>.

The unsubstituted 1,2,4-oxadiazole has been prepared from formamidoxime and the mixed anhydride of acetic and formic acid, or formamide <67BSB92>. 5-Unsubstituted 1,2,4-oxadiazoles are formed by heating the condensation products of amide oximes with formic acid <63CI(M)1238>. Alternatively, amidoximes are treated with triethyl orthoformate in the presence or absence of



Scheme 35

catalytic amounts of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <73JCS(P1)47, 85H(23)2819, 92KGS964, 93JHC497>, or with Vilsmeier–Arnold reagents $\text{Me}_2\text{N}=\text{CHCl}^+ \text{X}^-$ <94KGS534> (see, for example, Scheme 36 <67JMC208>).



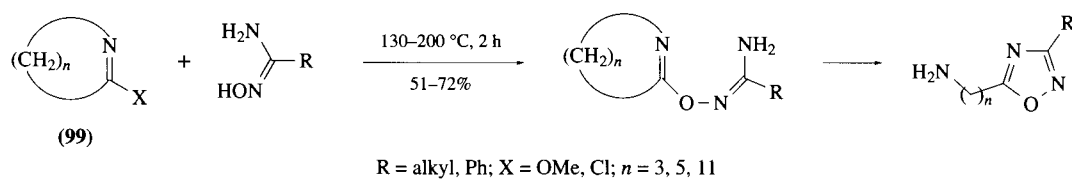
Scheme 36

With lactam acetals (**98**), cyclic imidic chlorides (**99**) ($\text{X} = \text{Cl}$), lactim ethers (**99**) ($\text{X} = \text{OMe}$), or certain iminium salts (**100**) amidoximes form 5-(aminoalkyl) substituted oxadiazoles (Scheme 37) <78LA306>.

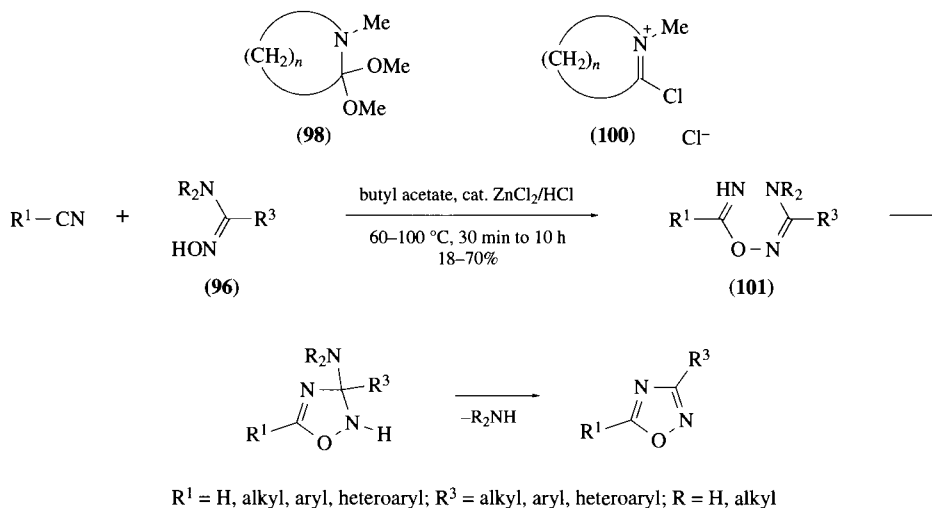
The interaction of amidoximes (**96**) with nitrites in the presence of ZnCl_2 and HCl affords 1,2,4-oxadiazoles (Scheme 38) <90T3941, 94IZV118>. The activation volumes for cyclocondensations of benzamidoxime with benzonitrile and acetonitrile are negative ($-14.6 \text{ mL mol}^{-1}$, $-18.5 \text{ mL mol}^{-1}$ respectively). Thus, pressure accelerates the condensation <87NKK1807>.

At ambient pressure, secondary cyanamides R_2NCN react with amidoximes to give 5-(dialkylamino)-1,2,4-oxadiazoles <91IZV2166>. However, at 400 MPa mainly 5-[(dialkylamino)-aminomethylenamino]-1,2,4-oxadiazoles are formed.

Phenylcyanate and amidoximes react in the presence of sodium ethoxide to give 5-amino-1,2,4-

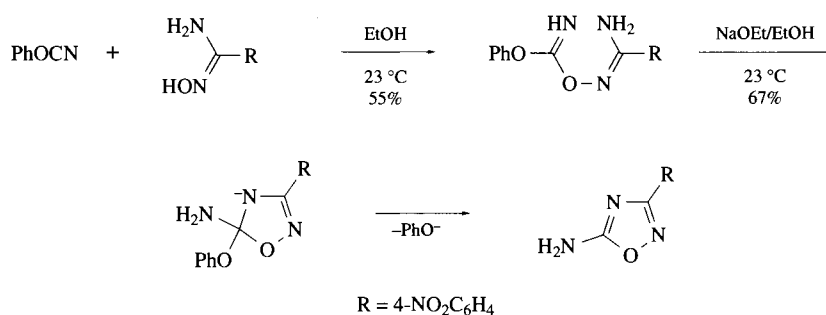


Scheme 37

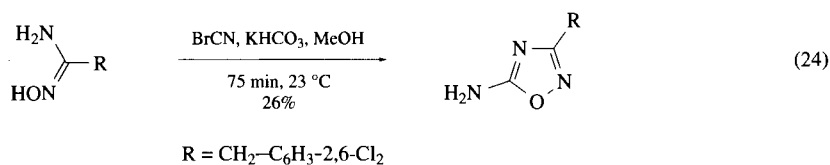


Scheme 38

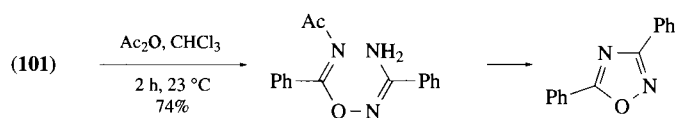
oxadiazoles (Scheme 39) <74ZC270>, compounds which have also been prepared from cyanogen bromide and amidoximes (Equation (24)) <92T6335>.



Scheme 39

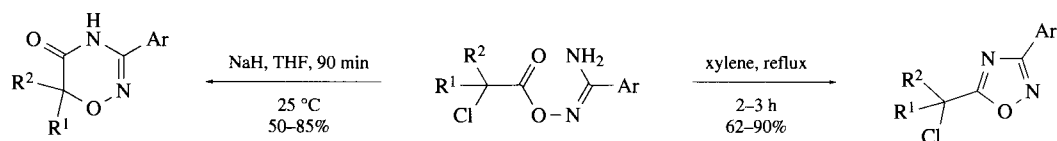


Treatment of arylamidoximes (96) with *N*-chlorosuccinimide or other oxidizing reagents affords imidates (101) (R¹ = H; R² = aryl), which after acylation can be cyclized to oxadiazoles in high yields (Scheme 40) <80JCS(P2)1792>.



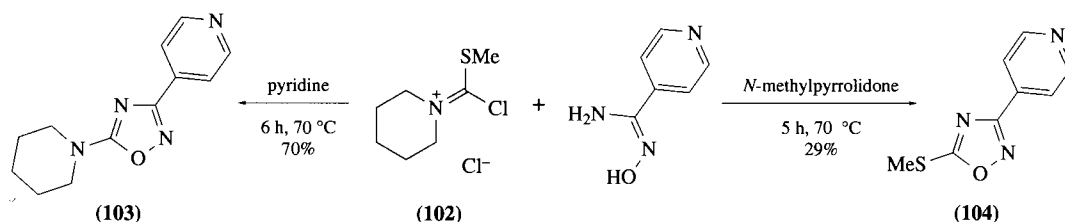
Scheme 40

Thermal condensation of α -chlorocarboxylic chlorides with amidoximes affords 1,2,4-oxadiazoles. However, in the presence of a strong base (NaH) 1,2,4-oxadiazin-5-ones were isolated (Scheme 41) <87H(26)163>.



Scheme 41

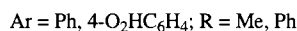
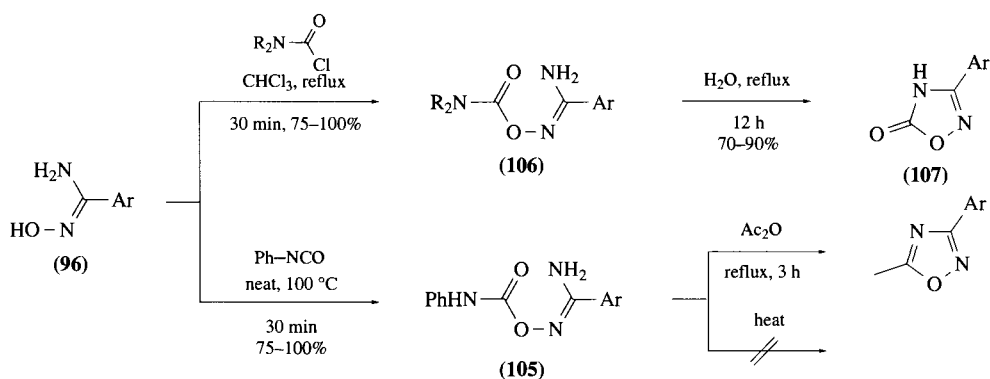
Chloroiminium salts, for example (102), give either oxadiazoles (103) or (104) depending on the basicity of the solvent (Scheme 42) <65CB1293>.



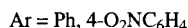
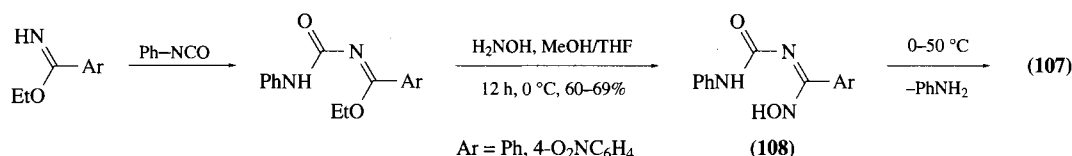
Scheme 42

Amidoximes (96) react at the hydroxy group with isocyanates or carbamoyl chlorides. The resulting urethanes (105) can be cyclized in boiling acetic anhydride (Scheme 43). *N,N*-Disubstituted urethanes (106) as well as the *N*-carbamoyl compounds (108), give oxadiazolinones (107) (Schemes 43 and 44) <63HCA1073>.

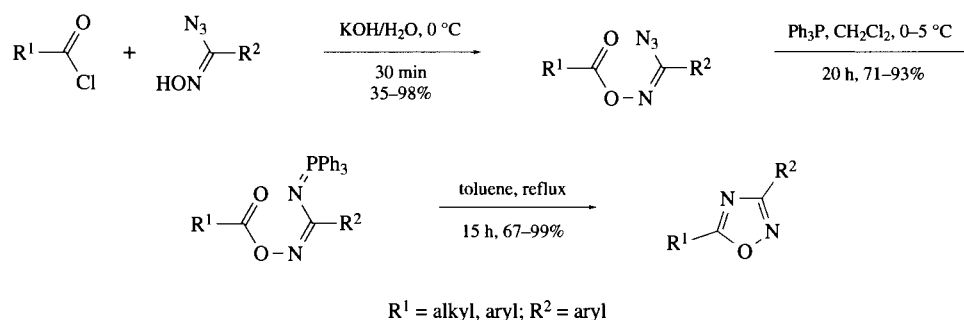
Treatment of *O*-acylated azido oximes (care!) with triphenylphosphane affords iminophosphoranes, which undergo intramolecular Staudinger reaction to oxadiazoles (Scheme 45) <86S843>.



Scheme 43



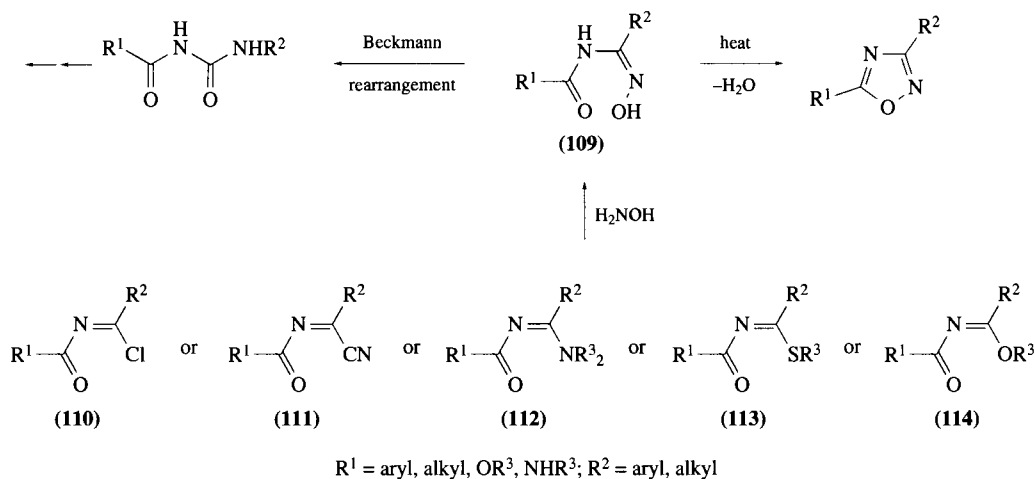
Scheme 44



Scheme 45

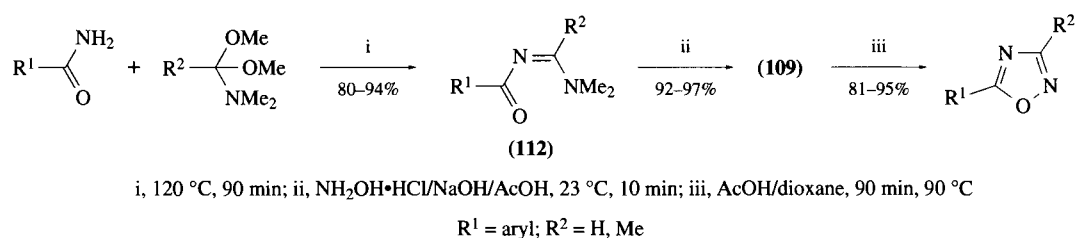
4.04.8.1.2 1,2,4-Oxadiazoles by cyclization of *N*-acylamidoximes

N-Acylamidoximes (**109**) give 1,2,4-oxadiazoles at lower temperatures than do *O*-acylamidoximes (**97**). In many cases, *N*-acylamidoximes cyclize spontaneously at room temperature or below. However, even under strongly basic conditions, Beckmann rearrangement of (**109**) to a urea can be faster than cyclization to an oxadiazole (Scheme 46) <86JCS(P2)727>.



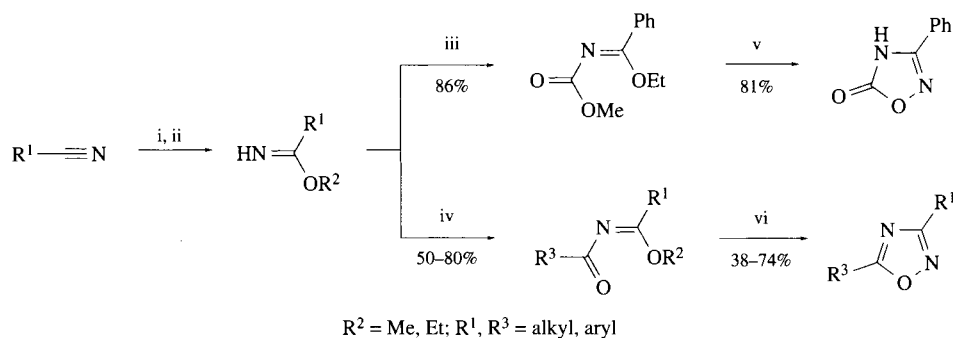
Scheme 46

N-Acylamidoximes (**109**) cannot be prepared by acylation of amidoximes because *O*-acylation is much faster <64BSB518, 65JOC4359, 89ZOR661>. Occasionally, acyl migration from O to NH_2 seems to occur <86JMC1540>. Reactions of *N*-acylimidic chlorides (**110**) <88AP(321)527>, cyanides (**111**) <68NKZ900>, acylamidines (**112**), *N*-acyl(alkylthio)imides (**113**) <65T1681>, or *N*-acyl(alkoxy)imides (**114**) <68NKZ900>, for example *N*-acyl-*O*-alkylisoureas <64BSB518> with hydroxylamine afford oxadiazoles via (**109**) (Scheme 46). Thus, acylamidines (**112**), prepared by reaction of amides with *N,N*-dimethylformamide dimethylacetals, react with hydroxylamine to give *N*-acylamidoximes (**109**), which can be cyclized to oxadiazoles (Scheme 47) <79JOC4160>.



Scheme 47

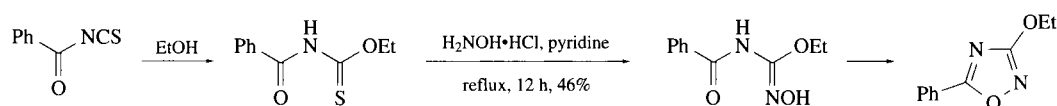
Other suitable starting materials for *N*-acylamidoximes are nitriles, for example, Scheme 48 <83S483>.



i, $R^2\text{OH}/\text{HCl}$ gas, Et_2O , 24 h, 0–5 °C; ii, $\text{KOH}/\text{H}_2\text{O}$; iii, $\text{MeO}-\text{C}(=\text{O})\text{Cl}$ /collidine, hexane, 24 h, reflux, $R^1 = \text{Ph}$
 iv, $R^3\text{COCl}/\text{Et}_3\text{N}$, toluene, 12 h, 0–23 °C
 v, H_2NOH , MeOH , 5 h reflux,; vi, H_2NOH , MeOH , 18 h, 23–65 °C

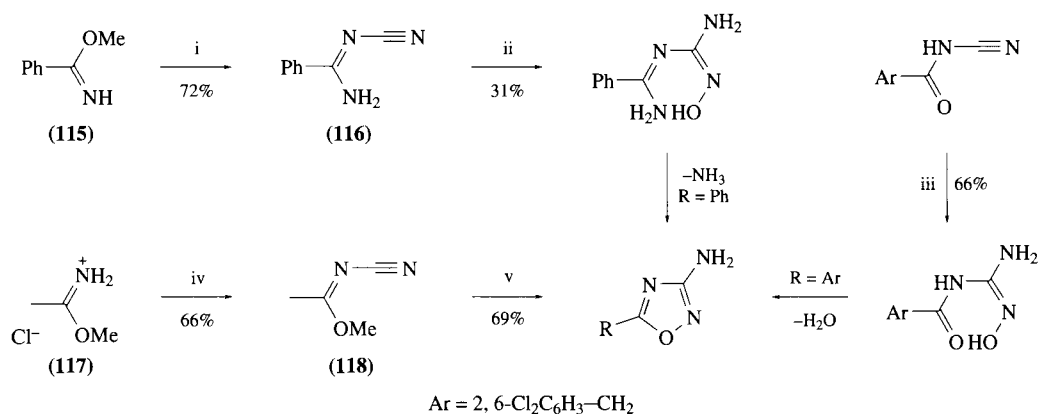
Scheme 48

Furthermore, *N*-acylamidoximes are formed by reaction of *N*-acylthioamides with hydroxylamine (Scheme 49) <81JHC1197, 81T1415>.



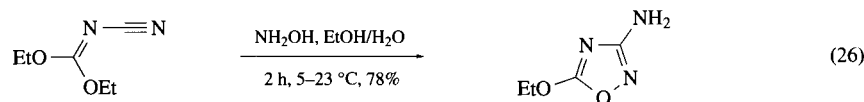
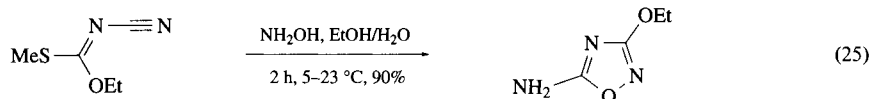
Scheme 49

Imidates such as (115) react with cyanamide to give *N*-cyanoamidines (116), while the hydrochloride (117) is transformed to (118). Both (116) and (118) give 3-amino-1,2,4-oxadiazoles on treatment with hydroxylamine (Scheme 50) <81JHC37, 86JMC1540, 92JMC3691>. However, other alkylidene cyanamides form either mixtures of 3- and 5-amino-1,2,4-oxadiazoles <87JHC275> or exclusively the 5-amino compounds (Equations (25), (26)) <94BCJ307>.

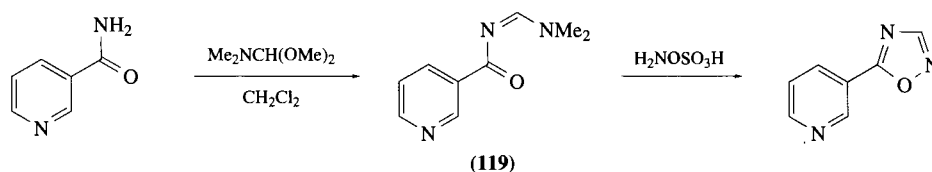


i, H_2NCN , MeOH , 12 h, 23 °C; ii, NH_2OH , pyridine/ EtOH , 30 min reflux; iii, $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine/ EtOH , 23 °C, 12 h
 iv, H_2NCN , MeOH , 3 h, 23 °C; NH_2OH , EtOH , Et_3N , 30 min, 23–40 °C

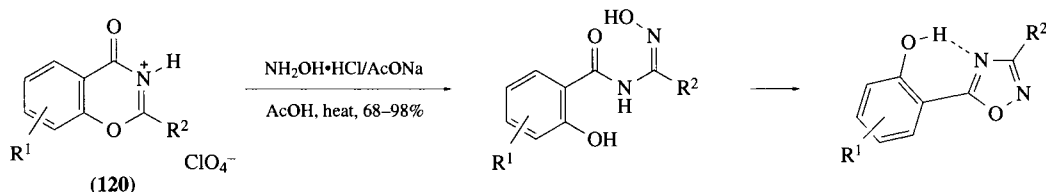
Scheme 50



Substituted acylamidines, such as **(119)**, have been cyclized to oxadiazoles with hydroxylamine-*O*-sulfonic acid (Scheme 51) <91JMC1086>. Mechanistically related reactions include formations of oxadiazoles from oxazinium salts **(120)** (Scheme 52) <92KGS540>, and other oxadiazole-forming ring transformations <94H(38)113>, such as **(121)**→**(122)** (Scheme 53) <89CB1107>.

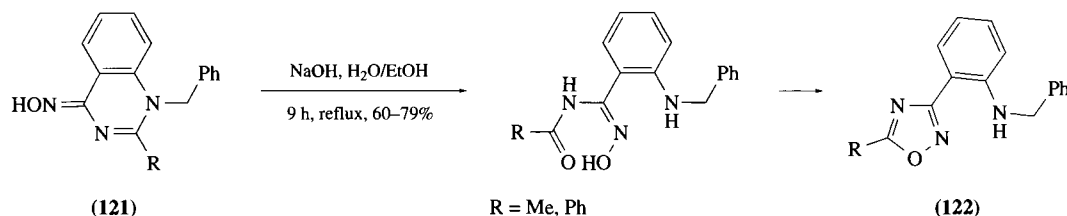


Scheme 51



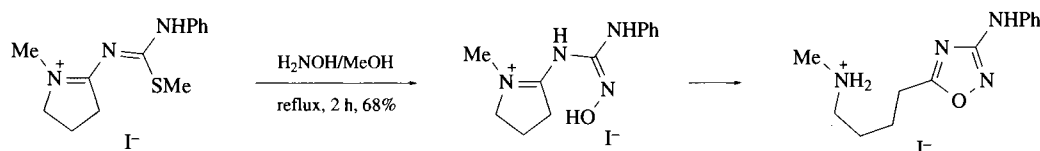
R¹ = H, 3,4-, 4,5-, 5,6-benzo; R² = Me, aryl, vinyl

Scheme 52



R = Me, Ph

Scheme 53



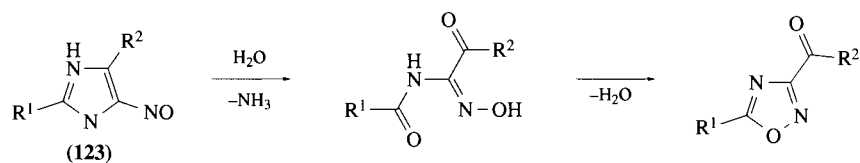
Scheme 54

Amidinium oximes readily cyclize to oxadiazoles (Scheme 54) <91AP(324)963>.

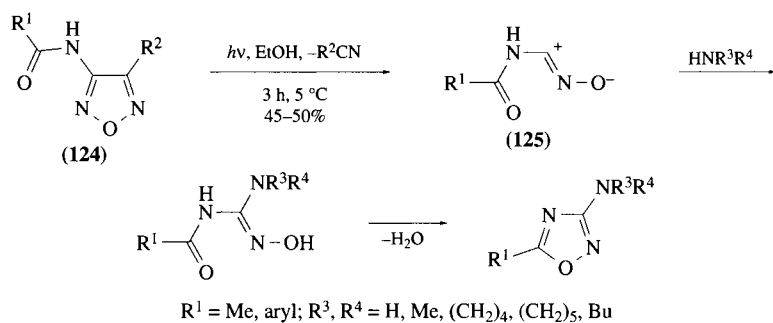
4-Nitrosoimidazoles **(123)** are instantaneously hydrolyzed to *N*-acylamidoximes, which cyclize to 3-acyl-1,2,4-oxadiazoles (Scheme 55) <73JHC357, 92CC1394>.

Irradiation of furazans **(124)** in the presence of secondary amines R³R⁴NH leads to 3-amino-1,2,4-oxadiazoles, possibly via dipolar intermediates **(125)** (Scheme 56) <92H(34)2313>.

Nitrosation of the 2-acylamino-1,3-dicarbonyl compound **(126)** affords an intermediate **(127)**, which is spontaneously hydrolyzed to an *N*-acylamidoxime. Elimination of water produces the oxadiazole **(128)** (Scheme 57) <58CB1123>. Similar results have been obtained for some acyclic

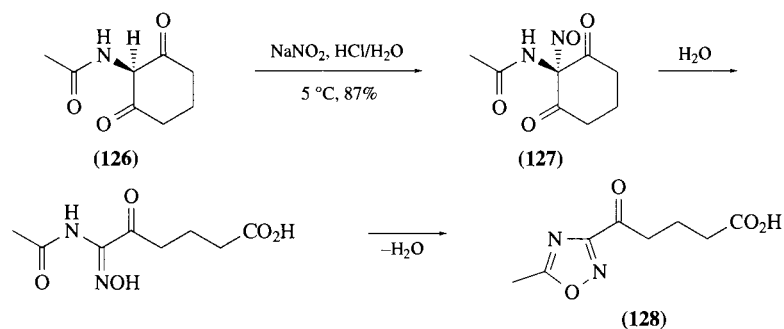


Scheme 55



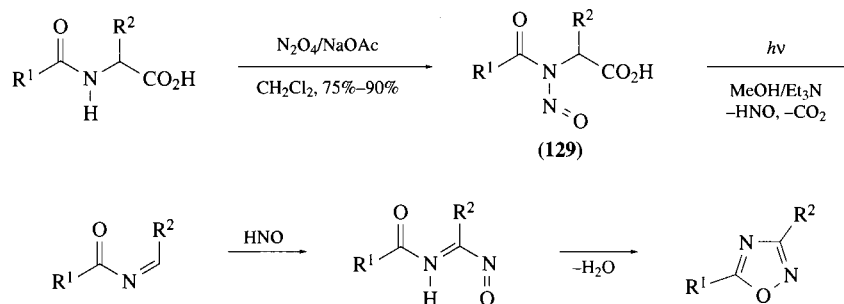
Scheme 56

acylamino malonic monoesters $\langle 61\text{CB}757 \rangle$ and for amidoketones $\text{R}^1\text{—CO—CH}_2\text{—NH—CO—R}^2$ $\langle 71\text{JPR}667 \rangle$. However, tertiary amides $\text{R}^1\text{—CO—CH}_2\text{—NR}^3\text{—CO—R}^2$ ($\text{R}^3 \neq \text{H}$) cannot be nitrated. This leads to the conclusion that the reaction starts with an electrophilic attack of NO^+ on nitrogen followed by rearrangement to the C-nitroso isomer. Nitrosation of *N*-(4-methylpyridyl)benzamides affords 5-aryl-3-(4-methylpyridyl)-1,2,4-oxadiazoles $\langle 83\text{JHC}1403 \rangle$.



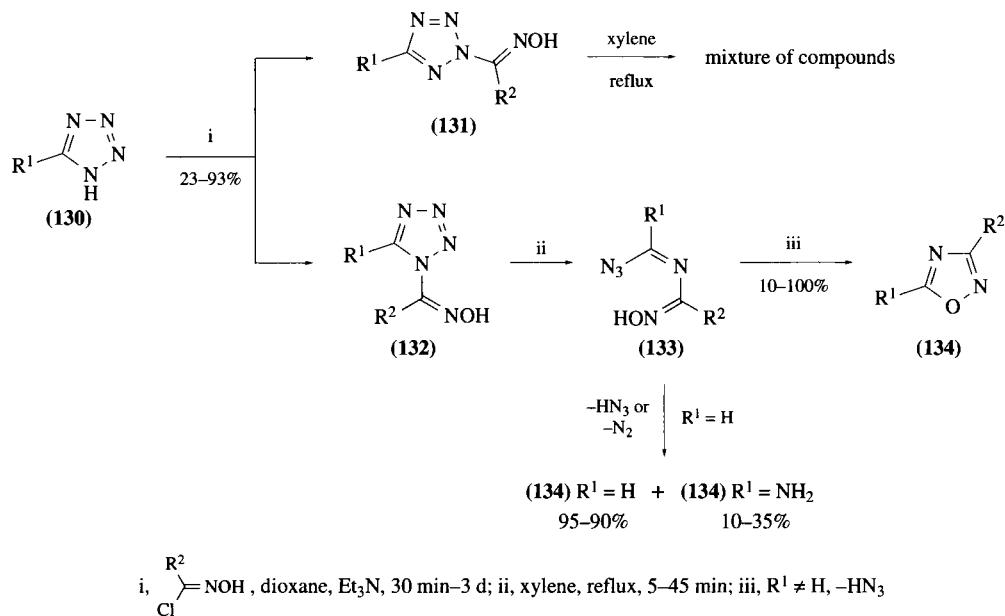
Scheme 57

In connection with nitroso induced biological transformations, a photoreaction of *N*-nitrosamido acids (129) leading to oxadiazoles in the presence of base seems to be of interest (Scheme 58) $\langle 86\text{JCS(P)}2727 \rangle$.



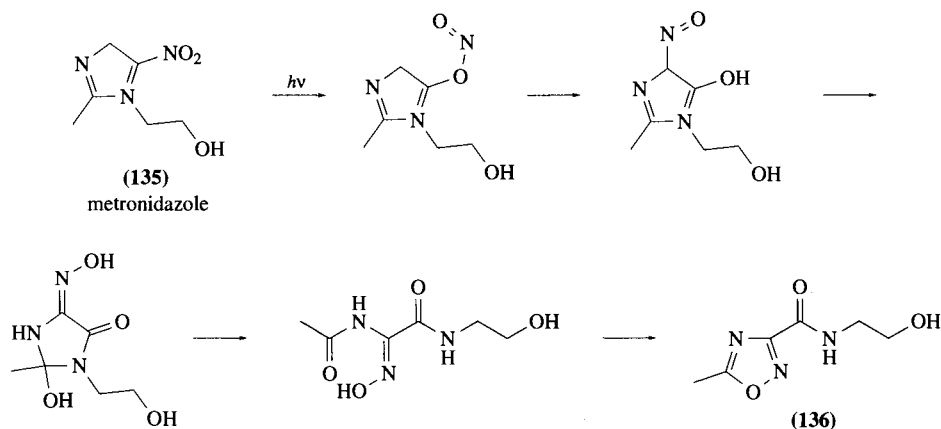
Scheme 58

Tetrazoles (130) and nitrile oxides form mixtures of isomers (131) and (132) (Scheme 59). While thermolysis of (132) ($R^1 \neq H$) gives 1,2,4-oxadiazoles (134) via azides (133) almost quantitatively, compounds (131) decompose to mixtures of products (Scheme 59) <87BSB675>.



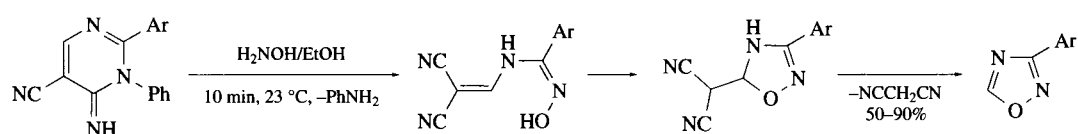
Scheme 59

Metronidazole (135) is a γ -radiation sensitizer of hypoxic cells in cancer radiotherapy. Irradiation with UV light in oxygen-free neutral aqueous solution results in quantitative rearrangement to the oxadiazole (136) (Scheme 60) <87HCA171, 87JCS(P1)1817>.

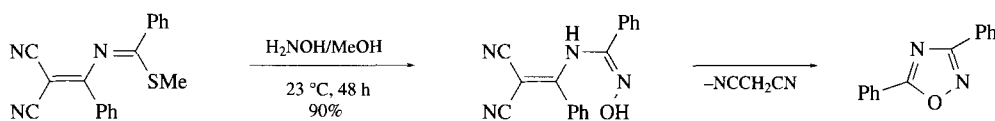


Scheme 60

A synthesis of 5-unsubstituted 3-aryl-1,2,4-oxadiazoles starts from easily accessible *N*-(dicyanovinyl)amidoximes (Schemes 61, 62) <86JAN111, 94H(38)113>.



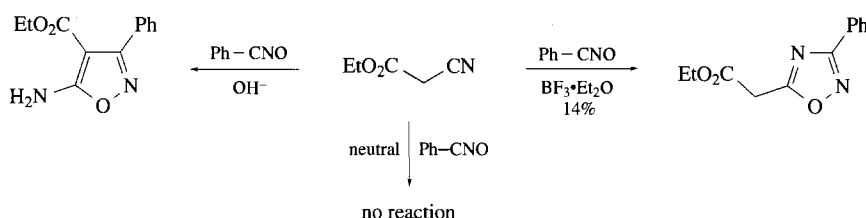
Scheme 61



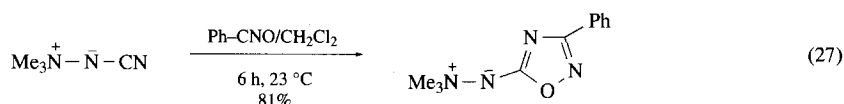
Scheme 62

4.04.8.1.3 1,2,4-Oxadiazoles by cycloadditions of nitrile oxides to nitriles

The dipolarophilicity of aliphatic nitriles towards nitrile oxides (**138**) is low <72CB2825>. Aromatic and electron-deficient nitriles show enhanced reactivities <67JOC1577, 75G701>. However, under Lewis acid catalysis ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) even aliphatic nitriles like acetonitrile form cycloadducts <67TL331, 91JOC1332, 93KGS402>. For instance, the anion formed from ethyl cyanoacetate in alkaline solution adds benzonitrile oxide across the $\text{C}=\text{C}$ double bond to give a 1,2-oxazole. No reaction occurs in neutral medium, while in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ a 1,2,4-oxadiazole is formed (Scheme (63)). Benzonitrile oxide adds to the nitrile group of trialkylaminocyanimides—and not to the anionoid nitrogen atom (Equation (27)) <90IZV2084>.

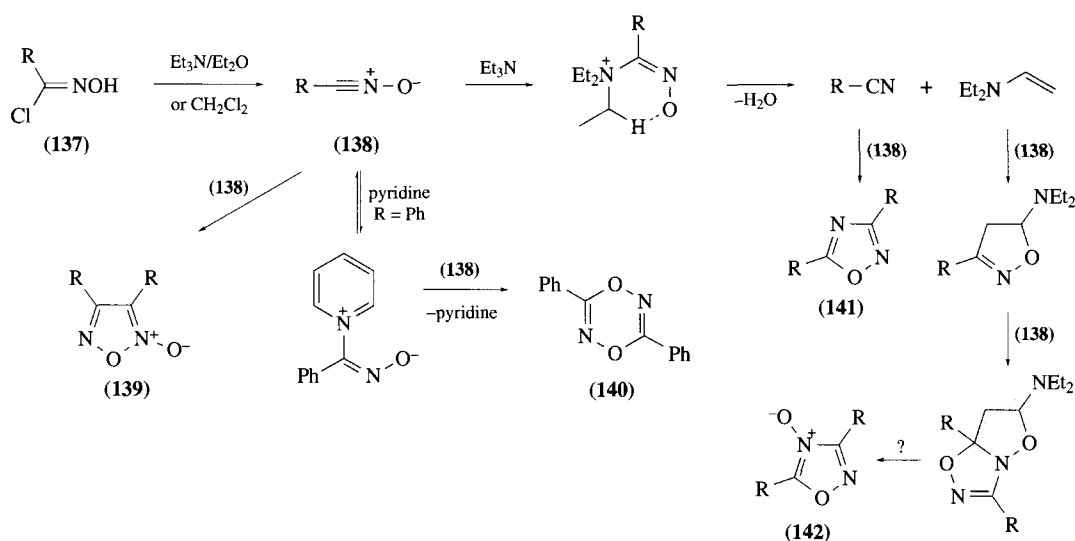


Scheme 63



As substitute for hydrogen cyanide, which does not add aromatic nitrile oxides, 1,3,5-triazine has been recommended for the preparation of 5-unsubstituted 1,2,4-oxadiazoles <78BCJ1484>.

Nitrile oxides (**138**) are usually generated *in situ* by dehydrochlorination of hydroxamoyl chlorides (**137**) <87JCS(P1)607, 87SC1199> or by dehydration of primary nitroalkanes <60JA5339, 80CPB3296>, or by other methods (Scheme 64) <68T5251, 73S156, 79JCR(S)314>.

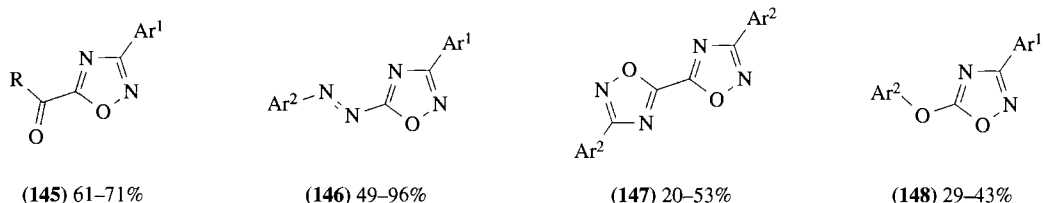
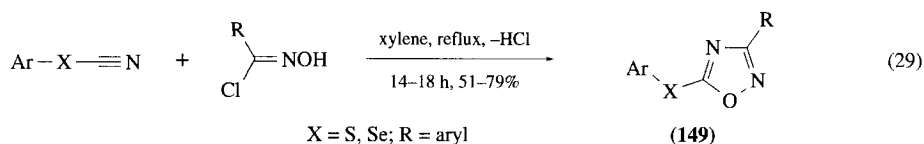
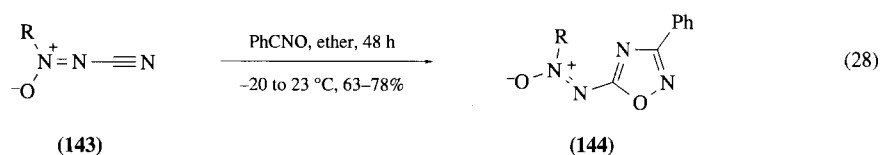


Scheme 64

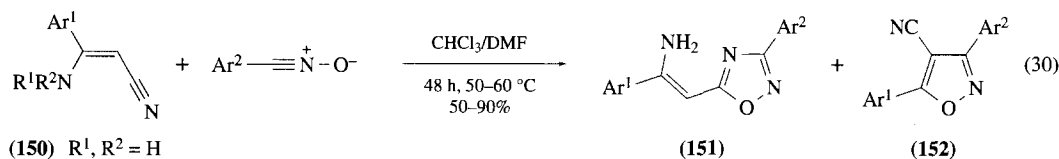
Common side reactions of cycloadditions of nitrile oxides are their dimerization to furoxanes (**139**) and to 1,2,4-oxadiazole-4-oxides (**142**) <73S156> (BF_3 catalysis <90KGS909>; trimethylamine catalysis <76JCS(P1)1825>). Furthermore, if oxime chlorides, such as (**137**) ($\text{R} = \text{Ph}$), are dehydrochlorinated in the presence of triethylamine variable amounts of oxadiazoles, (**141**) are formed even in the absence of a nitrile <83TL4377>. Dimerization of nitrile oxides to dioxadiazines (**140**) occurs in inert solvents promoted by excess of BF_3 <69G165> or in the presence of pyridine or imidazoles (Scheme 64) <88T4917, 90G1>.

The kinetic data for cycloadditions of 2,4,6-trimethylbenzonitrile oxide to benzonitriles are consistent with a concerted although asynchronous reaction with a transition state, in which the formation of the $\text{O}-\text{C}$ bond is more advanced than the making of the $\text{C}-\text{N}$ bond <90JCS(P2)245>.

Cyanoazoxy compounds (**143**) <91IZV1647>, acyl cyanides <72CB2825>, azocyanides, cyanogen <88HCA1681>, trinitroacetonitrile <86ZOR2618>, α,α -dichloronitriles <93KGS402>, α -acetoxy nitriles <90T8179>, aryl cyanates <66CB317>, and aryl thio- and selenocyanates <87JCS(P1)607> are good dipolarophiles for nitrile oxides to give oxadiazoles (**144**)–(**149**) (e.g., Equations (28) and (29)).

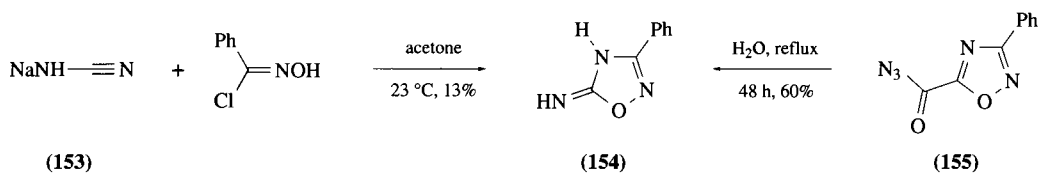


Arylnitrile oxides undergo cycloaddition to one or two vicinal nitrile groups of tetracyanoethene, whilst the $\text{C}=\text{C}$ double bond remains unaffected <76JOC620>. In other cases, such as (**150**), both the nitrile group and the α,β -alkenic bond are attacked <89JHC1683, 90JCS(P2)245>. Attack by the amino group of (**150**) on the nitrile oxide gives side products. Predominant addition of the nitrile oxide to the $\text{C}\equiv\text{N}$ triple bond is only observed for primary or secondary amines (**150**). For dialkylamino derivatives (**150**) cycloaddition occurs exclusively to the $\text{C}=\text{C}$ double bond to give (**152**), indicating that the nitrile group is not activated by conjugation with the enamine system (Equation (30)). This has led to the assumption that hydrogen bonding between NH and the nitrile oxide oxygen atom is responsible for the formation of the oxadiazoles (**151**) <89JCR(S)246>.

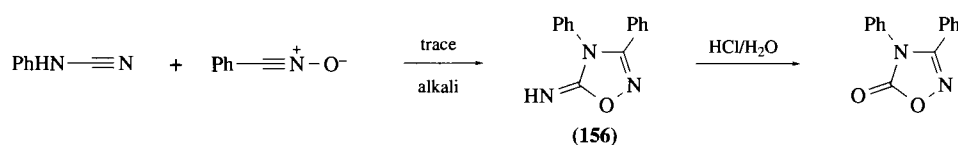


Benzhydroxamic chloride reacts with sodium cyanamide (**153**) in dry acetone to give (**154**), a compound which has alternatively been prepared by Curtius rearrangement of the azide (**155**)

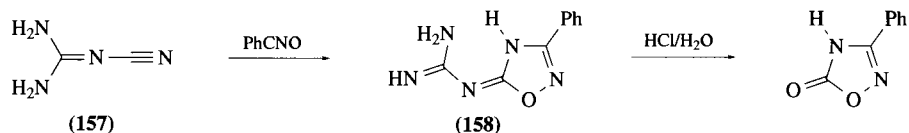
(Scheme 65) <60G1290>. Oxadiazolines (**156**) are produced by cycloaddition of cyanamides and nitrile oxides aryl (Scheme 66) <66JPR221>. Thus, for un- and monosubstituted cyanamides, cycloaddition occurs to the C=N double bond of a tautomeric carbodiimide form rather than to a nitrile triple bond. On the other hand, dicyandiamide (**157**) and benzonitrile oxide furnish (**158**) (Scheme 67).



Scheme 65

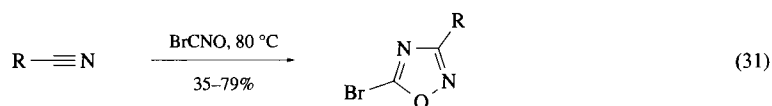


Scheme 66



Scheme 67

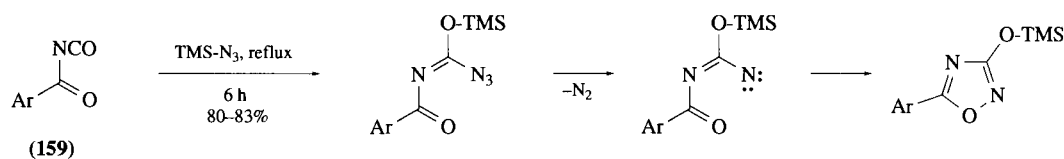
Nonactivated nitriles undergo cycloaddition with especially reactive nitrile oxides (e.g., trifluoroacetonitrile oxide <84JOC919> or bromocyanogen oxide <89JHC23>, acylcyanide oxides <87JHC697>, or cyanogen monooxide (Equation (31)) <91IZV1916>.



4.04.8.1.4 1,2,4-Oxadiazoles by electrocyclic ring closure of nitrenoids

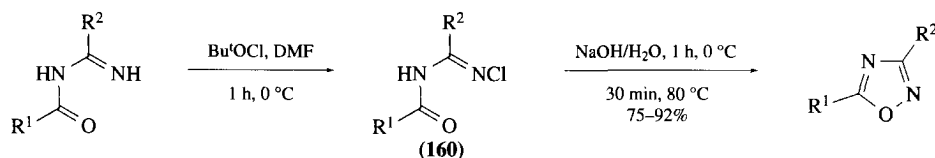
One principal access to 1,2,4-oxadiazoles consists of N—O bond formation by electrocyclic ring closure of nitrenoids N—CR¹=N—CR²=O. For instance, heating acyl isocyanates (**159**) with trimethylsilyl azide affords high yields of 1,2,4-oxadiazoles (Scheme 68) <79JCS(P1)185, 80JOC5130>.

Similarly, elimination of HCl from *N*-chloroamidines (**160**) (Scheme 69) <84BCJ1116> and ther-

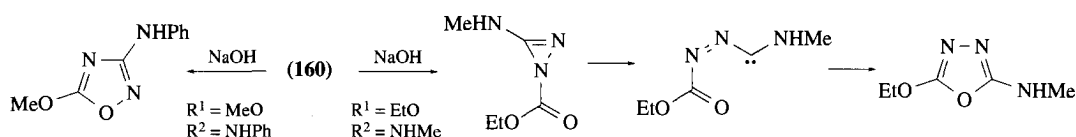
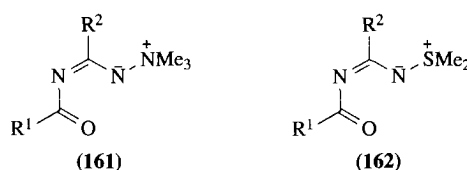


Scheme 68

molyzes of ylides (**161**) <83JHC69> or (**162**) <77BCJ1793> give oxadiazoles under mild conditions. However, depending on the substituents, isomeric 1,3,4-oxadiazoles may be isolated instead of the 1,2,4-oxadiazoles (Scheme 70) <78BSB493, 80HCA841>.



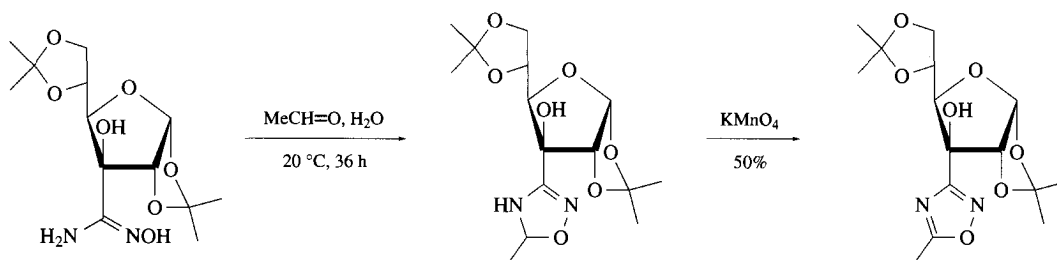
Scheme 69



Scheme 70

4.04.8.1.5 1,2,4-Oxadiazoles from 4,5-dihydro-1,2,4-oxadiazoles

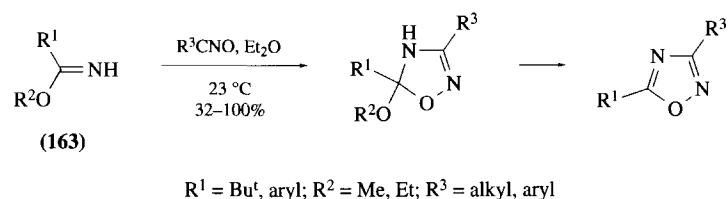
4,5-Dihydro-1,2,4-oxadiazoles with hydrogen atoms in the 4- and 5-positions are readily oxidized to 1,2,4-oxadiazoles with air or potassium permanganate <87JHC101>, chlorine <75JOC2481>, or *N*-bromosuccinimide <86MI 404-02>. This has been used, for example, for the preparation of oxadiazoles substituted with a carbohydrate moiety (Scheme 71) <86MI 404-02>.



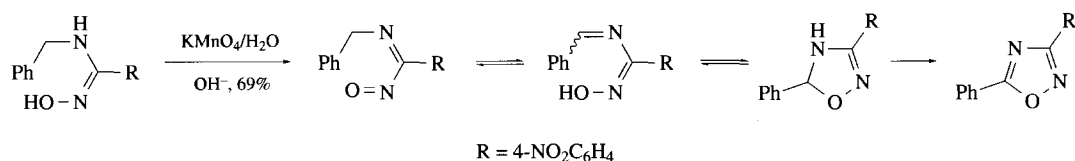
Scheme 71

Aliphatic and aromatic nitrile oxides react with imidates (**163**) to give oxadiazoles (Scheme 72) <69TL311>. The reaction proceeds also for imidates derived from nitriles, which themselves do not react with nitrile oxides. Therefore, it seems unlikely that nitriles are intermediates in this cyclo-addition. Similarly, amidines, guanidine, isothioureas, and 4,5-dihydro-1,2-oxazoles, respectively, have been used to prepare oxadiazoles <72JCS(P1)1711, 83CPB4181, 92CPB1610, 92JMC3691>. Oxidation of

N-benzylamidoximes with potassium permanganate affords 5-phenyl-1,2,4-oxadiazoles (Scheme 73) <93ZOB2635>.



Scheme 72

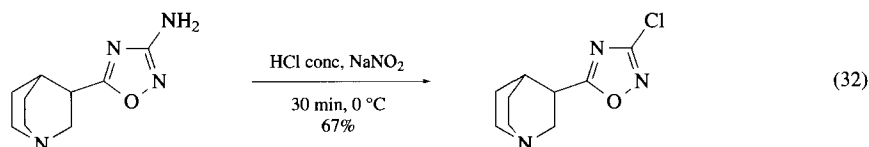


Scheme 73

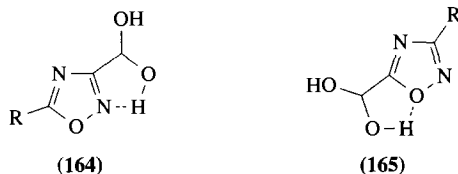
Cycloaddition of nitrile oxides to the double bond of aldoximes under BF_3 catalysis affords 4,5-dihydro-4-hydroxy-1,2,4-oxadiazoles, from which water can be eliminated. Oxadiazoles are obtained in low yields <86IZV2151, 90IZV625>.

4.04.8.1.6 Modification of 1,2,4-oxadiazoles

1,2,4-Oxadiazoles have been modified by various conventional methods <63G482, 66JCS(C)1522, 73JCS(P1)2769, 79JHC311, 82M781, 86JMC2174, 91MI 404-01>. For instance, 3-aminooxadiazoles are transformed into their chloro derivatives by diazotization in concentrated hydrochloric acid (Equation (32)) <69BSB47, 90JMC1128>.



From 3- or 5-chloromethyl-1,2,4-oxadiazoles, the 3- or 5-carbaldehydes, respectively, have been prepared by the Kröhnke reaction <79JHC1469>. These aldehydes exist predominantly as hydrates (164) and (165), which are stabilized by intramolecular hydrogen bonds.



3-Oxadiazolynitrile oxides undergo cycladditions with alkynes, alkenes <87JCS(P1)2593, 91KGS827>, and nitriles <91KGS1121>.

3- Or 5-vinyl-1,2,4-oxadiazoles have been polymerized <63USP3074957>.

4.04.8.1.7 Miscellaneous syntheses of 1,2,4-oxadiazoles

1,2,4-Oxadiazolidine-3,5-dione is bis (*O*-silylated) by hexamethyldisilazane <81JMC1172>.

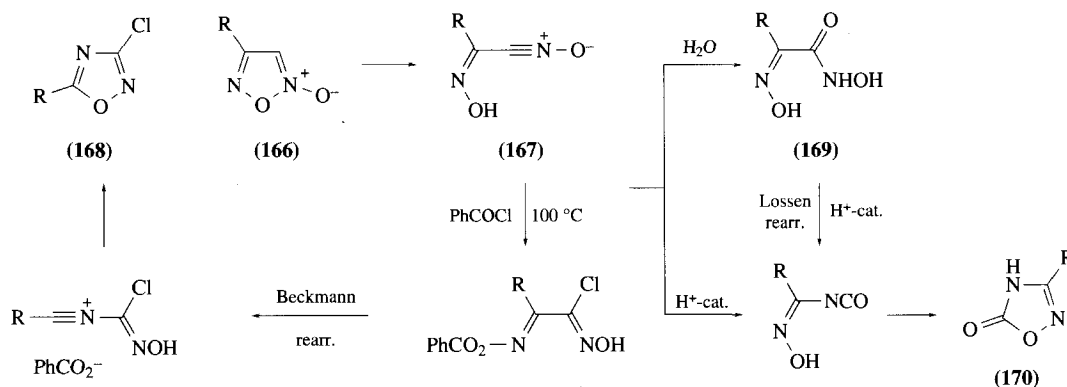
Oxidation of amidoximes can lead to 1,2,4-oxadiazoles <73S156>.

Heating of aromatic aldehydes with nitroethane and ammonium acetate in glacial acetic acid affords 3-aryl-5-methyl-1,2,4-oxadiazoles in moderate yields <85JOC1182>.

The sulfur atoms in certain 1,2,4-dithiazolidines can be replaced by hydroxylamine to give 1,2,4-oxadiazoles <80PHA48>.

Furoxanes (**166**) are thermally rearranged to stable nitrile oxides (**167**) <72JOC593, 88KGS258, 90LA335>, which react with benzoyl chloride to give 3-chlorooxadiazoles (**168**) <B-71MI 404-01>. The nitrile oxides (**167**), catalyzed by acetic acid, give mixtures of (**169**) and the oxadiazolone (**170**) (Scheme 74) <72JOC593>.

Asymmetric 1,2,4-oxadiazoles have been separated into enantiomers by HPLC using an acetylated cyclodextrin as stationary phase <91MI 404-02>.

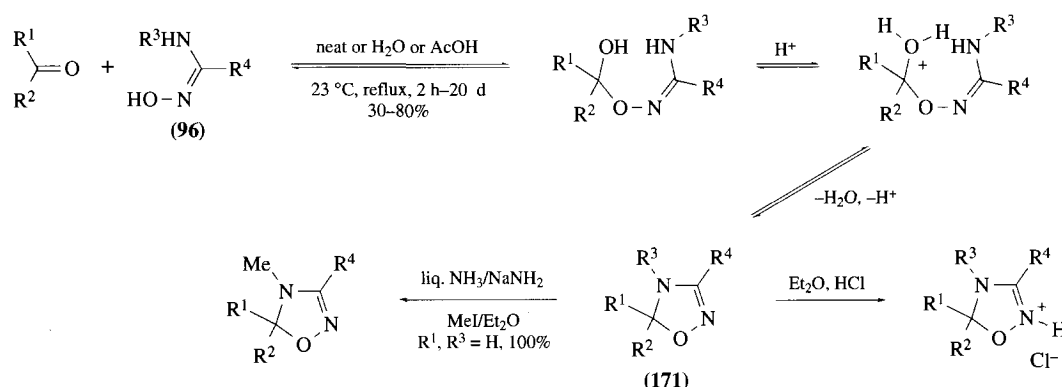


Scheme 74

4.04.8.2 Ring Syntheses of 4,5-Dihydro-1,2,4-oxadiazoles

4.04.8.2.1 Condensation of amidoximes with carbonyl compounds

A general method for the preparation of 4,5-dihydro-1,2,4-oxadiazoles (**171**) involves the condensation of amidoximes with aldehydes or ketones, or azomethines <84UKZ515>, a reaction invented by Tiemann <1889CB2412, 87JHC101, 90H(31)233, 93AP(326)383>. The reaction is reversible: on treatment with aqueous acid the hemiaminals (**171**) are hydrolyzed to the carbonyl compounds and (**96**) (Scheme 75).

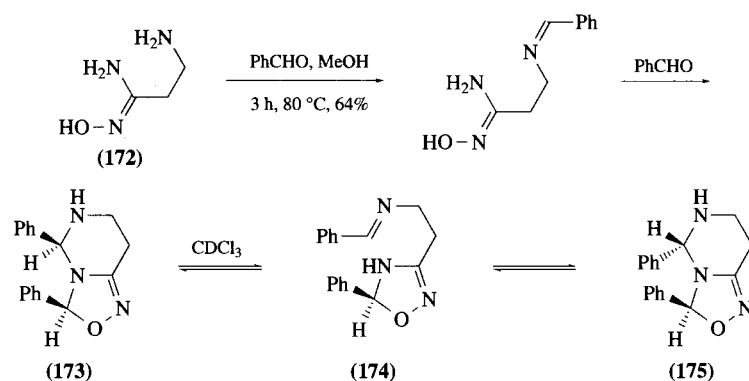


Scheme 75

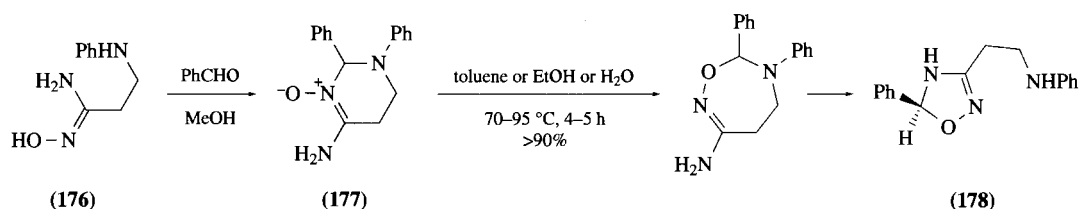
N,N-Dimethylformamide diethyl acetal serves as an aldehyde equivalent to give 5-dimethylamino-4,5-dihydro-1,2,4-oxadiazoles <86MI 404-04>. Oxadiazoles (**171**) ($\text{R}^3 = \text{H}$) can be methylated or benzylated at N(4). With HCl or trichloroacetic acid compounds (**171**) are protonated on N(2) <73BSF2996>.

Complications arise if the amidoxime contains additional amino groups, for example (**172**) and (**176**) <91CBI199>. In solution (**173**), (**174**), and (**175**) form equilibria (Scheme 76) <91CB2065>.

The nitron (177) rearranges under the influence of heat to the oxadiazoline (178) (Scheme 77) <83TL5763>.

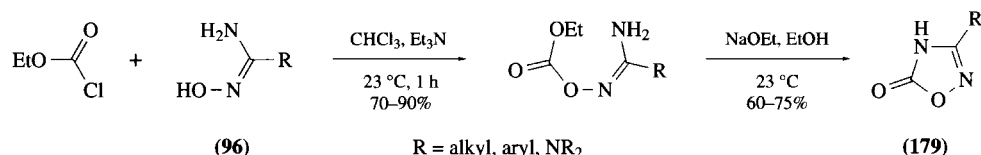


Scheme 76

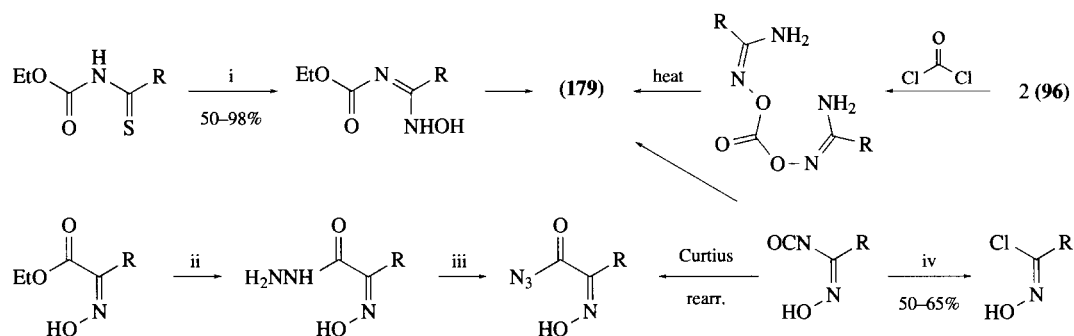


Scheme 77

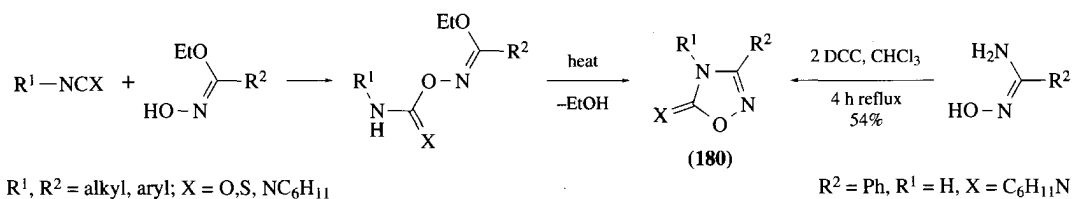
In the Tiemann oxadiazole synthesis (Section 4.04.8.1.1), if chloroformates <70AP(303)488, 91JHC311>, phosgene <88IC3100>, triphosgene <93H(36)1027>, or carbonyldiimidazole <89M81> are chosen as the acid component, 4,5-dihydro-1,2,4-oxadiazole-5-ones (179) are produced (Scheme 78). With thiophosgene, the 5-thiones are formed <91PS(62)47>. Other syntheses of (179) (Scheme 79) <63HCA1073, 79JHC689, 83S483, 91JHC1715> and (180) (Scheme 80) <86JHC1657, 86MI 404-05> are shown.



Scheme 78

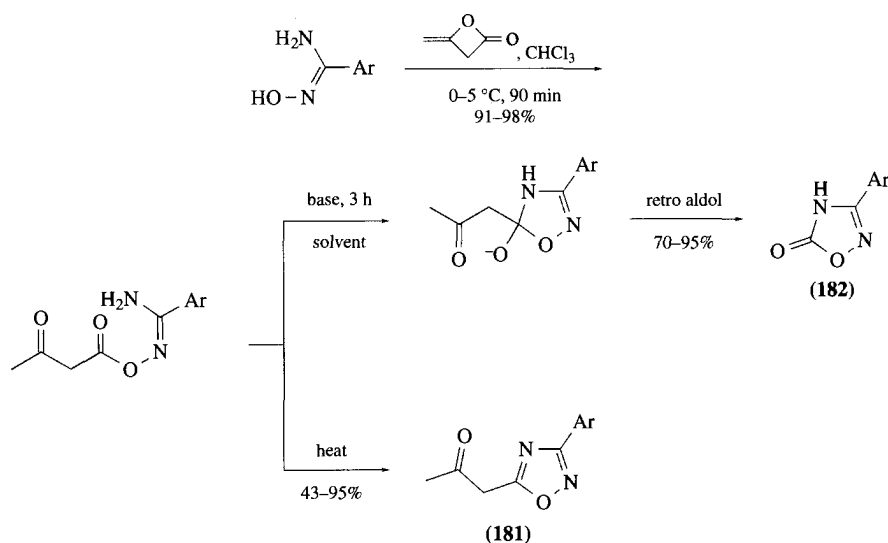


Scheme 79



Scheme 80

Heating arylamidoximes with diketene yields the oxadiazoles (181). However, in the presence of a strong base, the oxadiazolones (182) are formed (Scheme 81) <82CPB336, 82M781>.

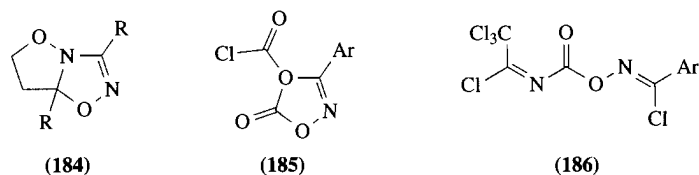


Scheme 81

4.04.8.2.2 Cycloaddition of nitrile oxides to azomethines

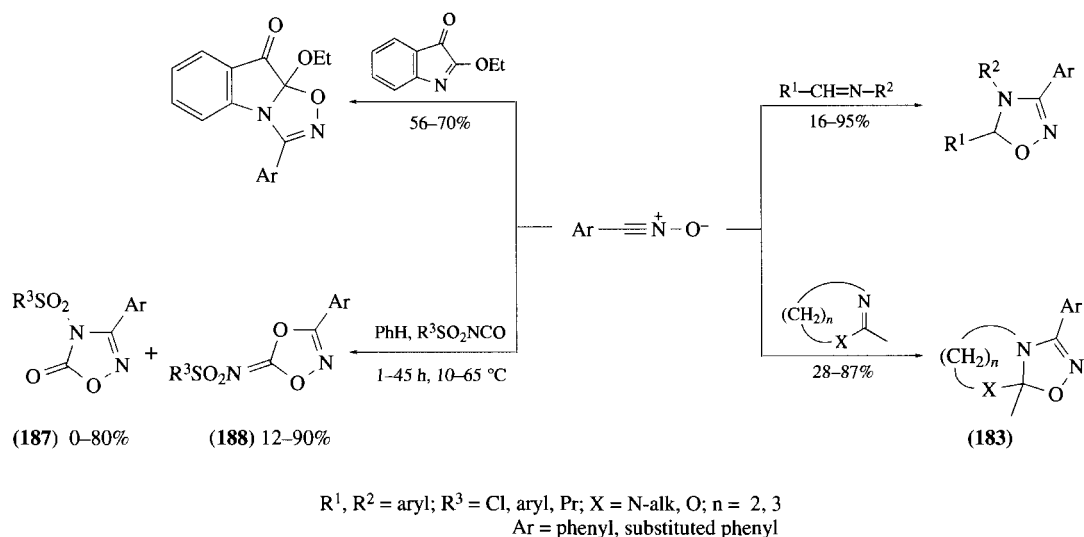
Another general route to 4,5-dihydro-1,2,4-oxadiazoles is the 1,3-dipolar cycloaddition of nitrile oxides to the C=N double bond of azomethines, a process with a high degree of synchrony and little charge separation in the transition state <64G478, 87CJC2050, 89KGS663, 90JHC1425, 90TL2635, 91SL189, 92KGS687>. Occasionally, the cycloaddition may occur from a hydrogen bonded complex of the nitrile oxide and the imine <80JCR(S)348>.

Bicyclic compounds, such as (183) <71AG(E)810, 71AG882>, are produced from cyclic azomethines (Scheme 82) <89JHC1619, 90JHC371, 90JHC1185, 90T7865, 91JHC481, 94T5159>. Oxadiazoles (184) are side-products of the cycloaddition of nitrile oxides to alkenes. Compounds (184) arise from cycloaddition of excess of nitrile oxide to the C=N bonds of primarily formed 1,2-oxazoles <92JCS(P1)2033>.



Stable aryl nitrile oxides undergo cycloaddition to the C=N bond of chlorocarbonyl isocyanate to give compounds (185) <90ZOR339>. In contrast, cycloaddition of nitrile oxides to trichloroacetyl isocyanate occurs across the C=O double bond leaving the isocyanate group unaffected. From

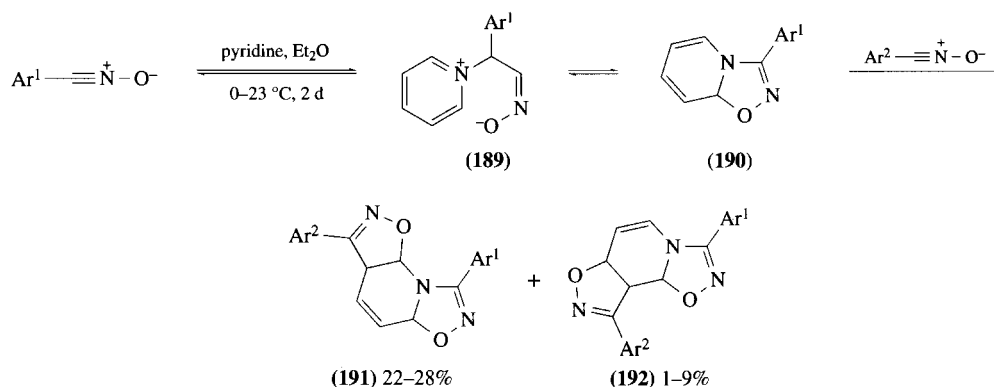
pentachloroethyl isocyanate and aryl nitrile oxides, compounds (**186**) are obtained <89UKZ1071>, while sulfonyl and acyl isocyanates furnish mixtures of (**187**) and (**188**) (Scheme 82) <91ZOR1262, 93UKZ48>. With phenylisocyanate, the cycloaddition of 2,4,6-trimethylbenzonitrile oxide to the C=N bond requires 15 months at 20 °C <72CB2825>.



Scheme 82

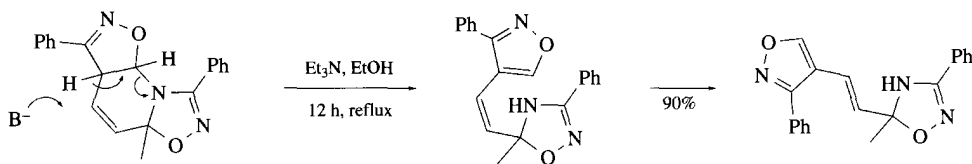
Nitrile oxides react with the C=N double bond of di- or unsubstituted hydrazones to yield 4-amino-4,5-dihydro-1,2,4-oxadiazoles. Monoalkylhydrazones give mixtures of 4-alkylamino-4,5-dihydro-1,2,4-oxadiazoles and 1,2,4,5-oxatriazines <91JHC1229, 91KGS262>. Arylnitrile oxides undergo cycloaddition to the C=N double bonds of carbodiimides <92IZV2430>. Another method for the preparation of 4,5-dihydro-5-oxo-1,2,4-oxadiazoles is the cycloaddition of nitrile oxides to 1,3-disubstituted guanidines <82NKK1791>. Much work has been done concerning the periselectivity of the cycloaddition of nitrile oxides to molecules containing C=C and C=N bonds <91JHC73, 92H(34)1583, 92JHC1593, 93T7001, 94T3773>.

While aryl nitrile oxides dimerize in protic solvents and in pure pyridine (cf. 4.04.8.1.3.), they form bis(adducts) (**191**) and (**192**) via zwitterions (**189**) with pyridine in apolar solvents (Scheme 83) <89JHC757, 90G1>. Significantly, the cycloaddition of the nitrile oxide to pyridine to give (**190**) is not a concerted process. Heterocycles (**191**) undergo base catalyzed ring cleavage (Scheme 84).

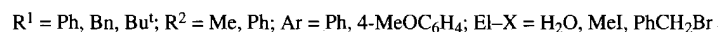
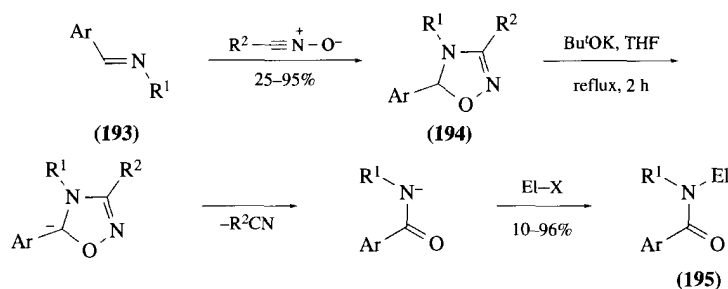


Scheme 83

Cycloreversion of oxadiazolines (**194**) (with an anion stabilizing substituent in the 5-position) with a base affords amide anions, which can be intercepted with electrophiles El-X to give (**195**) (Scheme 85). The sequence can be used to convert an aromatic aldehyde via the imine (**193**) into an amide (**195**) <91SL189>.



Scheme 84

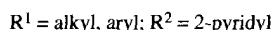
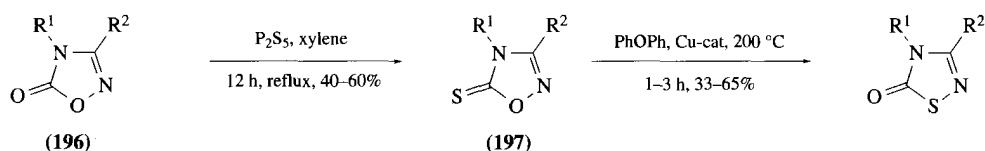


Scheme 85

4.04.8.2.3 Miscellaneous syntheses of 4,5-dihydro-1,2,4-oxadiazoles

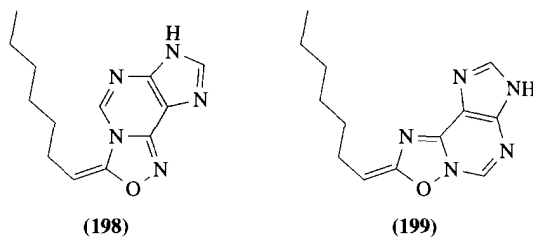
3,5-Dialkyl-1,2,4-oxadiazoles are reduced with diborane in tetrahydrofuran or sodium borohydride in ethanol to 4,5-dihydro-1,2,4-oxadiazoles <73BSF2996, 78JHC1373>.

The lactones (196) can be transformed into the 5-thiones (197) by treatment with an excess of phosphorus pentasulfide (Scheme 86) <92PS(73)93>. Alternatively, compounds (197) are prepared from amidoximes with thiophosgene <92PS(66)321> (cf. Section 4.04.8.2.1). On heating at 200°C in diphenylether in the presence of catalytic amounts of copper or silver, thiones (197) rearrange to thiadiazoles (Scheme 86). Without a catalyst this rearrangement can be achieved by heating at 250°C for five to eleven hours, or photochemically <83JCS(P1)687, 91PS(62)47>.

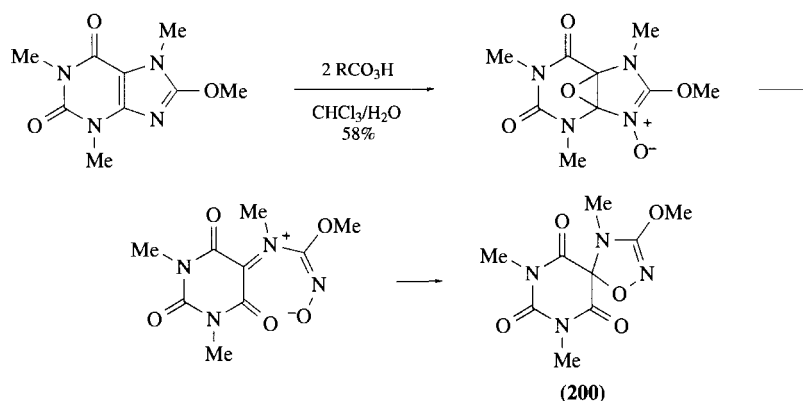


Scheme 86

Interaction of lipid hydroperoxides with DNA gives fluorescent products, which cause structural changes in the DNA. Of the fluorescent products formed in the reaction of methyl linoleate hydroperoxide with adenine, FeSO_4 , and ascorbic acid the 4,5- and 2,5-dihydrooxadiazoles (198) and (199) have been identified <88BBA(962)371>.



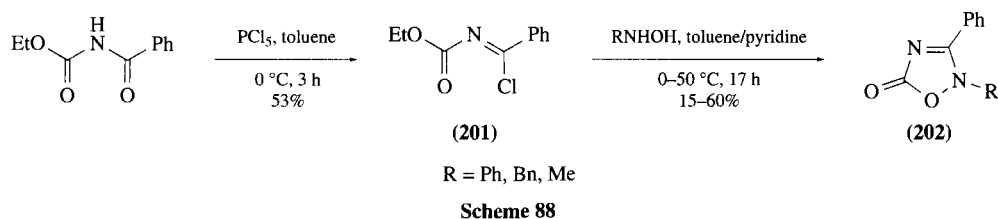
Xanthenes substituted at the 8-position with an oxygen or nitrogen atom are oxidized with peracids to 4,5-dihydro-1,2,4-oxadiazoles (200) (Scheme 87) <94OPP353>.



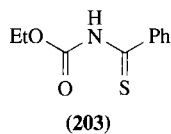
Scheme 87

4.04.8.3 Ring Syntheses of 2,5-Dihydro-1,2,4-oxadiazoles

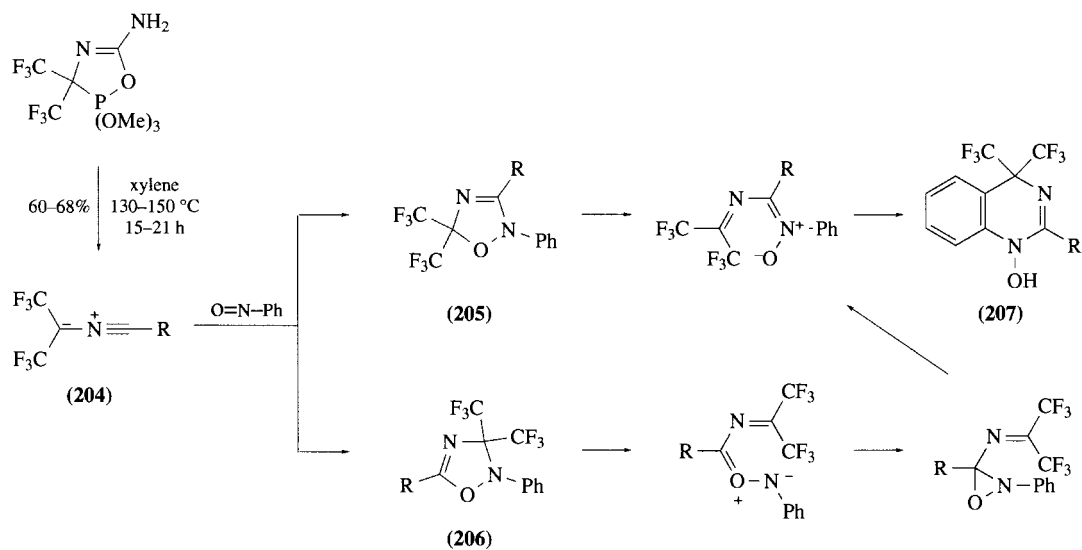
The 2,5-dihydro-1,2,4-oxadiazol-5-ones (**202**) are obtained by treating the imidic chloride (**201**) or the thioamide (**203**) with *N*-monosubstituted hydroxylamines (Scheme 88) [76JOC3233, 77JHC765].



Scheme 88

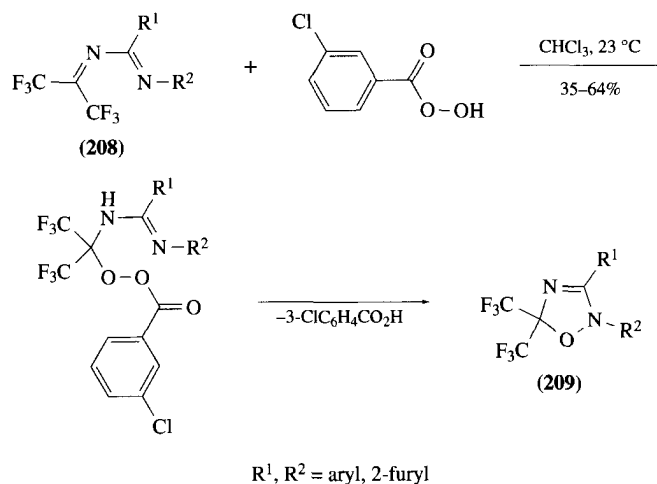


Cycloaddition of nitrile ylides (**204**) to nitroso compounds gives mixtures of (**205**) and (**206**), which both slowly rearrange to quinazolines (**207**) (Scheme 89) [77CB605].



Scheme 89

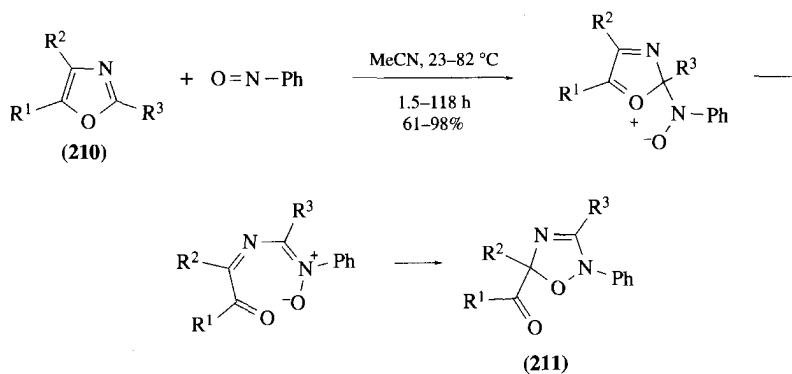
Alkylideneamidines (**208**) are oxidized by *m*-chloroperbenzoic acid to oxadiazolines (**209**) (Scheme 90) <87JFC(37)53>.



R¹, R² = aryl, 2-furyl

Scheme 90

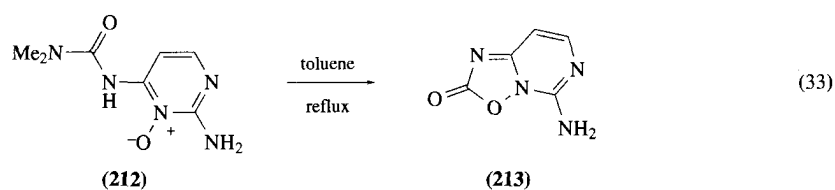
Reaction of nitrosobenzene with oxazoles (**210**) affords 5-acyloxadiazolines (**211**) (Scheme 91) <91CL1221>.



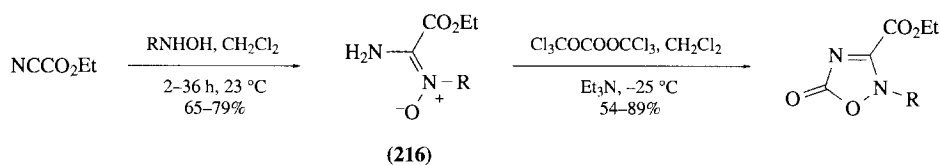
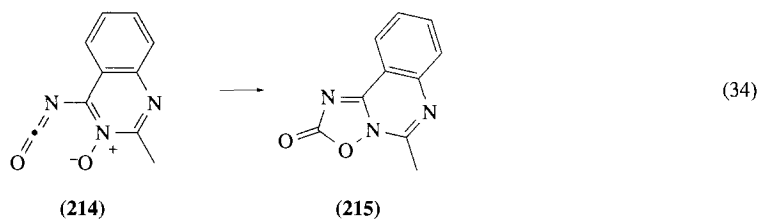
R¹ = *O*-alkyl, Me; R² = H, alkyl, aryl, CO₂Et; R³ = alkyl, aryl

Scheme 91

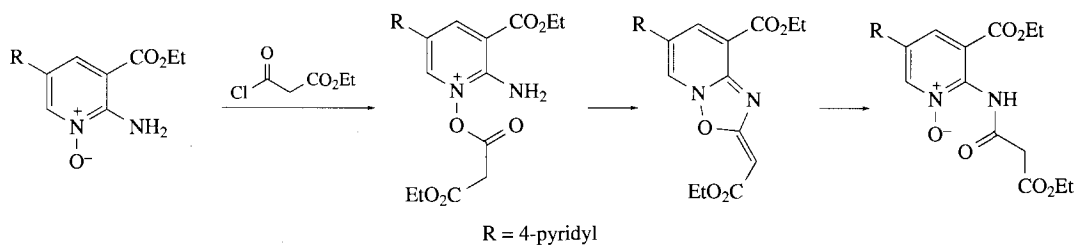
Nitrones (**212**) are cyclized in refluxing toluene to (**213**) (Equation (33)), while nitrones (**214**) undergo ring closure affording (**215**) (Equation (34)) <76TL3615>. The cyclization of (**216**) with triphosgene (Scheme 92) <92T6335> and acylations of 2-aminopyridine-*N*-oxides are related reactions (Scheme 93 and Equation (35)) <57JA678, 91JPR637>.



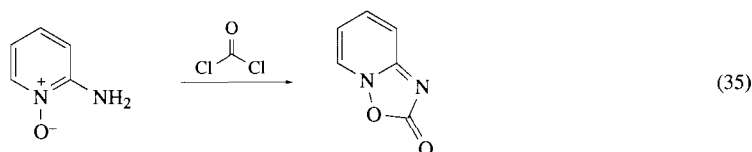
(33)



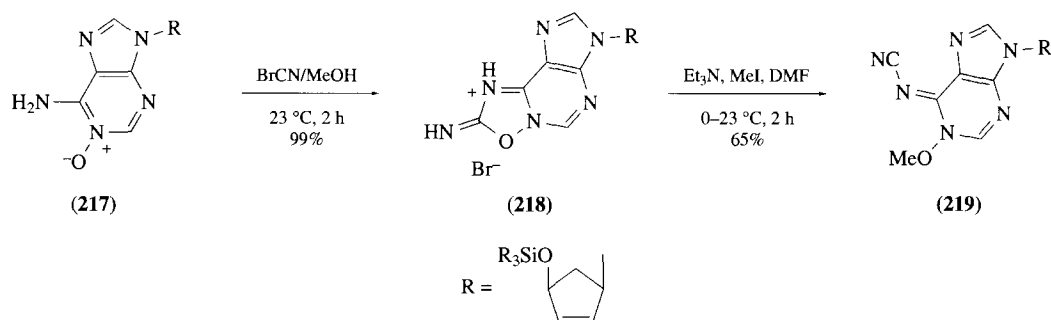
Scheme 92



Scheme 93



In a reaction sequence for adenine to guanine transformation, *N*-oxides (**217**) are treated with cyanogen bromide to give the oxadiazolinium bromides (**218**), which are opened to cyanamides (**219**) (Scheme 94) <91JCS(P1)2467, 92MI 404-01>.

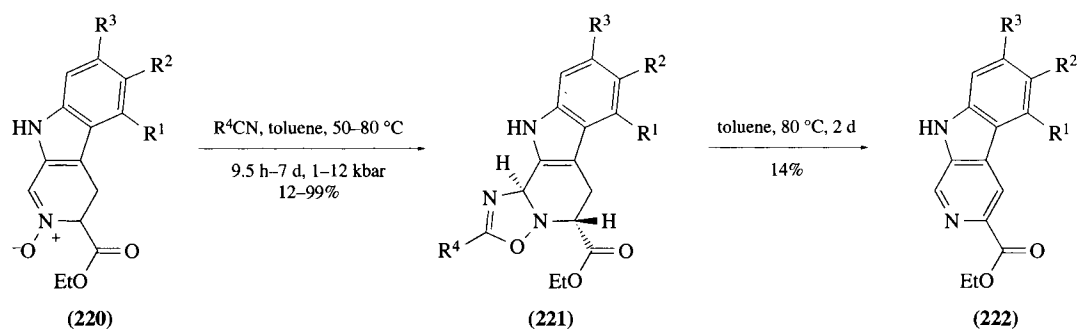


Scheme 94

4.04.8.4 Ring Syntheses of 2,3-Dihydro-1,2,4-oxadiazoles

A general method for the preparation of 2,3-dihydro-1,2,4-oxadiazoles (**221**) is the 1,3-dipolar cycloaddition of nitrones (**220**) to nitriles (Scheme 95) <80ZOB138, 88T6491, 94CC331>. The cycloaddition occurs with complete regio- and stereoselectivity. On prolonged heating 2,3-dihydrooxadiazoles undergo decomposition to amides and azomethines (e.g., (**221**) → (**222**)) or ring opening to *N*-

acylamidines with concomitant shift of H(3) to N(4). No cycloaddition takes place with nonactivated nitriles such as cyclopropane carbonitrile.

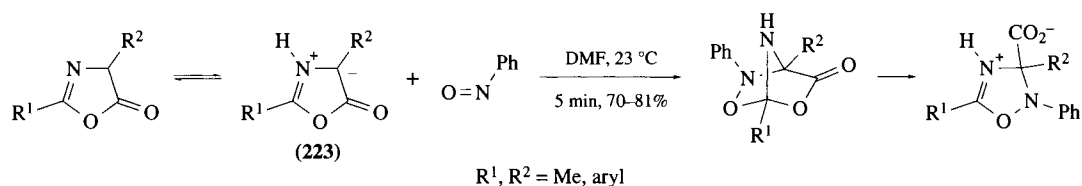


$R^1, R^2, R^3 = H, OMe, Cl$; $R^4 = \text{aryl, vinyl, alkyl, NMe}_2, CO_2Et$

$R^1, R^2, R^3 = H$; $R^4 = Ph$

Scheme 95

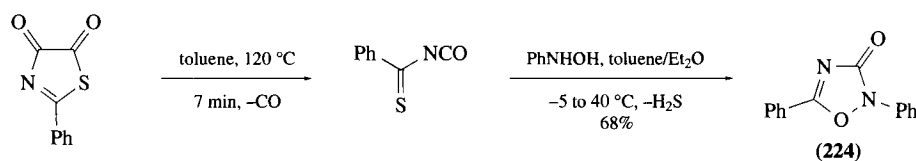
Alternatively, 2,3-dihydro-1,2,4-oxadiazoles are prepared by cycloaddition of nitroso compounds to azomethine ylides (223) (Scheme 96) <87T2223>.



$R^1, R^2 = Me, \text{aryl}$

Scheme 96

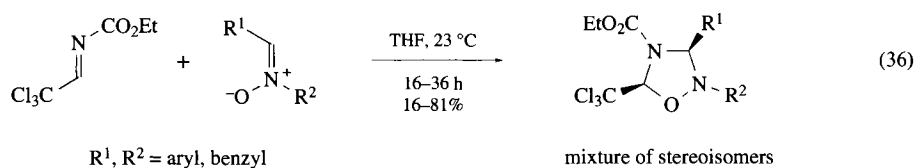
The urea (224) has been prepared from thiobenzoyl isocyanate and phenylhydroxylamine (Scheme 97) <77JHC765>.

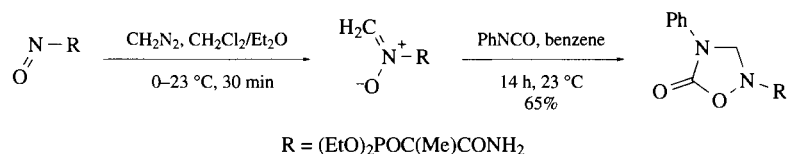
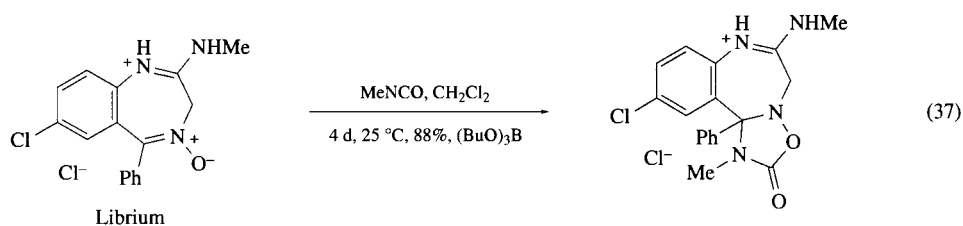


Scheme 97

4.04.8.5 Ring Syntheses and Reactivity of 1,2,4-Oxadiazolidines

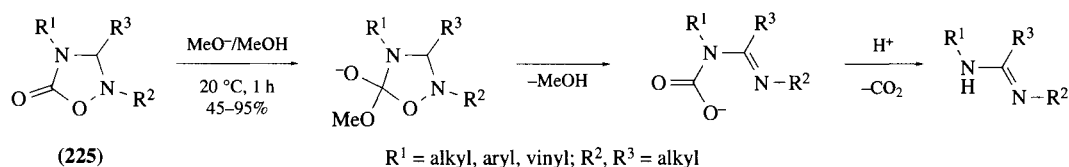
A general route to 1,2,4-oxadiazolidines is given by 1,3-dipolar cycloaddition of nitrones to $C=N$ double bonds (e.g., Equations (36) and (37), Scheme 98) <87AP(320)210, 87JCS(P1)2593, 90ZOB2235, 92JCR(S)32, 93T10693, 94TL5977>, a method first applied by Beckmann <1894CB1957>.





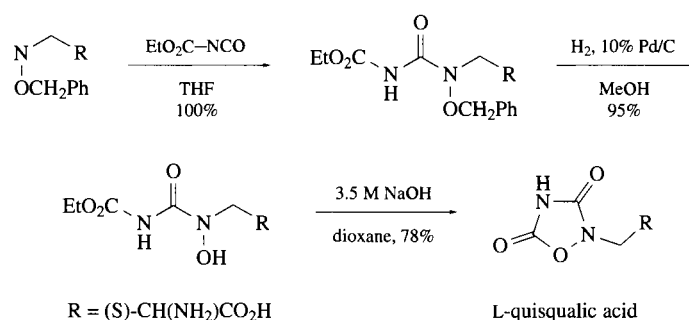
Scheme 98

Nucleophiles (MeO^- , OH^-) convert oxadiazolidinones (**225**) into amidines (Scheme 99) <93T10693>.



Scheme 99

The 1,2,4-oxadiazolidinedione ring is part of the natural amino acid L-quisqualic acid. The ring can be constructed by cyclization of ethyl 4-hydroxyallophanate (Scheme 100) <84CC1156, 85CC256, 93TA2041>.



Scheme 100

Examples of the preparation of 1,2,4-oxadiazolidines (**226**) are shown in Scheme 101 <81AP(314)294, 90KGS984, 91S265, 93MI 404-01>.

The dione (**226**) ($X=O$, $R^1, R^2=H$) is attacked by electrophiles on N(2). Thus, fusion of (**226**) ($X=O$, $R^1, R^2=H$) with tetra-*O*-acetyl- β -D-ribofuranose affords 2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-oxadiazolidine-3,5-dione <81JMC1172>. Quisqualic acid is biomimetically synthesized (8–10%) by alkylation of (**226**) ($X=O$, $R^1, R^2=H$) with *O*-acetylserine in the presence of pyridoxal-5'-phosphate and metal ions <74CPB473, 86CPB1473>. A synthesis of the neurodepressant quisqualamine has been described (Scheme 102) <82S781>.

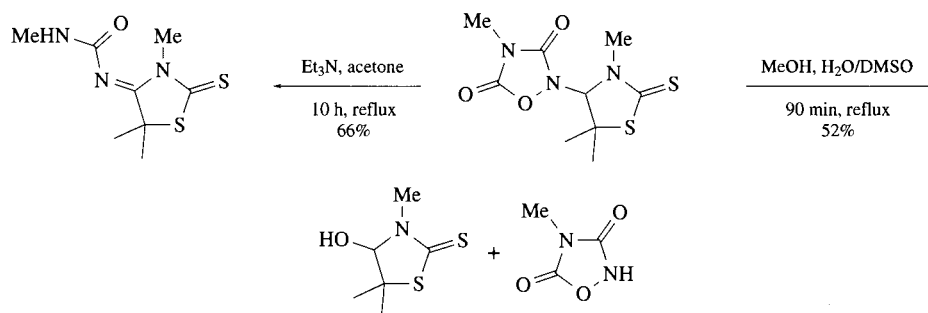
The 1,2,4-oxadiazolidine-3,5-dione ring is an excellent leaving group. For example, compound (**227**) seems to be superior to carbonyl diimidazole for the preparation of activated amides from carboxylic acid (4-methyl-1,2,4-oxadiazolidine-2,4-dione: $pK_a = 4.03$ <81AP(314)294>). Applications as coupling reagent in peptide chemistry or for the transformation of carboxylic acids into β -keto

CN1C(=O)OC(=O)N1C(=O)OC(=O)N2C(=O)OC(=O)N2C

(227)

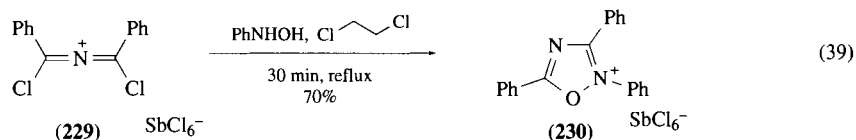
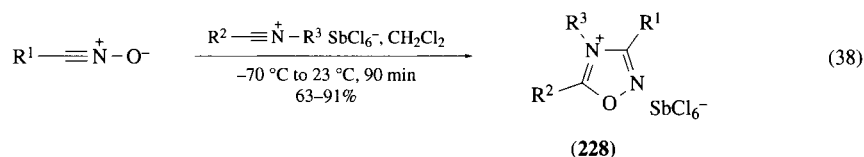


Nitrilium salts are more reactive 1,3-dipolarophiles than nitriles. With stable nitrile oxides, oxadiazolium salts (**228**) are obtained (Equation (38)). With unstable nitrile oxides the cycloaddition

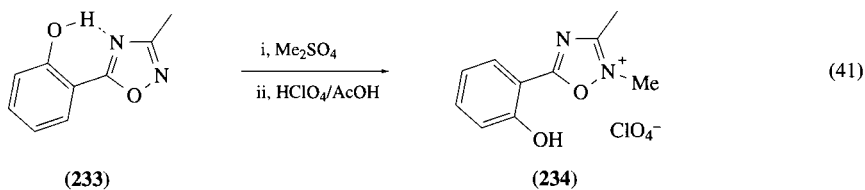
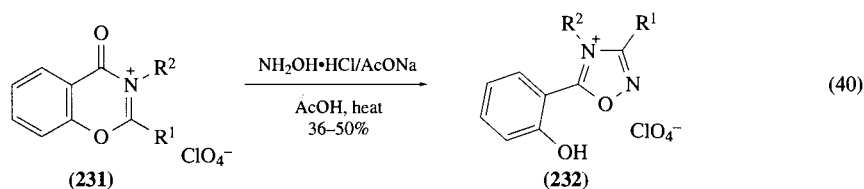


Scheme 104

is carried out in two steps. <93CB109>. The 2-azoniaallene salt (**229**) reacts with hydroxylamine to give the salt (**230**) (Equation (39)) <89S918, 93IJC(B)422>.



Treatment of the perchlorates (**231**) with hydroxylamine yields (**232**) (Equation (40)), while oxadiazoles (**233**) are methylated to (**234**) (Equation (41)) <92KGS280>.



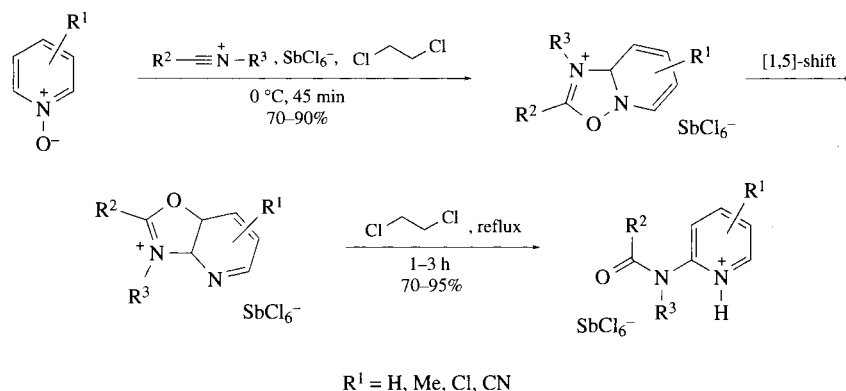
The reactions of nitrilium salts with nitrones usually give tars. However, pyridine-*N*-oxides afford oxazolium salts, which rearrange in solution to more stable amides (Scheme 105) <71TL1947, 75JOC41>.

Deprotonation of the salt (**235**) with triethylamine affords a carbene (ylide), which rearranges to the (unstable) carbodiimide (**236**) (Scheme 106) <70TL3453>.

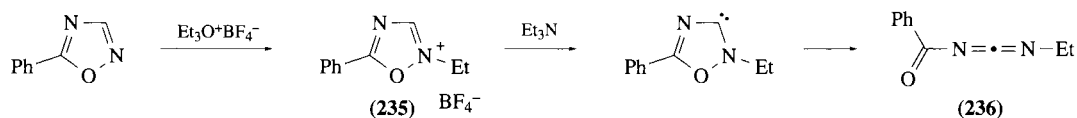
4.04.9 IMPORTANT 1,2,4-OXADIAZOLES AND APPLICATIONS

4.04.9.1 Applications of Fully Conjugated 1,2,4-Oxadiazoles

1,2,4-Oxadiazoles owe their importance mainly to their biological activities. A basic idea behind many developments is that the 1,2,4-oxadiazole ring is a hydrolysis resisting bioisosteric replacement for an ester functionality <90JMC1128, 91JMC140, 91QSAR109>.

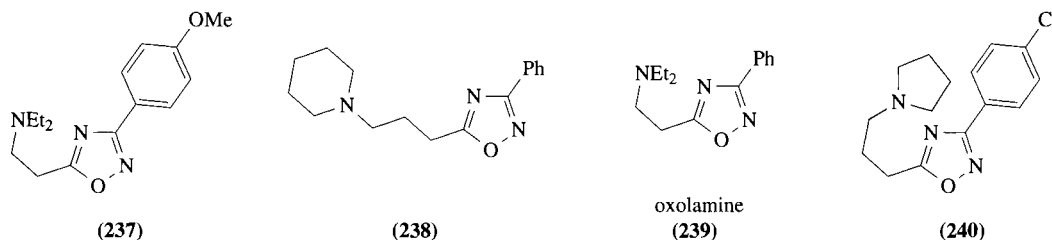


Scheme 105

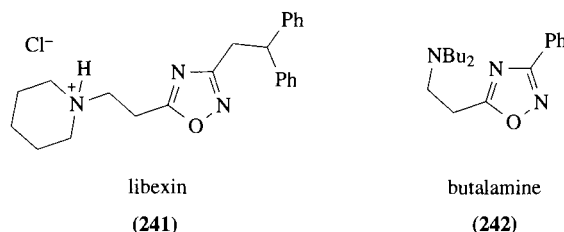


Scheme 106

The first systematic pharmacological screening of a hundred 5-aminoalkyl-1,2,4-oxadiazoles was undertaken by Palazzo *et al.* <61MI 404-02>. Compound (237) shows antiinflammatory analgesic properties higher than aspirin, while (238) has antiinflammatory but no analgesic activities. Oxolamine (239) is more active than codeine against cough induced by inhalation of an irritant, while (240) is superior to papaverine in peripheral antitussive activity and as a coronary dilator <62AF545>.

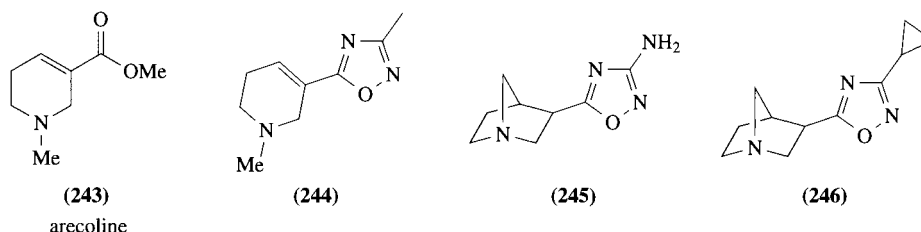


Another drug with antitussive properties is Libexin (241). Butalamine (242) causes coronary vasodilation, local anesthesia, analgesia, a papaverine-like action in duodenal preparations and smooth muscle relaxation <69JPP474>.

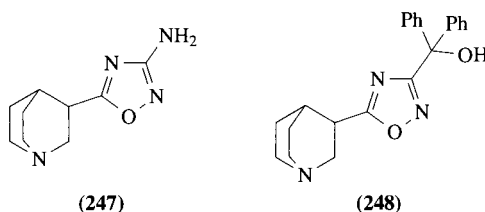


Most notable is the discovery that 1,2,4-oxadiazoles show pronounced efficacy as agonists for cortical muscarinic receptors <90MI 404-02, 91JMC1086>. It is believed that such compounds, which directly stimulate postsynaptic receptors usually activated by endogenous acetylcholine in healthy subjects, are beneficial for the treatment of memory and cognitive disorders associated with Alzheimer's disease. Aiming to improve the clinical profile of the muscarinic agonist arecoline (243), the metabolically labile methyl ester functionality was replaced by the oxadiazole ring. Compound (244) proved to be more potent than arecoline. It turned out that affinity for the agonist binding site was markedly dependent on the nature of the oxadiazole 3-substituent (hydrogen bonding) <93AX(B)356>.

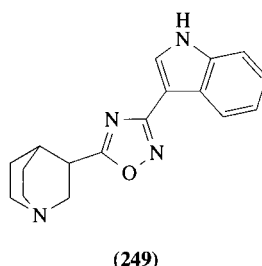
The amine (**245**) proved to be a highly efficacious muscarinic agonist, being 200-fold more potent than arecoline and displaying efficacy at cortical muscarinic receptors greater than acetylcholine itself <90JMC2690>. Compound (**246**) is a new drug candidate <92CC817, 93JCS(P1)1421>.



Increasing the size and lipophilicity of the 3-substituent of oxadiazoles results in compounds with an antagonist profile for muscarinic receptors. Thus, while (**247**) is an agonist, (**248**) is one of the most potent, nonquaternized muscarinic antagonists known <90JMC1128>.

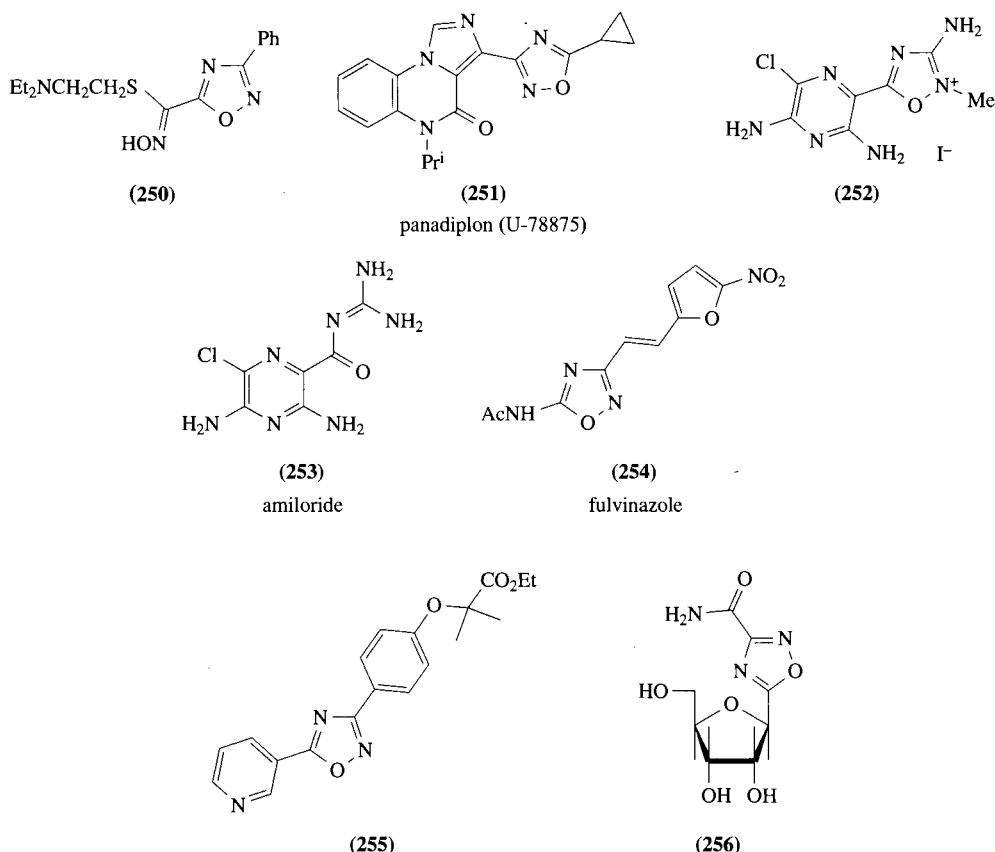


A series of indole oxadiazoles, such as (**249**), have been shown to be potent antagonists of the 5-hydroxytryptamine receptors <91JMC140>.

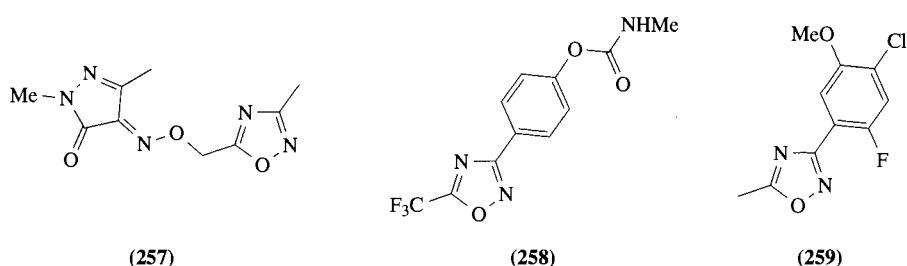


Related oxadiazoles have been tested as squalene synthetase inhibitors for treatment of hypercholesterolemia <92USP5135935>. Oximes like (**250**) might have potential as pretreatment drugs to prevent poisoning following exposure to organophosphonates <86JMC2174>. Panadiplon (**251**) is an anxiolytic agent causing inhibition of flunitrazepam binding to benzodiazepine receptors in the living brain <92MIP9200298, 94EJM393>. Other 3-cyclopropyl-1,2,4-oxadiazoles are partial or full benzodiazepine receptor agonists useful in treatment of central nervous system ailments <89JCS(P1)1889, 94JMC758>. The 3-amino-1,2,4-oxadiazolium salt (**252**) has electrolyte excretion profiles similar to that of amiloride (**253**) <86JMC1540>. Many more physiological activities of 1,2,4-oxadiazoles have been studied and patented. For instance, the drug fulvinazole (**254**) is an anti-schistosomal agent, which, however, has proven to be carcinogenic in mice <84MI 404-01>.

Compound (**255**) inhibits the cholesterol biosynthesis at the stage of the transformation of acetate into mevalonate <73CPB1641>. 3,5-Diamino-1,2,4-oxadiazoles show H₂-antihistaminic activity <86AF1011>. Certain 1,2,4-oxadiazoles proved to be orally active aldose reductase inhibitors for treatment of diabetes-associated disorders <92JMC457>. 3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1,2,4-oxadiazoles show antiinflammatory properties devoid of ulcerogenic potential <92JMC3691>. The 5-glycosyloxadiazole (**256**) is an inhibitor of leukemia L1210 and P388. Furthermore, this compound shows antiviral activities against vaccinia and HSV-2 viral lines, with very little cellular toxicity <85JHC1747>. Cephalosporins with 1,2,4-oxadiazolyl substituents modify the β -lactam activity of cephalosporins <85JMC1234>. Certain oxadiazoles have been tested as fluorescence markers for hypoxic tumor cells <91BP533>. Oxadiazoles unsubstituted in the 5-position are anthelmintics <85JMC1234>.



There are more than 100 patents for plant protection by 1,2,4-oxadiazoles. For instance, the oxime ether (257) is claimed to be more effective than known compounds against *Phytophthora infestans* when applied protectively to tomatoes <87GEP(O)3528753>. Sprays of 5-trifluoromethyl-1,2,4-oxadiazoles, such as (258), show 90–100% protection against *Erysiphe graminis* in barley <89JAP(K)63162680>. Other oxadiazoles, for example (259), show complete control of diverse weeds with no damage to rice crops <91JAP(K)02250873>.

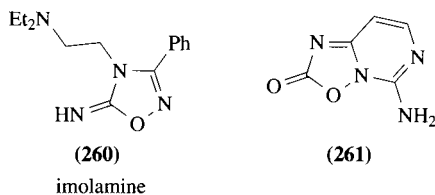


1,2,4-Oxadiazoles are used as liquid crystalline mesophases <92MI 404-02>. Filletting sealants for fuel tanks for high performance aircraft are based on triazine-cross-linked 1,2,4-oxadiazole polymers <83USP394345>. Graphite can be manufactured from other oxadiazole-containing polymers <87EUP203581>. Azo dyes containing 1,2,4-oxadiazoles play a role in thermal transfer printing <91EUP420036>. Oxadiazoles are constituents of fluorescence whiteners <85EUP136259>.

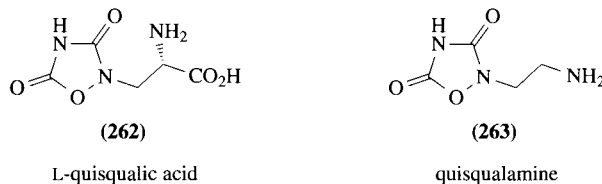
4.04.9.2 Applications of Partially or Fully Saturated 1,2,4-Oxadiazoles

For a number of 4,5-dihydro-1,2,4-oxadiazoles, some activity against the fungus *Neurospora crassa* and against *Mycobacterium smegmatis* has been observed <87JHC101>. The drug imolamine (260) has a papaverine-like effect on animals and has found application in the treatment of

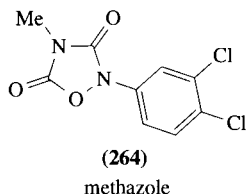
angina pectoris <69JPP474>. Certain 4,5-dihydro-1,2,4-oxadiazol-5-ones are antiinflammatories <92USP5114958> or muscarinic agents <92USP5066662>. Compounds such as (261) are claimed to effect regrowth of hair <89MIP8900996>.



The neuroexcitatoric L-quisqualic acid (262), first isolated from the seeds of *Quisqualis indica* <75YZ176> and now commercially available (Fluka), functions as an agonist at the quisqualate excitatory amino acid receptor in the mammalian central nervous system <74MI 404-01, 89PNA(86)1411, 89PNA(86)3404, 92JMC4602, 92JMC4720>. A large body of information on the biological activities of quisqualic acid has been collected. Quisqualamine (263) depresses electric activities of mammalian and amphibian neurons <78JPP364>.



2,4-Disubstituted 1,2,4-oxadiazolidines, such as methazole (264), have been tested as herbicides. These compounds are assumed to decompose to ureas, the active herbicidal agents <91EUP384250, 93MI 404-01>.



1,2,4-Oxadiazolin-5-ones, for example (227), are used in photographic materials as additives to hardeners of colloid layers <93JAP(K)04306646>, to enhance reaction rate constants in color photography <93JAP(K)04220644>, or in other roles in photography <93JAP(K)04255845>.

4.05

1,2,5-Oxadiazoles

R. MICHAEL PATON

University of Edinburgh, UK

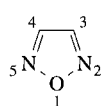
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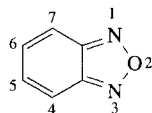
4.05.1 INTRODUCTION

The 1,2,5-oxadiazole ring system has been the subject of intensive investigation since the first examples were reported in the 1850s. While much of the early work involved structure elucidation, particularly for the *N*-oxides, current interest centers mainly on their reactivity and synthetic applications of their chemistry.

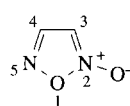
The nomenclature for this class of heterocycles has evolved over the years. The name furazan originally proposed by Wolff <1890LA(260)79> for the parent ring (1) has been favored by *Chemical Abstracts*; from volume 121, however, they are cataloged under the systematic name 1,2,5-oxadiazole. Similarly, benzofurazan (2) has been recategorized as 2,1,3-benzoxadiazole. For mainly historical reasons associated with early uncertainty concerning their structure, the corresponding mono-*N*-oxides (3) and (4) acquired a separate nomenclature based on the name furoxan <84CHEC-1(6)393>. Although they have been listed as furazan oxide and benzofurazan oxide in *Chemical Abstracts* the terms furoxan and benzofuroxan are still in common usage and, as their chemistries are often quite distinct from those of the parent systems, these names seem worthy of retention and are used throughout this chapter.



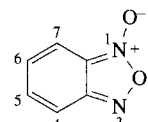
(1)



(2)



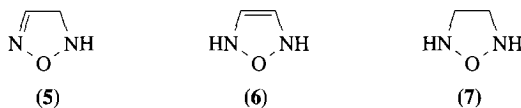
(3)



(4)

There have been several reviews on the area since the mid-1980s, including general surveys covering furazans <84H(22)1571> and furoxans <85H(23)399>, and more specialized accounts of particular topics such as the chemistry of aminofurazans <84KGS1155>, of fused furazans <92CCC978> and furoxans <88MI 405-01>, of furazans fused to five-membered rings <95JHC371>, heterocyclic rearrangements of benzofuroxans <93H(35)483>, and the synthesis of furazans by rearrangement of 3-acyl-1-oxa-2-azole oximes <90KGS1443>. The most comprehensive account in English of the chemistry of furoxans and benzofuroxans remains that by Gasco and Boulton <81AHC(29)251>; the subject has also been dealt with in two monographs in Russian <B-81MI 405-01, B-83MI 405-01>.

The chemistry of the 1,2,5-oxadiazole ring system is predominantly that of the furazans themselves and their benzo derivatives, and of their *N*-oxides (furoxans and benzofuroxans), and this chapter is therefore arranged accordingly. The possible dihydro and tetrahydro compounds (5)–(7) are very rare; 1,2,5-oxadiazolidine (7), for example, is now listed in *Chemical Abstracts* but, as yet, has no entries. 1,2,5-Oxadiazoles fused to six-membered heterocyclic rings are dealt with in the appropriate chapter (7.09–7.13). The principal methods of synthesis and the fundamental chemical properties were well established and documented in 1984 when the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) was published; the aim of this chapter is therefore to update the coverage and to highlight new developments. Noteworthy features of the literature since 1984 include the first synthesis and characterization of the parent unsubstituted furoxan (3) <94MI 405-01>, a substantial increase in synthetic manipulations of substituents attached to the heterocyclic ring, and correspondingly the incorporation of 1,2,5-oxadiazoles into more complex molecules.



4.05.2 THEORETICAL METHODS

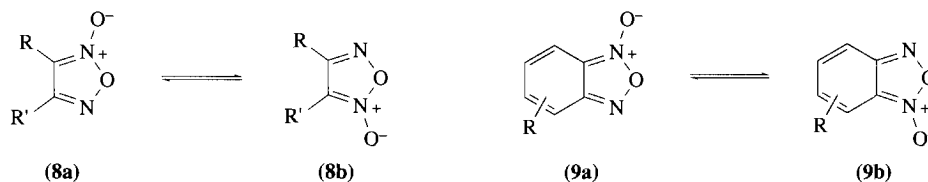
Molecular orbital calculations at various levels of approximation have been applied to both furazans and furoxans. *Ab initio* procedures using minimal (STO-3G) and split valence (3-21G) basis sets have been used to determine bond orders, total energies, ionization potentials, and dipole moments for the parent furazan and furoxan, and several derivatives $\langle 88\text{JCS(P2)661} \rangle$; the calculated molecular geometries (3-21G) are compared in Table 1 with those obtained experimentally.

Table 1 Observed and calculated geometries for furazan and furoxan.

	Bond lengths (Å)						Bond angles (deg.)						
	a	b	c	d	e	f	ab	bc	cd	de	ea	af	bf
Furazan													
observed ^a	1.373	1.303	1.421	1.303	1.373		105.5	108.9	108.9	105.5	111.2		
calculated ^b	1.427	1.279	1.444	1.279	1.427		105.5	110.1	110.1	105.5	108.8		
Furoxan													
observed ^c	1.441	1.302	1.401	1.292	1.379	1.240	107.2	107.2	111.9	106.6	107.1	116.4	136.4
calculated ^b	1.430	1.295	1.424	1.284	1.442	1.289	108.0	107.7	112.3	105.3	106.7	118.8	133.2

^a $\langle 88\text{ZN(A)597} \rangle$. ^b $\langle 88\text{JCS(P2)661} \rangle$. ^c $\langle 94\text{MI 405-01} \rangle$.

Several investigations have been devoted to the 2-oxide and 5-oxide tautomers and the pathway for their interconversion (see Section 4.05.5.2.1). The structures and relative stabilities of furoxan (3) and its open-chain tautomers have been calculated using *ab initio* Hartree–Fock (HF/3-21G, HF/3-21G*) and Moller–Plesset (MP4/6-31-G*, MP2/6-31G*) procedures $\langle 92\text{MI 405-01} \rangle$; the results provide support for a mechanism involving *cis*-1,2-dinitrosoethene as an intermediate/transition state with an energy ca. 120 kJ mol⁻¹ above that for furoxan. The presence of the *vicinal* nitroso groups strengthens the C—N bonds and weakens the C=C bonds $\langle 88\text{JPC5094} \rangle$. It is reported that semiempirical MINDO/3 calculations are capable of predicting the relative stabilities of isomeric pairs of various monocyclic furoxans (8a) and (8b) $\langle 86\text{KGS264} \rangle$.



In the benzofuroxan series *ab initio* calculations at the MP2 level give qualitatively correct predictions of structure, whereas semiempirical AM1, PM3 treatment is less satisfactory showing a preference for the dinitroso tautomer $\langle 94\text{JPC12933} \rangle$. The most likely intermediate in the interconversion of (9a) and (9b) is considered to be *anti*-1,2-dinitrosobenzene which is predicted to have an energy 50 kJ mol⁻¹ above that of benzofuroxan itself $\langle 94\text{JOC6431} \rangle$. Other calculated properties include diamagnetic susceptibilities and IR, UV, and PE data.

4.05.3 EXPERIMENTAL STRUCTURAL METHODS

4.05.3.1 Molecular Dimensions

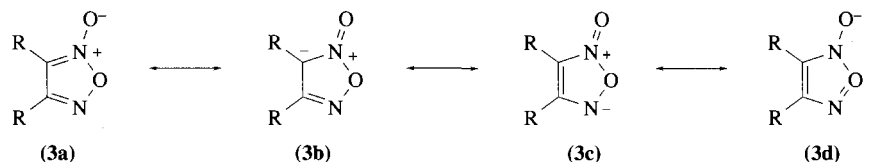
4.05.3.1.1 Furazans

The structure of furazan (**1**) which was first reported in 1965 <65JCP(43)166> has been redetermined using double resonance modulation microwave spectroscopy <88ZN(A)597>. The bond lengths and bond angles for the heterocyclic ring are given in Table 1 where they are compared with those obtained from MO calculations.

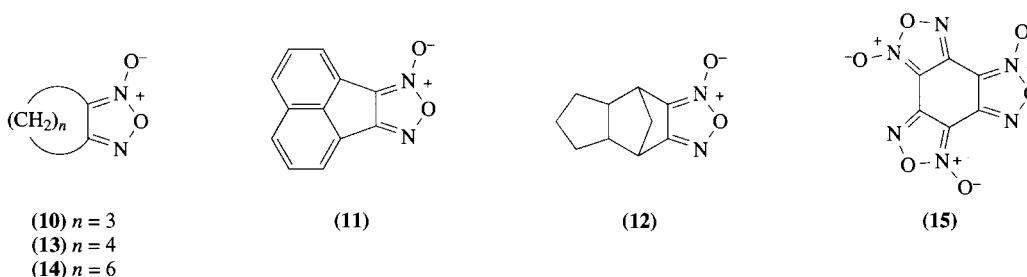
X-ray crystallography has been extensively used for structure determination and there are now in excess of 50 compounds on the Cambridge data base. Analysis of these shows that the heterocyclic ring has C_{2v} symmetry and is essentially planar with no atoms more than 0.01 Å from the best plane. π -Bond orders are typically 70–80% for N(2)—C(3) and C(4)—N(5), and 40–50% for C(3)—C(4), suggesting significant π -electron delocalization; in contrast O(1)—N(2) and N(5)—O(1) are essentially single bonds. The geometry of the heterocyclic ring of benzofurazans shows similar trends and there is significant double bond fixation in the fused homocyclic ring <70SA(A)2133>. The nuclear quadrupole coupling constants for the nitrogen atoms of furazan have also been redetermined <88ZN(A)607>.

4.05.3.1.2 Furoxans

A greater range of monocyclic and ring-fused furoxans have been examined, with more than 60 structures reported to date. The parent furoxan (**3**) isolated in 1994 has been fully characterized and its crystal structure determined <94MI 405-01>; its bond lengths and angles listed in Table 1 are broadly in accord with those predicted from MO calculations. As for furazans the oxadiazole ring of furoxans is near planar but the exocyclic oxygen attached to N-2 causes significant distortion. Noteworthy features of the reported structures are the long O(1)—N(2) and short N(2)—O(exo) bonds. C(3)—C(4) is also shortened corresponding to ca. 30% double-bond character, and N(2)—C(3) is longer than C(4)—N(5), consistent with contributions from (**3b**)–(**3d**) to the resonance hybrid.



Benzofuroxan <79AX(B)3076> and its derivatives show a similar pattern of heterocyclic ring bond lengths and angles with short N(1)—O(exo) and long O(2)—N(3) bonds. In the homocyclic ring C(4)—C(5) and C(6)—C(7) are notably shorter than C(5)—C(6) implying significant bond localization in accord with their chemical reactivity (Section 4.05.7.2.3). Ring-strained trimethylene-furoxan (**10**), acenaphthofuroxan (**11**) and bicyclooctanofuroxan (**12**) all have exceptionally long O(1)—N(2) bonds in the range 1.48–1.50 Å compared with tetramethylene and hexamethylenefuroxans (**13**) and (**14**), a fact that may be related to their tendency of the former to undergo facile ring cleavage (Section 4.05.5.2.2). Benzotrifuroxan (**15**) also has long O(1)—N(2) bonds (ca. 1.48 Å).



4.05.3.2 NMR Spectra

Proton and ^{13}C NMR spectroscopy has been extensively used for the characterization of furazans and particularly furoxans, and their ^{14}N , ^{15}N , and ^{17}O spectra have also been investigated. The chemical shifts for the ring atoms of furazan, furoxan, and their benzo derivatives are given in Table 2.

Table 2 NMR chemical shifts (^1H , ^{13}C , ^{15}N , ^{17}O) for the 1,2,5-oxadiazole ring atoms of furazan, benzofurazan and their *N*-oxides.

Compound	3-H	4-H	C(3)	C(4)	N(2)	N(5)	O(1)	O-exo
Furazan ^a	7.92	7.92	142.0	142.0	-33.5	-33.5	450	
Benzofurazan ^b			148.6	148.6	-35.6	-35.6	^c	
Furoxan ^c	7.44	8.50	105.2	146.8	-15.4	3.9	507.5	364.0
Benzofuroxan ^d			113.7	152.2	-25.3	-13.2	^e	^e

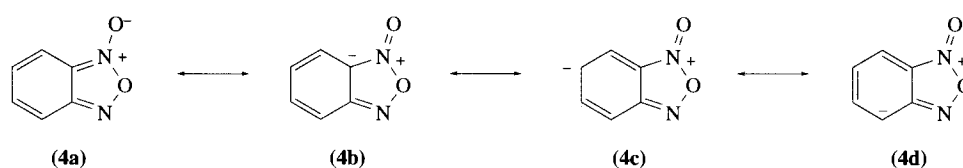
^aIn $(\text{CD}_3)_2\text{CO}$ <92KGS1101>. ^bIn $(\text{CD}_3)_2\text{SO}$ <84OMR(22)215, 89MI 405-01>. ^cIn $(\text{CD}_3)_2\text{CO}$ <94MI 405-01>.

^dIn CDCl_3 (^{13}C) <95MI 405-01> and $(\text{CD}_3)_2\text{CO}$ (^{15}N) <78JOC2542>. ^eNot reported.

The signals for protons directly attached to the heterocyclic ring show a strong solvent dependence; the δ_{H} value for the parent furazan varies from 7.92 (acetone- d_6) to 8.19 (CDCl_3) and 8.66 ppm (neat), and comparable trends are observed for monosubstituted analogues. The NMR spectra of monosubstituted furazans have been the subject of systematic study <92KGS1101>. In the furoxan series distinctive signals are observed for 3-H and 4-H at 7.2–7.5 and 8.5–8.6 ppm respectively, the lower chemical shifts for 3-H being in accord with the contribution of resonance structure (3b).

The exocyclic oxygen of furoxans exerts a strong shielding influence on protons of substituents attached to C(3), and for monocyclic furoxans and furoxans fused to non-aromatic rings this effect can be used to identify the individual isomers (8a) and (8b). For example, for dimethylfuroxan the signal at 2.16 ppm is assigned to the 3-methyl ($\text{MeC}=\text{NO}_2$) and that at 2.38 ppm to 4-methyl group ($\text{MeC}=\text{NO}$) by comparison with the corresponding peak for dimethylfurazan (2.31 ppm).

Comparison of the proton spectra of benzofuroxans with those of benzofurazans shows that all the signals are shifted to higher frequency <76OMR(8)158, 89CJC503>. For 7-H $\Delta\delta_{\text{H}}(\text{furoxan-furazan}) = -0.50$ ppm due to the shielding effect exerted by the *N*-oxide; the larger shifts for 4-H ($\Delta\delta = -0.25$) and 6-H ($\Delta\delta = -0.25$) compared with those for 5-H ($\Delta\delta = -0.09$) are attributable to the contributions of structures (4c) and (4d) to the resonance hybrid. The vicinal couplings for benzofurazan ($J_{4,5} = J_{6,7} = 9.3$ and $J_{5,6} = 6.4$ Hz) indicate significant bond localization in the homocyclic ring, consistent with the results obtained from microwave spectroscopy (Section 4.05.3.1), and similar observations have been made for benzofuroxans.



Proton NMR spectroscopy played a major role in establishing the structure and investigating the ring-chain tautomerism of benzofuroxans <93H(35)483>. The unsymmetrical ABCD spectrum observed at low temperature (-40°C) becomes well resolved and symmetrical (A_2B_2) at 100°C corresponding to the rapidly equilibrating mixture of the two isomers. Such dynamic resonance effects have allowed the calculation of exchange rates over a range of temperatures, thus providing thermodynamic activation parameters for the reaction. In contrast the 2- and 5-oxide isomers of most monocyclic furoxans interconvert less readily and the spectra of the individual compounds can be distinguished at ambient temperature.

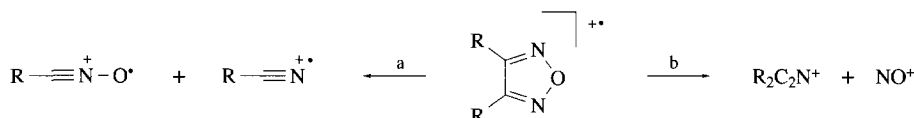
Carbon-13 NMR spectroscopy has also been utilized to probe the structure, isomers, and conformational aspects of 1,2,5-oxadiazole chemistry. The δ_{C} values for monocyclic furazans vary from 140 to 160 ppm depending on the substituent, and ^{13}C - ^1H couplings of ca. 200 Hz are observed for the parent furazan and monosubstituted derivatives <92KGS1101>. For furoxans the most noteworthy feature of their carbon spectra is the large displacement of the C(3) resonance to lower chemical shift. While the C(4) peak remains in the range 140–160 ppm that for C(3) is shifted to 100–125 ppm. At low temperatures benzofuroxan shows two peaks at 113.7 (C(3)) and 152.2 (C(4)) which coalesce on warming. The parent furoxan has ^{13}C - ^1H couplings of 211 Hz for C(3) and 202 Hz for

C(4), similar to that for furazan. For ring-strained furoxans such as (10) and (12) the C(4) signal is displaced to ca. 165 ppm.

In the ^{15}N NMR furazan and benzofurazan show the expected single absorptions at -33 and -36 ppm respectively. The two nitrogens in furoxans show distinct temperature dependent ^{15}N signals. δ_{N} values range from -26 to -15 for N(2) and -14 to $+4$ for N(5). For benzofuroxans the two peaks at -15 and 4 ppm observed at low temperature coalesce on heating. Broad ^{14}N NMR signals for these compounds have also been reported. Two signals in each of the ^{13}C and ^{15}N spectra of benzotrifuroxan establishes the trifuroxan structure (15) rather than hexanitrosobenzene. Furoxan (3) has ^{17}O signals at 508 and 364 ppm compared with 450 ppm for furazan; the corresponding figures for dimethylfuroxan are 460 and 350 ppm, and 475 for dimethylfurazan.

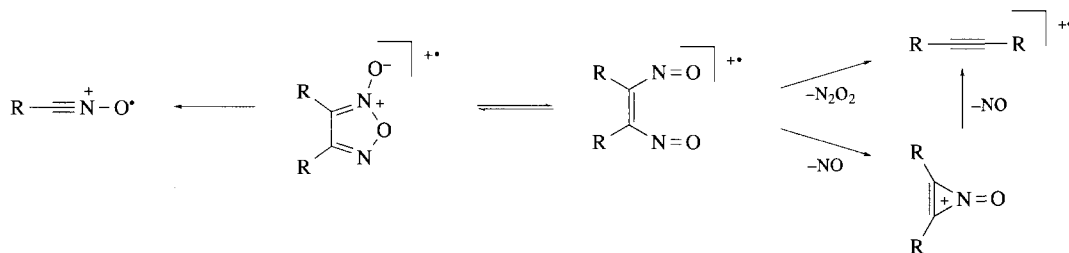
4.05.3.3 Mass Spectra

For monocyclic furazans there are two general modes of fragmentation under ionizing radiation. Initial ring opening at the weak O(1)—N(2) bond can be followed by fragmentation at C(3)—C(4) to yield nitrile and nitrile oxide ions (Scheme 1, path a), or by expulsion of NO (path b). Thus the parent furazan gives peaks at m/z 70 (M^+), 43 (HCNO^+), 40 ($\text{C}_2\text{H}_2\text{N}^+$), 30 (NO^+), and 27 (HCN^+) $\langle 65\text{JOC1854} \rangle$. Peaks attributable to RC^+ are also commonly observed.



Scheme 1

Unlike many aromatic *N*-oxides the $(M-16)^+$ peak for furoxans is often weak. Their spectra are usually characterized by significant peaks at $(M-30)^+$ and $(M-60)^+$ which are attributable to loss of NO and N_2O_2 respectively. For the parent furoxan the dominant fragment is $(M-30)$ $\langle 94\text{MI 405-01} \rangle$. These observations are consistent with the expected initial cleavage at O(1)—N(2) forming the 1,2-dinitrosoethene tautomer, followed by expulsion of nitric oxide (Scheme 2). As for furazans cleavage of C(3)—C(4) can also occur yielding two nitrile oxides, a process which closely parallels the thermal cycloreversion (see Section 4.05.5.2.2). Benzofuroxans have an additional fragmentation pathway resulting in loss of CO $\langle 87\text{OMS}(22)519, 89\text{OMS}(24)465 \rangle$.



Scheme 2

4.05.3.4 IR and UV Spectra, and Miscellaneous Methods

Furazans have characteristic peaks in the ranges 1525–1560 ($\text{C}=\text{N}-\text{O}$), 1430–1385 ($\text{N}-\text{O}$), and 1040–1030 and 890–880 cm^{-1} (heterocyclic ring). The high-resolution vibrational spectra for the unsubstituted furazan (1) has been examined in particular detail $\langle 91\text{ZN(A)841, 92ZN(A)499, 93ZN(A)605, 93ZN(A)692} \rangle$; FT-IR bands studied included ν_{12} (952.6123 cm^{-1}), ν_5 (1005.3536), ν_{11} (1175.3377), ν_3 (1316.2254), ν_4 (1036.1689), ν_2 (1418.4742). The results confirmed and refined conclusions drawn previously from laser/microwave double resonance experiments $\langle 91\text{ZN(A)599} \rangle$. Pure rotational spectra for vibrationally excited states of furazan and furazan- d_2 have also been reported $\langle 90\text{ZN(A)1117, 90ZN(A)1131} \rangle$. Furoxans have useful peaks at 1625–1600 ($\text{C}=\text{N}-\text{O}$), 1490–1400 ($\text{C}=\text{NO}_2$), 1360–1280 cm^{-1} ($\text{N}-\text{O}$), and at 1190–1150, 1030–1000, and 890–875 cm^{-1} (heterocyclic ring). For ring-

strained furoxans, for example (10) and (12), the C=N—O peak occurs at higher frequency (1675–1655 cm⁻¹).

UV absorption data are available for a wide range of furazans and furoxans. Dimethylfurazan has a band at 228–241 nm similar to those of other simple monocyclic furazans, and furoxan (3) has a peak at 263 nm which is typical of monocyclic derivatives (λ_{max} 255–295 nm, ϵ 3000–9800 dm³ mol⁻¹ cm⁻¹) (94MI 405-01). The more extended conjugation in the chromophores of benzofurazans and benzofuroxans results in the expected shifts of λ_{max} to longer wavelengths (typically 350–410 nm), and there often are two overlapping bands with some fine structure for substituted analogues. The lower energy band can extend well into the visible region when conjugating groups are present; for example 7-amino- and 7-alkylthio-4-nitrobenzofurazans absorb at ca. 465 and 425 nm respectively. The spectra are strongly solvent and pH dependent, and Meisenheimer complex formation results in substantial changes which can be utilized to study the kinetics and equilibria of this process.

4-Nitro- and 4,6-dinitrobenzofurazans exhibit strong visible fluorescence which is dependent on the electron-donating ability of substituents conjugated to the nitro groups and on steric interference with this conjugation. The fluorescence is particularly intense in the region 525–545 nm for 7-amino derivatives of the nitrobenzofurazans and, as these compounds are readily formed by nucleophilic attack of amines on the 7-halo-4-nitro- and 7-halo-4,6-dinitrobenzofurazans, the latter have found widespread use as analytical reagents (see Section 4.05.7.2.2 and 4.05.10).

The UV PE spectra of furazan and benzofurazan have been recorded and interpreted with the aid of *ab initio* MO calculations. X-ray photoelectron spectroscopic studies for benzotrifuroxan support the NMR assignment of structure as (15) rather than hexanitrosobenzene. The radical anions of benzofurazan and benzofuroxan, generated by alkali metal or electrochemical reduction have been studied by ESR spectroscopy.

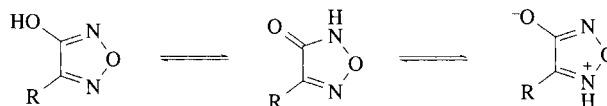
4.05.4 THERMODYNAMIC ASPECTS

Furazan is a stable liquid which can be distilled at atmospheric pressure (m.p. -2°C, b.p. 98°C at 760 mm Hg, d_4^{20} 1.168, η 1.4077 (64JA1863) whereas furoxan (m.p. 13°C, b.p. 40°C at 2 mm Hg, d_4^{20} 1.4044, η 1.5040 (94MI 405-01) decomposes at ca. 145°C. Benzofurazan and benzofuroxan are both stable solids melting at 55°C and 70–71°C respectively. The corresponding data for numerous substituted furazans, furoxans, and their benzo derivatives are to be found in earlier reviews. Of other thermochemical properties the mostly commonly studied are heats of combustion, and several comparisons have been made of furazans with their *N*-oxides. The dissociation enthalpy of the N—O bond in benzofuroxan has been deduced from the standard molar enthalpies of formation of benzofurazan and benzofuroxan, and from measurements of their enthalpies of combustion and sublimation by static-bomb calorimetry and microcalorimetry respectively (90MI 405-01); a value of $D(\text{N—O}) = 250.9 \pm 3.0$ kJ mol⁻¹ was obtained. The dipole moments of furazan and benzofurazan are 3.38 D and 4.04 D respectively and those of other substituted analogues generally fall in the range 4.0–4.8 D. These values are significantly larger than those for the corresponding 1,2,5-thia- and 1,2,5-selena-diazoles, an effect attributed to greater mesomeric charge transfer in both the latter series. Most alkyl and aryl substituted furoxans have dipole moments between 4.6 and 5.5 D, and the value for benzofuroxan is 5.29 D. The lipophilicities of substituted furazan and furoxans have been measured and analyzed using the CLOGP algorithm (92JCS(P2)1643).

The aromaticity of the parent furazan, as measured by the Bird unified aromaticity index I_A , is comparable with those of isoxazole and furan but markedly less than that of the sulfur analogue 1,2,5-thiadiazole (92T335). The calculated I_A values based on experimental bond lengths for furazan and related heterocycles in increasing order of aromaticity are as follows: 1,2,4-oxadiazole 48, isoxazole 52, furazan 53, furan 53, 1,2,5-selenadiazole 58, 1,3,4-oxadiazole 62, 1,2,5-thiadiazole 104. The aromaticity of various five-membered heterocycles including furazan have also been investigated using AM1 calculations (90JPR885). The effect of the *N*-oxide moiety in furoxans is to reduce the aromatic character of the ring compared with the corresponding furazan (93T8441); for example the I_A values for benzofurazan and benzofuroxan are 106 and 81 respectively. For the parent compound the value of $I_A = 35$, calculated from the crystal structure data reported in 1994 (94MI 405-01), is somewhat lower than that previously estimated from the predicted geometry ($I_A = 42$). In the furoxan series there are significant substituent-dependent variations with electron-withdrawing groups and steric distortion both reducing aromaticity. Thus dibenzoylfuroxan ($I_A = 24$) is less aromatic than diphenylfuroxan ($I_A = 49$), and for the series of alicyclic ring fused compounds

trimethylenefuroxan (**10**) ($I_A = 21$) is less aromatic than the tetramethylene compound (**13**) ($I_A = 32$) and hexamethylene analogue (**14**) ($I_A = 39$), consistent with the greater ring strain in the former compound.

The 1,2,5-oxadiazole ring is a stable system and annular-group tautomerism is not favored. Although three tautomeric forms can be drawn for 3-hydroxyfurazans (Scheme 3) IR and NMR data for chloroform solutions show only the presence of the hydroxy compound. Ring-chain tautomerism is an important feature of furoxan chemistry and the equilibration between the isomeric furoxans is discussed in detail later in this chapter (Section 4.05.5.2.1).



Scheme 3

4.05.5 REACTIVITY OF HETEROCYCLIC RING

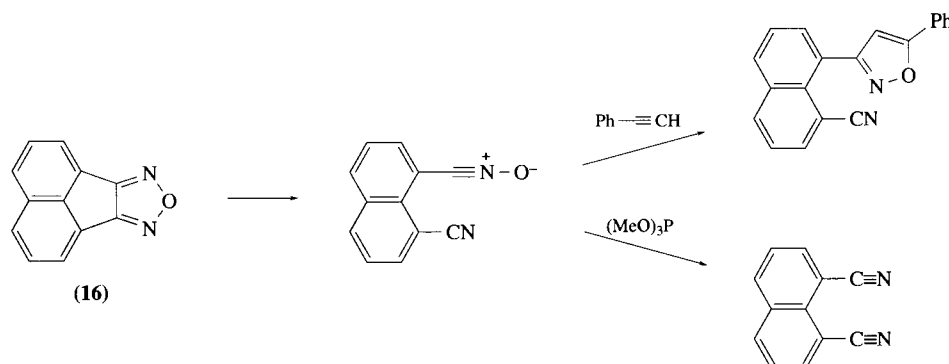
The fundamental chemical reactivity of the 1,2,5-oxadiazole ring was already well established and documented in 1984 at the time CHEC-I was published and this section is therefore intended to provide a resumé and an update; unless otherwise stated the content is cited in CHEC-I or in the reviews listed in the Introduction to this chapter. In view of the distinctive influence imparted by the presence of the *N*-oxide moiety on the reactions of the heterocycle separate sections are devoted to furazans (including benzofurazans) and their furoxan counterparts.

4.05.5.1 Furazans and Benzofurazans

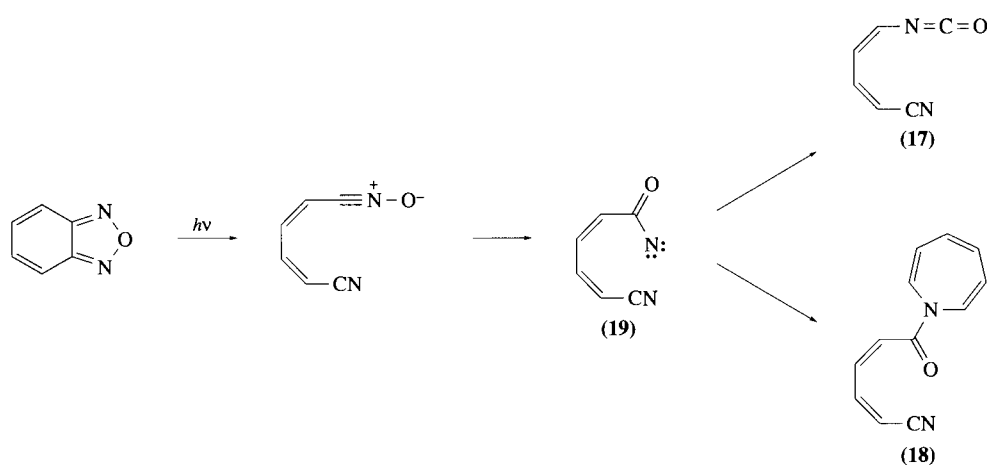
4.05.5.1.1 Thermal and photochemical ring cleavage

1,2,5-Oxadiazoles undergo thermal and photochemical ring cleavage at the O(1)—N(2) and C(3)—C(4) bonds to yield nitrile and nitrile oxide fragments, and products derived therefrom. In most cases the thermal reaction requires temperatures in excess of 200°C, but for ring-strained analogues less forcing conditions are needed. Thus diphenylfurazan decomposes at ca. 250°C to benzonitrile, phenyl isocyanate and 3,5-diphenyl-1,2,4-oxadiazole, the latter two products resulting from, respectively, isomerization of the initially formed benzonitrile oxide and its cycloaddition to benzonitrile; in the gas phase under flash vacuum pyrolysis (FVP) conditions (600°C, 10^{-3} mm Hg) the reaction is much cleaner affording benzonitrile and benzonitrile oxide in near quantitative yields <81TH 405-01>. In contrast, the more strained acenaphthofurazan (**16**) fragments at 120–150°C and the resulting nitrile oxide can be trapped by phenylethyne as its isoxazole cycloadduct or deoxygenated in the presence of trimethyl phosphite (Scheme 4) <73JOC1054>. Flash vacuum pyrolysis of diaminofurazan is reported to afford, among various other by-products, aminoisocyanate (H_2NNCO), presumably formed via initial fragmentation to aminoformonitrile oxide <89CB745>. Kinetic parameters have been measured for the gas-phase decomposition of several furazans including the parent compound, and a biradical mechanism proposed which involves non-synchronous cleavage of the N—O and C—C bonds <87IZV221>; tetramethylenefurazan was found to react ten-fold more rapidly than the dimethyl analogue.

Benzofurazans are thermally more stable but can be cleaved photolytically. For example, benzofurazan itself in benzene affords cyanoisocyanate (**17**) and azepine (**18**), the latter being formed by reaction of the solvent with the putative intermediate acylnitrene (**19**) (Scheme 5); further supporting evidence for the proposed pathway is provided by trapping the nitrile oxide precursor with dimethyl acetylenedicarboxylate and isolation of the methylurethane derivative of the isocyanate <75JOC2880>. Photolysis of diphenylfurazan yields benzonitrile, diphenylfuroxan and 3,5-diphenyl-1,2,4-oxadiazole.



Scheme 4

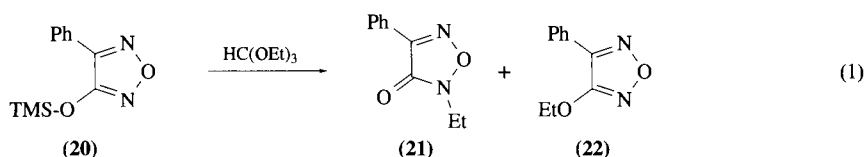


Scheme 5

4.05.5.1.2 Reactions with electrophiles and oxidizing agents

The heterocyclic ring shows low reactivity towards electrophiles; nitration, halogenation, and oxidation occur exclusively at substituent groups (Section 4.05.7). For example, benzofurazan undergoes nitration in the homocyclic ring and even 3-phenylfurazan is halogenated and nitrated in the phenyl substituent rather than at the unsubstituted 4-position. Direct oxidation of furazans to furoxans has not been reported and, in contrast to various other five-membered heterocyclic systems, the 1,2,5-oxadiazole ring is inert to cycloaddition with singlet oxygen ^{<88TL1003>}. The heterocyclic ring is similarly resistant to attack by acid; pK_a values of -4.9 and -8.4 have been estimated for protonation of methylphenylfurazan and benzofurazan respectively. One of the ring nitrogens can be alkylated under forcing conditions, for example, *N*-methylfurazinium salts are formed on heating with dimethyl sulfate ^{<74AJC1917, 95JCS(P1)1083>}; the reaction is approximately 7 and 62 times slower, respectively, than the corresponding methylations of 1,2,5-thiadiazole and isoxazole. The *N*-ethyl salts of furazan itself and 3-phenylfurazan have been prepared by the action of triethyloxonium tetrafluoroborate ^{<64JA1863>}. Examples in which the quaternized nitrogen is incorporated into a second heterocyclic ring have also been reported ^{<92KGS233>}.

Alkylation of silyloxy-furazan derivative (20) with triethyl orthoformate yields a mixture of 2-ethyl-1,2,5-oxadiazol-3(2*H*)-one (21) and *O*-ethyl compound (22) (Equation (1)) ^{<93T5905>}; compound (21), which was characterized by its distinctive spectroscopic properties, is a rare example of a tricoordinate *N*-substituted 1,2,5-oxadiazole.

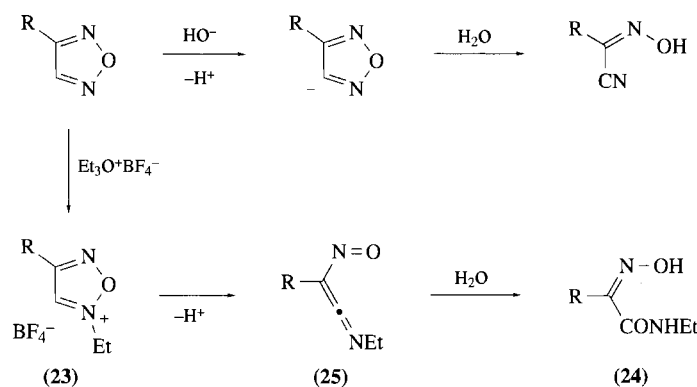


4.05.5.1.3 Reactions with nucleophiles and reducing agents

The heterocyclic ring of dialkyl/diarylfurazans and benzofurazans is resistant to attack by nucleophiles. However, when one of the substituents is a good leaving group then substitution can take place. 3-Nitro-4-phenylfurazan, for example, affords the 3-hydroxy derivative on heating with sodium hydroxide <93T5905> and displacement of nitrite by alkoxy nucleophiles <92MI 405-02> and by ammonia <95MI 405-02> has also been reported. Treatment of alkylfurazans with butyllithium results in deprotonation in the substituent leaving the heterocycle intact, whereas the oxadiazole ring of benzofurazan is cleaved by phenyllithium.

Furazans are more susceptible to reduction than oxidation. Benzofurazan is converted by tin and hydrochloric acid to *o*-phenylenediamine, but catalytic hydrogenation takes place preferentially in the homocyclic ring to afford tetramethylenefurazan. Zinc and acetic acid can reduce the oxadiazole moiety selectively in the presence of various other heterocyclic systems, including pyrimidines and pyrazines. 1,2-Diamines may also be formed on reaction with sodium borohydride but lithium aluminum hydride causes fragmentation of the C(3)—C(4) bond yielding primary amines as the final products, and treatment with phosphites results in both fragmentation and deoxygenation to nitriles. Polarographic studies suggest that furazans undergo irreversible reduction via one-electron transfer followed by cleavage of the N—O bond in the resulting radical anion <83ZOB2511>.

Although most furazans are stable to alkali the parent compound and mono-substituted analogues are isomerized to the oximes of α -ketonitriles in a sequence which involves initial deprotonation at the 4-position (Scheme 6) <65JOC1854>; 5-ethylfurazinium salts (**23**) react similarly to afford the *N*-ethyl(hydroxyimino)amide (**24**) via an intermediate nitrosoketenimine (**25**) <64JA1863>.

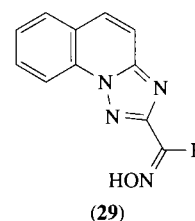
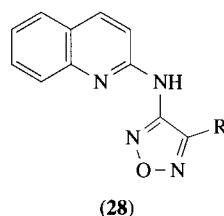
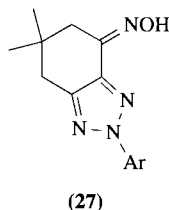
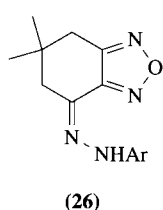
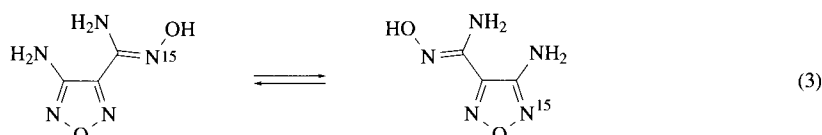
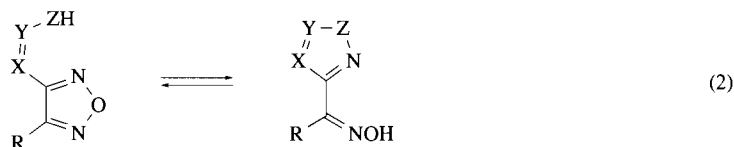


Scheme 6

4.05.5.1.4 Heterocyclic ring transformations

Various 3-heteroalkyl-substituted furazans undergo Boulton–Katritzky rearrangements in which the oxadiazole is converted into a new five-membered heterocycle bearing a hydroxyiminoalkyl group (Equation (2)). This process, which has been studied in some detail <81AHC(29)141, 90KGS1443>, can occur by a concerted electrocyclic mechanism or, in the presence of a base catalyst, in two steps via an anionic intermediate formed by intramolecular nucleophilic attack at nitrogen. The role of X=Y—Z can be filled by, for example, C=N—O, C=N—N, N=C—N and N=C—S yielding 3-hydroxyiminoalkyl-1,2,5-oxadiazoles, -1,2,3-triazoles, -1,2,4-triazoles, and -1,2,4-thiadiazoles respectively. Several examples of isomerization of *N,N*-dialkylfurazanamidoximes to furazan-ketoximes have been described <93ZOR1062> and evidence for the degenerate rearrangement of the parent system (Equation (3)) has been provided by ¹⁵N-labeling experiments <88KGS1701>. Isothiocyanates react with aminofurazans to form thioureas which isomerize to 5-amino-1,2,4-thiadiazole-3-ketoximes <86H(24)3433>. Arylhydrazone-furazan (**26**) undergoes thermal, photochemical, or base-induced rearrangement to oximetriazole (**27**) <85HCA1748>, and quinolylamino-furazan (**28**) isomerizes thermally to yield 2*H*-1,2,4-triazole (**29**) <93H(36)1577>. Further unrelated

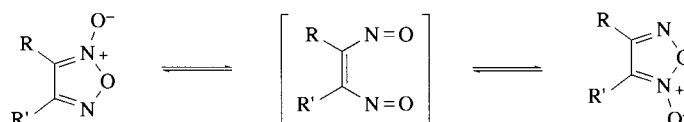
examples of transformations involving the heterocyclic ring include the photolytic conversion in the presence of ammonia of 3-benzamido-4-phenylfurazan to 3-amino-5-phenyl-1,2,4-oxadiazole <92H(34)2313> and the formation of the sodium salt of 1-hydroxy-5-cyanotetrazole on nitrosation of 3-amino-4-azidofurazan with sodium nitrite in acetic acid <88KGS1666>.



4.05.5.2 Furoxans and Benzofuroxans

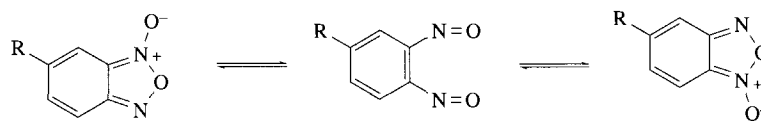
4.05.5.2.1 Ring-chain tautomerism

The distinctive character of furoxans compared with furazans is manifest most clearly in the interconversion of the 2-oxide and 5-oxide isomers, a phenomenon first observed by Ponzio <28G329> (although the structures were not correctly assigned at the time) and rationalized by Auwers <27CB2122>. The mechanism of this process has been the subject of investigation and discussion over many years. Although definitive evidence has yet to be presented the equilibration for monocyclic furoxans is presumed to proceed via an intermediate *cis*-1,2-dinitrosoalkene (Scheme 7), a hypothesis supported by *ab initio* MO calculations <92MI 405-01>. In the benzofuroxan series (Scheme 8) the involvement of the corresponding 1,2-dinitrosoarenes as intermediates, first proposed by Hammick *et al.* <31JCS3308> and later supported by Mallory <66JA61>, has been more firmly established by matrix isolation experiments <91CC1178, 91JOC5216, 92CL57>; photolysis (360 nm) of 2-nitrophenyl azide or benzofuroxan in an argon matrix at 14 K generated 1,2-dinitrosobenzene which was characterized by IR and UV spectroscopy, and subsequent thermolysis or photolysis (320 nm) afforded benzofuroxan. In both series the involvement of 1,2-dinitroso compounds as intermediates is supported by theoretical calculations <92MI 405-01, 94JOC6431, 94JPC12933>.



Scheme 7

A ring-opening/ring-closure pathway has also been proposed to explain the conversion of 4-phenylfuroxan to the 3-phenyl tautomer under electrochemical oxidation conditions <86IZV1691>. The factors influencing both the equilibrium constants and the equilibration rates have been dis-

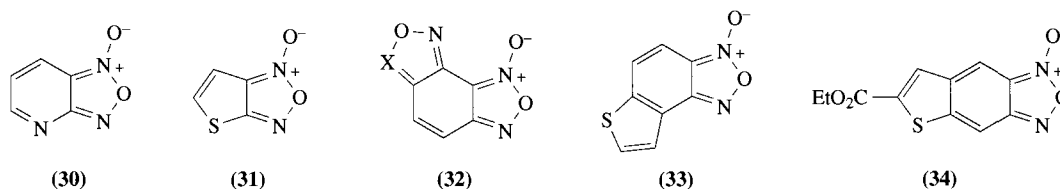


Scheme 8

cussed in depth in reviews by Ruccia *et al.* (81AHC(29)141), Gasco and Boulton (81AHC(29)251), and by Katritzky and Gordeev (93H(35)483). The kinetic and thermodynamic parameters for these furoxan isomerizations can often be measured by ^1H NMR spectroscopy (Section 4.05.3.2).

(i) *Isomerization rates*

The rate of equilibration is strongly substituent dependent. It is relatively slow for monocyclic compounds such as 4-formyl-3-methylfuroxan ($\Delta G^\ddagger$ 153 kJ mol $^{-1}$) for which temperatures of 100–200°C are required. Fusion to bond *c* of the heterocycle results in a modest rate acceleration attributable to strain. The energy barrier is substantially lower when the fused ring is aromatic, and for benzofuroxan itself the (degenerate) interconversion of the tautomers occurs at ambient temperature ($\Delta G^\ddagger$ 58 kJ mol $^{-1}$). In general the electronic effect of substituents in the benzo-ring is small, observed variations being within experimental error; the isomerization rates for 4,7-dihalo derivatives are, however, noticeably slower than those for the 5,6-isomers due to steric factors ($\delta\Delta G^\ddagger$ ca. 5 kJ mol $^{-1}$). Analogues with a heterocycle directly fused to the 1,2,5-oxadiazole such as pyrido[5,6-*c*]furoxan (**30**) and thieno[4,5-*c*]furoxan (**31**) show similar rates to those of benzofuroxans. The influence of additional rings fused to benzofuroxan has also been investigated; naphtho[1,2-*c*]furoxans isomerize more slowly ($\Delta G^\ddagger$ 83 kJ mol $^{-1}$). Significant variations are observed when a second heterocycle is fused to the carbocyclic ring of benzofuroxans. Furazano- and furoxanobenzofuroxans (**32**; X = N, N $^+$ —O $^-$) have high $\Delta G^\ddagger$ values (92 kJ mol $^{-1}$); similarly the 4,5-thieno-fused derivative (**33**) equilibrates ($\Delta G^\ddagger$ 69 kJ mol $^{-1}$) more slowly than benzofuroxan, whereas the linear 5,6-fused analogue (**34**) has a much lower energy barrier ($\Delta G^\ddagger$ 48 kJ mol $^{-1}$).



(ii) *Equilibrium constants*

The balance of the equilibrium is also substituent dependent and is influenced by several factors. The energy differences are small and in most cases less than 2 kJ mol $^{-1}$. In the monocyclic series steric factors are significant; electron-releasing groups including amino, phenoxy, and pyrrolidino favor the 4-position whereas the effect of electron-withdrawing substituents is less predictable. 5(6)-Substituted-benzofuroxan equilibria show attenuated electronic effects and steric factors are negligible; electron-acceptor groups (e.g. NO $_2$, EtO $_2$ C, CN) favor the 5-position, but electron-donating substituents have little effect. Stereoelectronic effects for 4(7)-substituted analogues are, as expected, more significant; a methyl group results in a ca. 2 kJ bias directing the exocyclic oxygen away from the substituent, and 7-nitrobenzofuroxan is sufficiently destabilized to be undetectable in the presence of the 4-nitro isomer. Furoxans with directly fused heterocyclic rings usually have heavily biased equilibria. Pyridofuroxan (**30**) is ca. 4 kJ mol $^{-1}$ more stable than its 6,5-isomer, an effect attributed to repulsion in the latter between the lone pair electrons of the aza group and the exocyclic oxygen of the furoxan; thienofuroxan (**31**) is similarly ca. 4 kJ mol $^{-1}$ more stable than its tautomer. The overall energies of various mono- and disubstituted furoxans have been calculated by the MINDO/3 method and the more stable isomer correctly predicted in each case (86KGS264).

4.05.5.2.2 Thermal ring cleavage

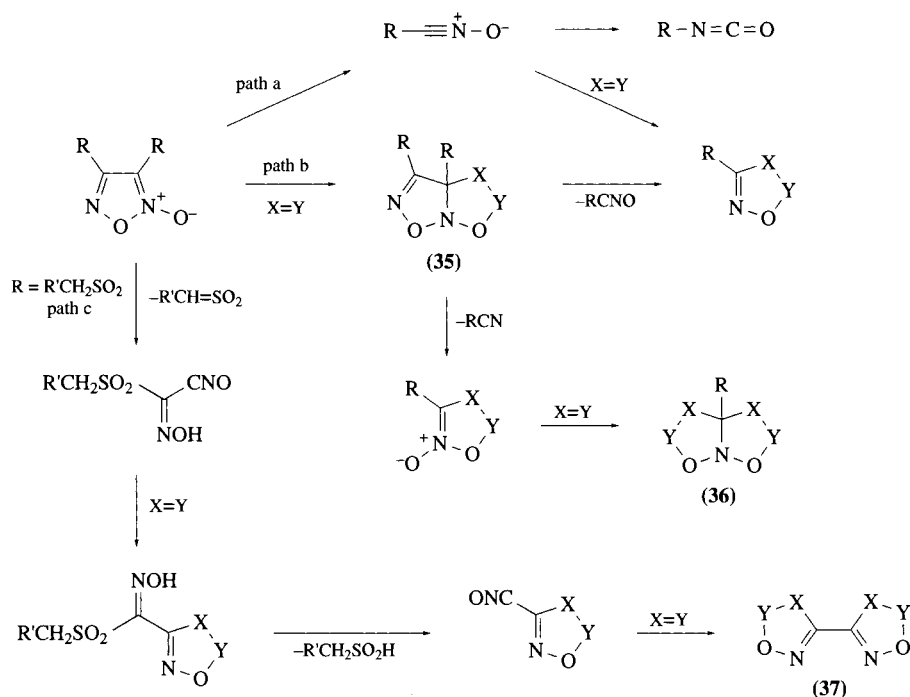
Thermolysis of monocyclic furoxans results in ring cleavage at O(1)—N(2) and C(3)—C(4) forming two nitrile oxide fragments, a process which is formally the reverse of one of the main furoxan preparation routes. As furoxans are often accessible by several other approaches (Section 4.05.9.3) this reaction represents a valuable means of generating nitrile oxides for synthetic purposes. Typically the furoxan is heated above its decomposition temperature in the presence of a suitable dipolarophile and the resulting nitrile oxide is trapped as its 1,3-dipolar cycloadduct. Temperatures in excess of 200°C are usually required and, in the absence of a dipolarophile, the nitrile oxide rearranges to the isomeric isocyanate. However, when the substituents are bulky the fragmentation is more facile; thus di-*t*-butyl- and bis(2-trimethylsilyloxyprop-2-yl)furoxans decompose at 135–165°C <85JA6023>. The FVP technique has proved to be of particular value for the generation and isolation of reactive nitrile oxides from furoxans where liquid phase reactions are complicated by by-product formation. For example, FVP of dicyanofuroxan affords cyanogen *N*-oxide ($\text{N}\equiv\text{C}-\text{C}\equiv\text{N}^+-\text{O}^-$) <95CC1901>, whereas heating in solution gives an oligomeric 1,2,4-oxadiazole resulting from cycloaddition reactions involving the nitrile and nitrile oxide moieties <91IZV1916>. Similarly FVP of dimethylfuroxan makes the short-lived acetonitrile oxide ($\text{MeC}\equiv\text{N}^+-\text{O}^-$) available for spectroscopic study <79TL2443>. The kinetics of the gas-phase decomposition of several furoxans have been investigated, including the parent member of the series, and a concerted mechanism proposed <87IZV221>. Dibromofuroxan is reported to fragment to cyanogen bis-*N*-oxide rather than $\text{BrC}\equiv\text{N}^+-\text{O}^-$ <95JPC6401>.

There are several alternative pathways by which nitrile oxide-derived products can be formed and the actual course adopted is substituent dependent. While it is well established that furoxans can fragment directly to nitrile oxides which are then trapped as their 1,3-dipolar cycloadducts (Scheme 9, path a), the same products could also result from a nitron-like reaction of the furoxan itself with the dipolarophile followed by expulsion of the second nitrile oxide from the bicyclic intermediate (35) (path b). Reaction of the $\text{C}=\text{N}^+-\text{O}^-$ unit as a 4- π component also explains the formation of bicyclic products (36) in which two dipolarophile moieties are incorporated at the expense of a nitrile fragment <85T727, 92JCR(S)256>. In contrast for bis(alkanesulfonyl)furoxans the major product is compound (37) formally derived from cyanogen bis-*N*-oxide ($\text{O}^--\text{N}^+\equiv\text{C}-\text{C}\equiv\text{N}^+-\text{O}^-$); the postulated mechanism (path c) involves successive cycles of nitrile oxide formation and cycloaddition, initially by extrusion of $\text{RCH}=\text{SO}_2$ and subsequently by elimination of a sulfinic acid fragment <86H(24)889>. Furoxan-3-carboxylic acids behave similarly eliminating carbon dioxide to generate the α -(hydroxyimino)alkanonitrile oxide ($\text{HON}=\text{CR}-\text{C}\equiv\text{N}^+-\text{O}^-$) which is either trapped as its cycloadduct in the presence of a suitable dipolarophile or cyclizes via the isocyanate to the corresponding 1,2,4-oxadiazol-5(4*H*)-one <90LA335>. Diacylfuroxans afford products derived both from simple cleavage to the acyl-nitrile oxide and from rearrangement to an α -acyl- α -(acyloxyimino)nitrile oxide [$\text{RCOC}(=\text{NOCOR})\text{C}\equiv\text{N}^+-\text{O}^-$] <81JOC316>.

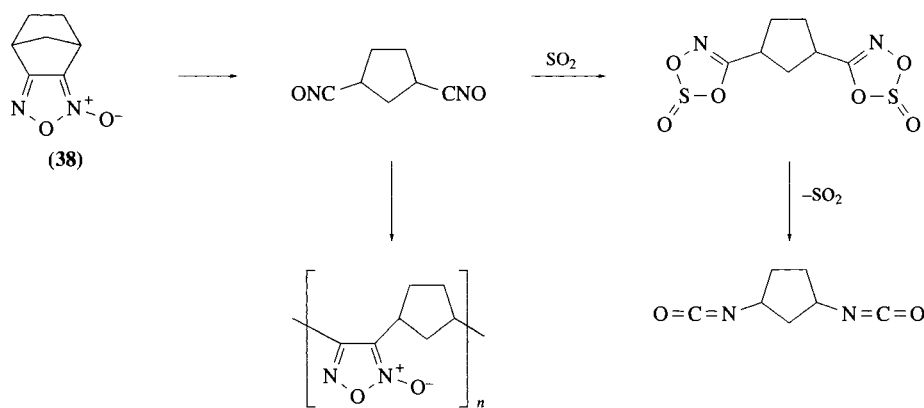
Cleavage of the heterocyclic ring of bicyclic furoxans generates bis(nitrile oxides) and diisocyanates. This process is particularly sensitive to ring strain effects; hexamethylenefuroxan (14) requires temperatures in excess of 220°C, whereas the trimethylene analogue (10) and norbornylene-derived furoxan (38) need only 80–100°C <86JCS(P1)601>. At these lower temperatures the rearrangement to isocyanate is slow and polyfuroxans are formed (Scheme 10); however, the process can be modified to promote isocyanate formation by the addition of sulfur dioxide which mediates the isomerization by trapping the nitrile oxides as thermally labile 1,3,2,4-dioxathiazol-2-ones. In general benzofuroxans are much more stable but, perhaps not surprisingly, benzotrifuroxan (15) is more thermally labile, fragmenting at one of the oxadiazole rings to yield products derived from 3,3'-bifuroxan-4,4'-bis(nitrile oxide) <91IZV1914>.

4.05.5.2.3 Reaction with electrophiles and oxidizing agents

The furoxan ring is notably resistant to electrophilic attack and reaction normally takes place at the substituents. Thus aryl groups attached to monocyclic furoxans and the homocyclic ring of benzofuroxans are nitrated and halogenated without disruption of the heterocycle. Reaction with acid is also slow; protonation is predicted to occur at N-5 <89KGS1261> and benzofuroxans have pK_a values of ca. 8, similar to those of benzofurazans. Monosubstituted furoxans are, as expected, less stable and can be hydrolyzed to the corresponding carboxylic acid. Treatment of the parent furoxan (3) with concentrated sulfuric acid results in rearrangement to (hydroxyimino)acetonitrile oxide ($\text{HON}=\text{CHC}\equiv\text{N}^+-\text{O}^-$) and subsequent dimerization to bis(hydroxyiminomethyl)furoxan



Scheme 9



Scheme 10

which is isolated in quantitative yield (94MI 405-01). Although quaternization is also slow, the formation of 1-hydroxybenzimidazole 3-oxide from benzofuroxan and methyl triflate (Section 4.05.5.2.5) is likely to involve initial reaction at N(3).

The heterocyclic ring is also resistant to oxidation except under forcing conditions. Ozonolysis of dialkylfuroxans with alkaline workup is reported to yield carboxylic acids (81PJC1233); in contrast attempted dye-sensitized photo-oxygenation failed (89JOC3732). Benzofuroxan is oxidized by persulfuric acid to 1,2-dinitrobenzene and the 4,6-dinitro compound similarly affords 1,2,3,4-tetra-nitrobenzene (81CC365). The electrochemical oxidation of furoxans has been investigated (86IZV1691, 92MI 405-03), and at sufficiently high anodic potential ($\sim 2\text{V}$) electron transfer occurs from the electron-rich exocyclic oxygen. The $E_{1/2}$ values are strongly substituent dependent; the process is favored in the case of benzofuroxans and aryl-substituted monocyclic furoxans but is inhibited by bulky groups.

4.05.5.2.4 Reaction with nucleophiles and reducing agents

The furoxan ring is more susceptible to nucleophilic attack and reduction than it is to reaction with electrophiles or oxidation. Grignard reagents react with disubstituted furoxans primarily at C-3 and, in most cases, the resulting adduct fragments to a nitrile and a nitronate salt which affords a ketone on workup.

Nucleophilic displacement of substituents at C(3) and C(4) has been examined in more detail and such reactions are proving to be a valuable route to novel furoxan derivatives. The nitro group in particular is found to be readily displaced by, for example, alkoxides, thiols, azide, and amines. Thus dinitrofuroxan provides a source of the 3-nitro-4-amino, azido, methylamino, methoxy, and phenylthio compounds <93MI 405-01, 95MI 405-03>; with methoxide both nitro groups are substituted yielding dimethoxyfuroxan. The nitro group in 3-chloro-4-nitrofuroxan is displaced on reaction with TMS-NR₂ yielding the 4-alkylamino compound <94KGS1133>. Displacement of halides and sulfonyl groups has also been reported. Monosubstituted furoxans are particularly susceptible to ring opening by base in a reaction similar to that observed for furazans (Section 4.05.5.1.3); for example, 3- and 4-phenylfuroxans afford, respectively, α -nitrophenylacetonitrile and products derived from α -(hydroxyimino)phenylacetonitrile oxide.

In the benzofuroxan series nucleophilic attack could in principle take place at N(1) or N(3). However reaction at N(3) is considered more likely and treatment with secondary amines yields *o*-nitroarylhydrazines <88JCS(P1)145>. Nucleophilic reactions take place preferentially in the homocyclic ring when it is activated by electron-withdrawing substituents (Section 4.05.7.2).

Furoxans can be reduced by a variety of reagents to yield furazans, α -dioximes, 1,2-diamines or aminomethyl compounds depending on the reaction conditions. Catalytic hydrogen usually affords the dioxime, although under forcing conditions ring cleavage at C(3)—C(4) as well as O(1)—N(2) can also occur; for example, tetramethylenefuroxan (13) is reduced by H₂, Pd/C at room temperature to cyclohexane-1,2-dione dioxime, whereas use of Raney nickel at 100°C yields 1,6-diaminohexane. Hydrazobenzene is a convenient reducing agent for the conversion of benzofuroxan to *o*-benzoquinone dioxime <80S146>. Sodium borohydride reduces dialkyl-, diaryl-, and benzofuroxans to the dioximes, but for diacylfuroxans reaction takes place in the substituent to give furoxan alcohols. Benzofuroxans are reduced to the *o*-nitroaniline by ferrous salts <94SC2707>, and to the *o*-phenylenediamine by sodium hydrogen selenide <94JCR(S)388> or ammonium sulfate-sodium borohydride <95SCL725>. Benzofuroxan is regarded as an effective reagent for the dehydrogenation of 1,4-dihydropyridines and 1,2-dihydroquinoxalines to the corresponding fully conjugated heterocycles, and for the preparation of 2-arylbenzimidazoles from *o*-arylenediamines and aromatic aldehydes <92SC281>. With lithium aluminum hydride reduction is accompanied by ring cleavage to give primary amine fragments. Electrochemical reduction affords the dioxime anion as the first-formed product <89IZV281>. Other reducing agents include zinc/acetic acid, tin(II) chloride with acid, sodium azide, and hydrazine hydrate. Furoxans are deoxygenated by trivalent phosphorus compounds to furazans. For simple dialkyl and diaryl compounds temperatures in the range 140–160°C are used, while more forcing conditions cause ring cleavage and further reduction to nitriles. Ring-strained analogues and benzofuroxans, on the other hand, react much more readily; for example, acenaphthofuroxan (11) yields acenaphthofurazan at room temperature and 1,8-dicyanonaphthalene on heating. Nucleophilic reactions leading to new heterocyclic systems are discussed in the next section.

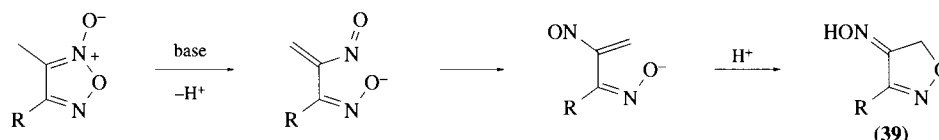
4.05.5.2.5 Heterocyclic ring transformations

The conversion of furoxans into other heterocyclic systems continues to be the subject of intensive investigation. The following subsections give a brief survey of the three main categories: transformation of monocyclic furoxans into isoxazoles, furazans and pyrazoles; rearrangements involving benzofuroxans; and the conversion of benzofuroxans into quinoxaline and benzimidazole oxides. For detailed coverage the reader is referred to more comprehensive reviews <75S415, 76H(4)767, 81AHC(29)251, 88MI 405-01, 93H(35)483>.

(i) Rearrangements involving monocyclic furoxans

Several other heterocyclic systems are accessible from monocyclic furoxans. In addition to providing a source of nitrile oxides and cycloadducts derived therefrom (Section 4.05.5.2.2), they

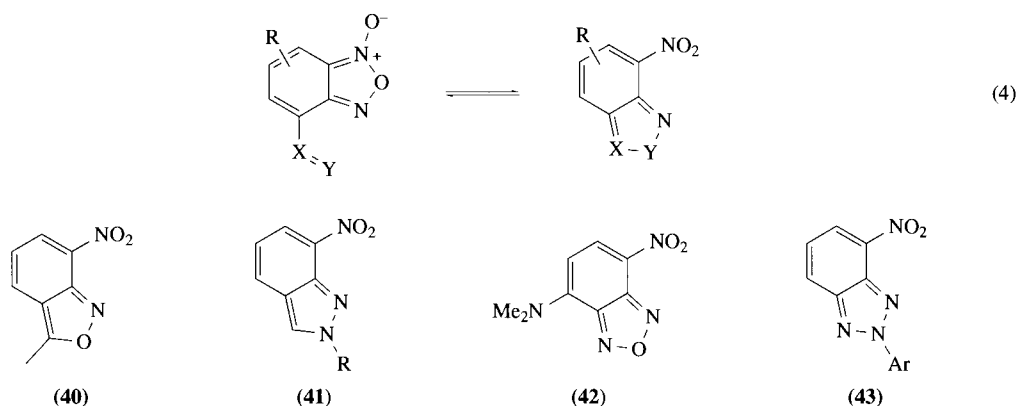
undergo various complex rearrangements. The best documented is the so-called 'isoxazoline transposition' or Angeli's rearrangement (Scheme 11) which involves the conversion of methylfuroxans by treatment with alkoxides or alcoholic alkali hydroxides into the oximes of isoxazolidin-4-ones (39) <81G167>. Other monocyclic transformations include Boulton-Katritzky rearrangement of 4-acylfurazan oximes into α -nitroalkylfurazans <82G181>, and the reactions of primary amines and ammonia with diacylfuroxans to yield 3-amino-4-nitroso-5-arylisoxazoles which rearrange thermally to 3-amino-4-acylfurazans <69JHC317>.



Scheme 11

(ii) Rearrangements of 4-substituted benzofuroxans

Benzofuroxans bearing unsaturated groups at the 4-position undergo bicyclic rearrangement to 4(7)-nitro-substituted benzo-fused heterocycles as illustrated in Equation (4). This class of reaction has been examined in some detail from both a synthetic and mechanistic point of view <93H(35)483>, and it has been established that the role of X=Y can be filled by several types of unsaturation including C=O, N=O, C=N, and N=N. The broad scope of the process and its synthetic utility is illustrated by the following examples. 4-Acetylbenzofuroxan, generated by thermal denitrogenation of 3-azido-2-nitroacetophenone, rearranges spontaneously to methylantranil (40). 4-Iminoalkyl derivatives including anils, hydrazones, and oximes behave similarly; thus nitroindazoles (41) are formed from 4-formylbenzofuroxan and primary amines. Nitrosation of 5-(dimethylamino)benzofuroxan affords 4-(dimethylamino)-7-nitrobenzofurazan (42) due to spontaneous rearrangement of the intermediate 4-nitroso compound. A similar rearrangement is also observed for 4-arylazobenzofuroxans yielding 4-nitrobenzo-1,2,3-triazoles (43). The corresponding isomerizations of 4(7)-nitrobenzofuroxans have been the subject of particular attention; the ease of the reaction is illustrated by the conversion of the 5-methyl-4-nitro compound to 7-methyl-4-nitrobenzofuroxan on gentle heating and the need for 5-chloro-4,6-dinitrobenzofuroxan to be stored below 0°C in order to avoid rearrangement to the 7-chloro isomer. The balance of the equilibrium in such cases is dependent on steric, electronic, conformational, and strain effects; for example, 6,7-methylene-4-nitrobenzofuroxan rearranges rapidly and irreversibly to the 5,6-methylene isomer, whereas the reverse reaction predominates for the trimethylene analogues <92JHC123>. An unusual N→S migration of oxygen is apparently involved in the formation of 4,7-di(phenylsulfonyl)benzofurazan from 7-phenylsulfinyl-4-phenylsulfonylbenzofuroxan <88JCS(P1)145>.

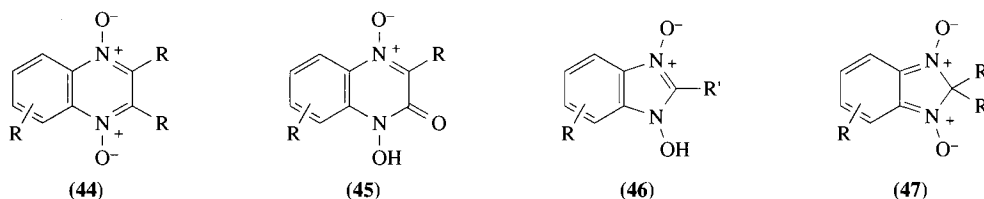


(iii) Transformation of benzofuroxans into quinoxaline and benzimidazole oxides

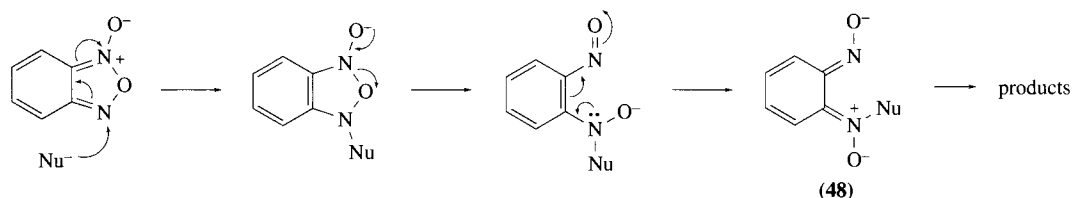
Benzofuroxans react readily with enamines, or with aldehydes or ketones in the presence of ammonia or an amine, to form quinoxaline-1,4-dioxides (44) together with the amine fragment of

the enamine. This process, which is sometimes referred to as 'the Beirut reaction' <76H(4)767>, formally involves insertion of a two-carbon fragment of the co-reactant between the N—O groups of the furoxan. It is compatible with various of substituted benzofuroxans and heterocyclic-fused analogues, and the scope is further broadened by replacing the enamine with an enolate anion derived from β -diketones, which reacts similarly yielding 2-acylquinoxalines. In the absence of the α -hydrogen required for elimination the 2,3-dihydroquinoxaline intermediate can sometimes be isolated. The corresponding reaction with ynamines leads directly to 2-aminoquinoxalines without the need for the elimination step. Alternative elimination processes can lead to quinoxaline mono-oxides. For example, benzofuroxan with cinnamaldehyde and morpholine gives 3-phenylquinoxaline-1-oxide, the formyl group being removed by base. 1-Hydroxyquinoxaline-2-one-4-oxides (**45**) are the main products from several related reactions including those with β -ketonitriles, α -substituted β -ketoesters, and α -(methylthio)ketones <81AHC(29)251>. Polycyclic compounds at various oxidation levels are also readily accessible; for example, 2-hydroxyphenazine is formed when the phenolate anion or *p*-benzoquinone or hydroquinone is the substrate, and benzo[a]phenazine di-*N*-oxide can be prepared similarly from 2-naphthol. As various quinoxalines show useful biological activity, for example as antibacterials, they feature strongly in the patent literature, and their synthesis and the mechanisms of the above reactions have been studied in great detail.

The second class of benzo-fused heterocycles accessible from benzofuroxans are benzimidazole oxides. In this case only one carbon from the co-reactant is incorporated in the product. With primary nitroalkanes 2-substituted 1-hydroxybenzimidazole-3-oxides (**46**) are formed via displacement of nitrite, and β -sulfones behave similarly. The nitrile group of α -cyanoacetamides is likewise eliminated to afford 2-amide derivatives (**46**; $R' = \text{CONR}_2$), and the corresponding esters are formed in addition to the expected quinoxaline dioxides from acetoacetate esters. Under similar conditions secondary nitroalkyl compounds afford 2,2-disubstituted 2*H*-benzimidazole-1,3-dioxides (**47**). Benzimidazoles can also result from reaction of benzofuroxans with phosphorus ylides <86T3631>, nitrones <85H(23)1625>, and diazo compounds <75TL3577>.



The mechanisms of the above reactions have been the subject of longstanding debate. While not all aspects are fully established it is generally accepted that there is a common pathway for the early stages (Scheme 12) which involves nucleophilic attack at N(3) of the benzofuroxan (or possibly at one of the nitroso groups of its *o*-dinitroso tautomer) followed by cleavage of O(2)—N(3) to generate di-*N*-oxide (**48**), with subsequent cyclization to either five- or six-membered ring products being dependent on the nature of the nucleophilic component. A similar pathway has been invoked to explain the formation of 2-phenyl-2*H*-1,2,3-benzotriazole-1-oxide from the reaction with the sodium salt of formanilide <89SC2141>. In contrast sodium azide with 4,7-di(phenylsulfonyl)benzofuroxan which affords 6,8-di(phenylsulfonyl)-5-nitro-tetrazolo[1,5-*a*]azepine is believed to involve nucleophilic attack of the azide at C-7a <88JCS(P1)145>.



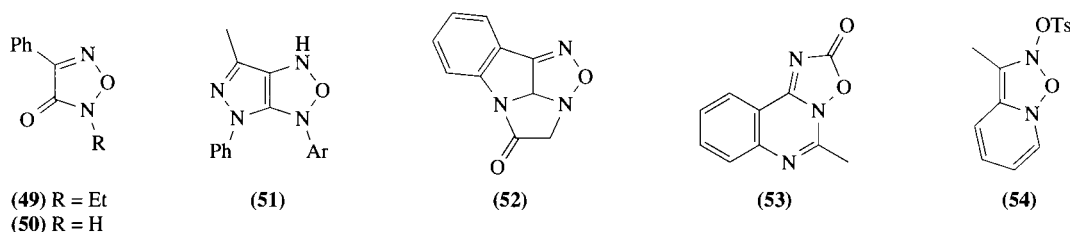
Scheme 12

4.05.6 REACTIVITY OF NONCONJUGATED RINGS

Examples of compounds incorporating nonconjugated 1,2,5-oxadiazole rings are rare and most of the early claims of such structures remain unsubstantiated or have subsequently been disproved.

Tautomerism involving substituents is not favored and even the 3-hydroxy compounds for which lactam tautomers can be proposed (Scheme 3) react exclusively in the conjugated form. Thus *N*-ethyl-1,2,5-oxadiazol-3(2*H*)-one (**49**) is prepared via a 3-silyloxy derivative rather than by direct alkylation of lactam (**50**) <93T5905>.

There are few reports of dihydro-1,2,5-oxadiazoles (1,2,5-oxadiazolines, (**5**)/(**6**)) and 1,2,5-oxadiazolidines (**7**) appear to be unknown. Several examples of *N*-alkyl/aryl-2,5-dihydro-1,2,5-oxadiazoles have been described but the early literature can be misleading and the reported formation of compound (**51**) seems improbable <11LA(385)1>. Oxadiazoline (**52**) <70BCJ2986> has since been shown to be compound (**53**) <76TL3615>, and the structures of the adducts derived from cycloaddition of alkenes with formonitrile oxide and hydroxyiminoacetonitrile oxide which were originally believed to be oxadiazolines <74JHC63> have also been revised <85T5181>. Later reports of 2,5-dihydrofuroxans include the isolation tosyloxyoxadiazolopyridine (**54**) and its tetrahydro derivative <83CPB2269>.



4.05.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The inherent stability of the 1,2,5-oxadiazole ring permits a range of functional group manipulations to be performed on substituent groups without disruption of the heterocycle and, as indicated in the ring synthesis section (Section 4.05.9), it is now appreciated that this approach often provides the best route to a particular furazan or furoxan compound. Since 1984 when CHEC-I was published there has therefore been a greater emphasis on examining substituent group chemistry, particularly in the monocyclic series. These developments are summarized in the following sections; unless otherwise stated common behavior is assumed for furazans and furoxans.

4.05.7.1 Monocyclic Furazans and Furoxans

4.05.7.1.1 Alkyl and aryl furazans and furoxans

Although alkyl and aryl furazans and furoxans have been known for many years there have been relatively few studies of the reactivity of these substituents.

In the aryl series nitration has been examined in greatest detail and it has been established that the 1,2,5-oxadiazole ring exerts an *ortho/para*-directing influence, and that *para* products predominate except when an electron-withdrawing group is present <83JHC1419>; it is also noteworthy that monophenylfurazan and both the monophenylfuroxans are nitrated in the phenyl group leaving the heterocycle intact <83G811>. Chlorosulfonation of diphenylfurazan affords the *p,p'*-bis(chlorosulfonyl) derivative <85JHC1211> and not the *m,m'* compound as previously reported <83JCS(P1)2181>.

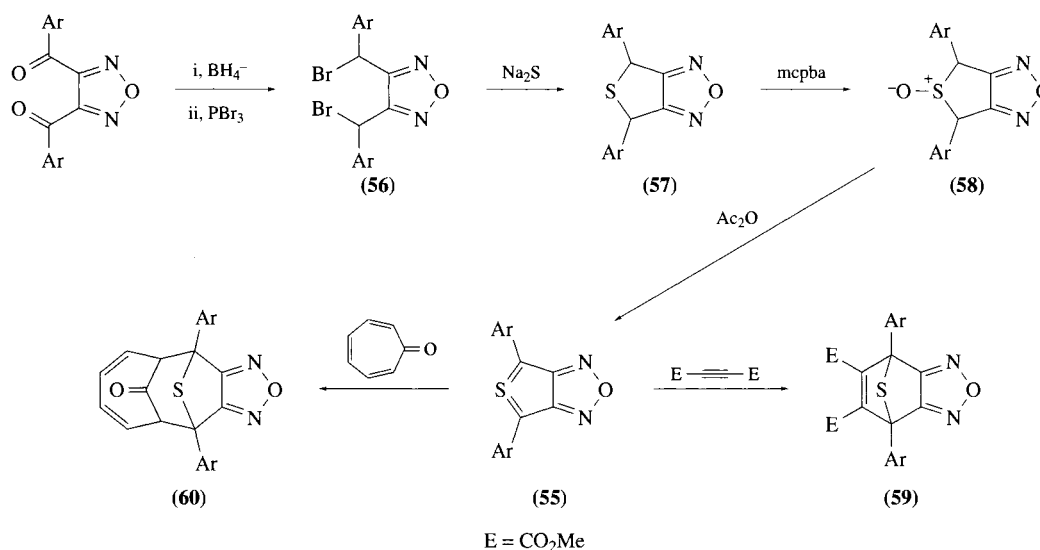
Methyl-substituted furazans and furoxans have been examined as sources of functionalized analogues. Treatment with NBS yields the monobromo compounds which undergo a range of nucleophilic substitutions, for example with amines, azide, hydroxide, and thiolate anions; in the furoxan series the 3-position is brominated selectively <95JHC811>. α -Metallation offers an alternative approach for functionalization of the methyl compounds <92IZV365>. For example, both the mono- and dithio derivatives have been generated from dimethylfurazan and treated with various electrophiles including alkyl halides and carbon dioxide, the latter affording the corresponding acetic acid <81JHC1247>. 3-Methylfuroxans with base undergo the isoxazoline transposition (Scheme 11, Section 4.05.5.2.5). Alkyl groups are oxidized to carboxylic acids on treatment with permanganate.

Alkenyl-1,2,5-oxadiazoles have received little attention but can be prepared by the normal substituent group manipulations; thus mesylation of β -hydroxyethylfurazans followed by treatment with DBU affords the vinyl compound $\langle 81\text{JHC}1247 \rangle$.

4.05.7.1.2 Acyl-substituted furazans and furoxans

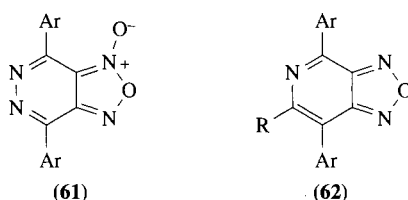
Acyl substituents at the 3- and/or 4-positions result in decreased hydrolytic stability compared with the alkyl and aryl derivatives described above. Despite this constraint most of the usual reactions of the carbonyl group are possible. Aldehydes $\langle 91\text{LA}1211 \rangle$ and ketones are oxidized to the carboxylic acid, borohydride reduction affords the expected alcohols, and epoxides are formed on reaction with diazomethane. Oximes and arylhydrazones are formed with hydroxylamine and arylhydrazines, and the products may subsequently undergo monocyclic rearrangement involving the oxadiazole to give the corresponding isomeric furazans and 1,2,3-triazoles (Section 4.05.5.1.4).

Diacylfurazans provide the starting point for the five-step synthesis of the nonclassical 10 π -electron thieno[3,4-*c*]furazan ring system (**55**) (Scheme 13), a sequence which well illustrates the diversity of reactions which can be carried out on substituents without effecting the oxadiazole ring $\langle 77\text{H}(6)1173 \rangle$. Borohydride reduction of the carbonyl groups followed by reaction with phosphorus tribromide affords dibromo derivative (**56**), which is converted to cyclic sulfide (**57**) using sodium sulfide; subsequent peracid oxidation to (**58**), and dehydration yields (**55**), which can also be prepared directly from the diacyl compound by treatment with phosphorus pentasulfide. The thiocarbonyl ylide portion of the product undergoes [3 + 2] cycloadditions with electron-deficient dipolarophiles such as DMAD to yield adducts (**59**) which either undergo fragmentation of the oxadiazole ring (Section 4.05.5.1.1) $\langle 80\text{H}(14)423 \rangle$ or desulfurization to the benzofurazan; reversible 6 + 3 cycloaddition with 2,4,6-cycloheptatrienone forming 1 : 1 adduct (**60**) has also been reported $\langle 80\text{CL}1031 \rangle$.



Scheme 13

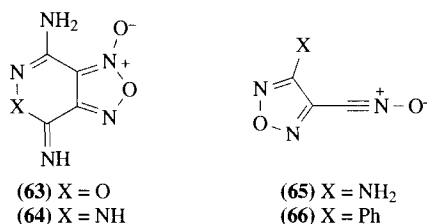
The condensation reactions of diacylfurazans and furoxans also provide a convenient means of constructing fused heterocyclic systems incorporating the 1,2,5-oxadiazole unit. Representative examples include the conversion of diaroylfuroxans into furoxano[3,4-*d*]pyradizines (**61**) using hydrazine $\langle 92\text{JHC}87 \rangle$, and the formation of furazano[3,4-*c*]pyridines (**62**) with primary amines and DBU $\langle 79\text{S}687 \rangle$.



4.05.7.1.3 Furazan- and furoxan-carboxylic acids and their derivatives

Furazan- and furoxan-carboxylic acids are thermally and hydrolytically unstable decomposing to α -(hydroxyimino)nitriles, but their amide, ester, halide, and nitrile derivatives are readily accessible and all undergo the expected functional group interconversions. Dicyanofuroxan reacts with hydroxylamine to give the fused oxazino compound (63) and the pyridazino analogue (64) is similarly formed with hydrazine <82H(19)1063>.

The first examples of furazan and furoxan nitrile oxides have been reported in the early 1990s. 4-Aminofurazan-3-carbonitrile oxide (65) was generated from the hydroximoyl chloride with base and its cycloaddition reactions investigated <92KGS687>, and the 4-phenyl analogue (66) is formed via the nitrolic acid derivative by treatment of the aldoxime with dinitrogen tetroxide <93LA441>. Furazan-3-amidoximes react in the usual way with nitriles to yield 3-(furazan-3-yl)-1,2,4-oxadiazoles <90T3941>.



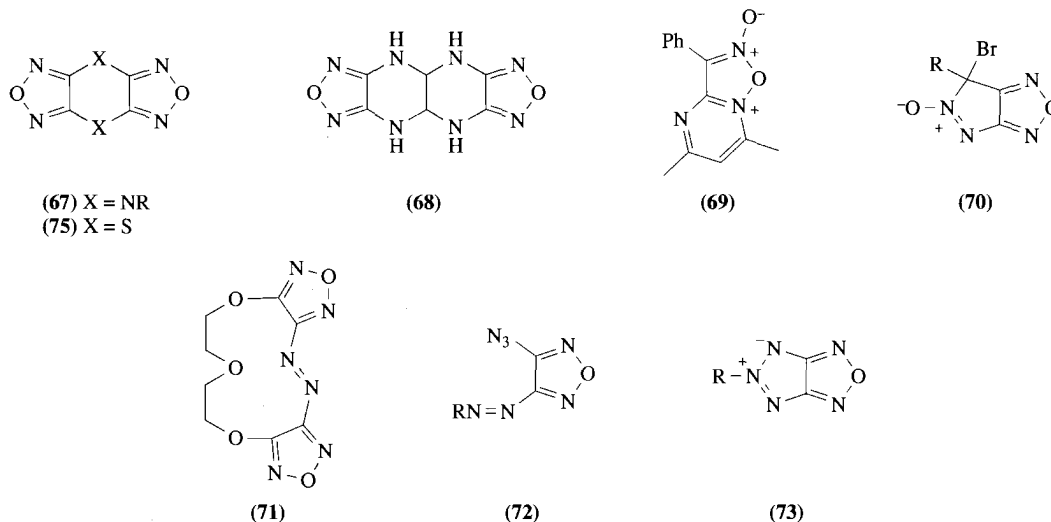
4.05.7.1.4 Amino- and nitrofurazans and furoxans, and their derivatives

The amino group has been the substituent studied in greatest detail and has been the focus of particular attention since the mid-1980s, not only as a source of simple derivatives, but also as a starting material for the construction of more complex systems including fused heterocycles and macrocycles incorporating one or more 1,2,5-oxadiazoles as subunits. Reaction at the more basic/nucleophilic exocyclic nitrogen allows a range of transformations to be accomplished without loss of the heterocycle. Urea and amide derivatives are readily prepared using isocyanates and anhydrides, and imines are formed with carbodiimides <88IZV2363>, aldehydes, and acetals. With isothiocyanates the thiourea adduct undergoes monocyclic rearrangement to a 1,2,4-thiadiazole <86H(24)3433> (see Section 4.05.5.1.4). Diazotization and reaction with sodium azide provides a route to furazan azides <93HAC521>. Furazanyl isocyanates are formed on phosgenation and phosphinimino and sulfinimino derivatives can be prepared by treatment with phosphine and dimethylsulfide ditriflates respectively <86JHC421, 86S490, 92IZV1922>. Oxidation of aminofurazans and furoxans has been the subject of several investigations. Dimethyldioxirane accomplishes clean conversion of aminofurazans to nitrofurazans <89JHC1883> and ammonium persulfate has also been employed to effect the same conversion, but mixtures of nitro, azo, and azoxy compounds may be formed with other oxidizing agents such as permanganate and peroxides <86JHC421, 94MI 405-02>; under milder conditions nitroso compounds can be isolated <90IZV1625>. Dibromoisocyanurate (DBI) is often used for the preparation of the azo compounds <93MI 405-02>.

3,4-Diaminofurazan has proved to be particularly useful for the synthesis of fused heterocycles. For example, reaction with oxalobis(hydroximoyl chloride) (HON=CCl—CCl=NOH) affords bis-furazanopyrimidine (67) <91JHC1677> and glyoxal reacts similarly to give 1:2 condensation product (68) <79S977>. Several furazano[3,4-*b*]-1,4-diazepines have also been prepared by acid-catalyzed reaction with ketones or 1,3-diones <86JHC1519, 89UKZ1064>, and furoxanopyrimidinium salt (69) is formed from 4-amino-3-phenylfuroxan and acetylacetone in the presence of perchloric acid <92KGS233>. 3-Amino-4-cyanofurazan has been converted into a series of furazano[3,4-*b*]pyridines by nickel-catalyzed condensation with β -diketones <94MI 405-03>, and pyrazolo[3,4-*c*]furazans (70) are accessible from 3-aminofurazan-4-ketoximes by bromination followed by treatment with DBI <93MI 405-02>. Macrocycles incorporating furazans have also been reported, including azofurazan crown ethers. For example, the 13-membered ring compound (71) was synthesized by ring closure of the corresponding diamino-bisfurazan, again using DBI, and a similar 26-membered ring compound was also described <92MI 405-02>. Macrocycles containing four and six furazans linked by azo and azoxy bridges have likewise been prepared from diaminofurazan <94MI 405-04>. Thermolysis of azidoazo compounds (72) yield the rarely encountered triazolofurazan ring system (73)

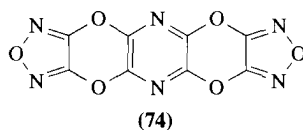
<93HAC521>. The chemistry of 1,2,5-oxadiazoles fused to heterocyclic rings has been reviewed <92CCC978, 95JHC371>.

Nitro-furazans and furoxans provide sources of various derivatives by displacement of nitrite (see Sections 4.05.5.1.3 and 4.05.5.2.4). For example, diaminofurazan is formed from 3-amino-4-nitrofurazan using ammonia under pressure <95MI 405-02>, and one or both of the nitro groups in dinitrofuroxan can be substituted by oxygen, nitrogen, and sulfur nucleophiles <93MI 405-01>; sulfinimino and phosphinimino compounds have been prepared similarly <93PS(78)309, 94OPP331>.



4.05.7.1.5 Furazan and furoxan alcohols and thiols, and their derivatives

1,2,5-Oxadiazoles bearing oxygen or sulfur atoms directly attached to the ring carbons are a little-studied class. It is reported that dihydroxyfurazan can be prepared from oxalyldi(hydroxamic acid) and that it provides a useful starting material for the synthesis of fused systems <92URP1752734>; for example, the linear pentacyclic compound (74) has been prepared by reaction with tetrachloropyrazine <92URP1715809>. Alkoxy derivatives are more common as they are available by displacement of nitrite or halide from the nitro/halo compound, and by this means crown ethers incorporating furazan subunits have been prepared. Silylation of 3-hydroxyfurazans affords the *O*-silylated derivative which yields a mixture of *O*- and *N*-alkyl products results on treatment with triethylorthoformate (Scheme 6).



Some alkyl and aryl-thio compounds are known, most being prepared by nucleophilic displacement of halo or nitro groups. Examples of furazans fused to dithianes have also been described; bis-furazan (75) can be prepared either by dehydration of the tetraoxime or by reaction of potassium thiocyanate with dinitrofurazan <95MI 405-03>.

4.05.7.1.6 Halofurazans and -furoxans, and miscellaneous derivatives

Various halo compounds have been prepared from the corresponding glyoximes. Their principal reaction is nucleophilic substitution, a process which can provide a route to less accessible derivatives. For example, chloride is displaced from 3-chloro-4-methylfuroxan by phenylthiolate to afford the phenyl furazanyl thioether <83JHC783>, and similar reactions with phosphinimino and sulfinimino groups have been reported (Section 4.05.5.2.4). Sulfonyl- and phosphono-1,2,5-oxadiazole are known but their chemistry has not been examined in any detail. Arylsulfonylfuroxans can be

prepared either by oxidation of the thiol or by dimerization of the corresponding nitrile oxide; on thermolysis they undergo cycloreversion (Section 4.05.5.2.2). 1,2,5-Oxadiazoles bearing a directly linked phosphorus atom have also been described; bis(dialkoxylphosphoryl)furoxans are formed by dimerization of the nitrile oxides <90S817, 94KGS1269>.

4.05.7.2 Homocyclic Ring of Benzofurazans and Benzofuroxans

In CHEC-I it was noted that the chemistry of the homocyclic ring, and its reactions with nucleophiles in particular, had been the focus of attention. Although most of the basic principles were already well established by that time the subject has continued to attract widespread interest since 1984 and there is now an extensive literature concerning the reactivity, chemical modification, and especially the biological and pharmacological/medical applications of this chemistry. The following sections deal with attack by electrophiles, by nucleophiles, and transformations involving ring substituents and miscellaneous reactions. Similar behavior is assumed for benzofurazans and benzofuroxans unless otherwise indicated.

4.05.7.2.1 Reactions with electrophiles

Nitration at the 4-position occurs readily and further reaction gives the 4,6-dinitro derivatives. 5-Substituted analogues react similarly, 5-chlorobenzofuroxan affording the 4-nitro-5-chloro compound and subsequently 5-chloro-4,6-dinitrobenzofuroxan <84H(22)271>. In such cases the isolated product may be the 7-substituted-4,6-dinitro compound due to rearrangement of the first-formed derivative (see Section 4.05.5.1.4).

Other electrophilic substitutions occur less readily. Nitrosation and diazo coupling require activating substituents; 4-aminobenzofurazan with arenediazonium salts gives a mixture of 4- and 6-arylazo compounds which yield triazolobenzofurazans on oxidation <94KGS1432>. Reaction of 4-fluorobenzofurazan with chlorosulfonic acid is reported to afford the 7-chlorosulfonyl derivative which is converted by aqueous ammonia into the corresponding sulfonamide <85JAP6072874>. Bromine in the presence of sunlight undergoes electrophilic addition rather than substitution.

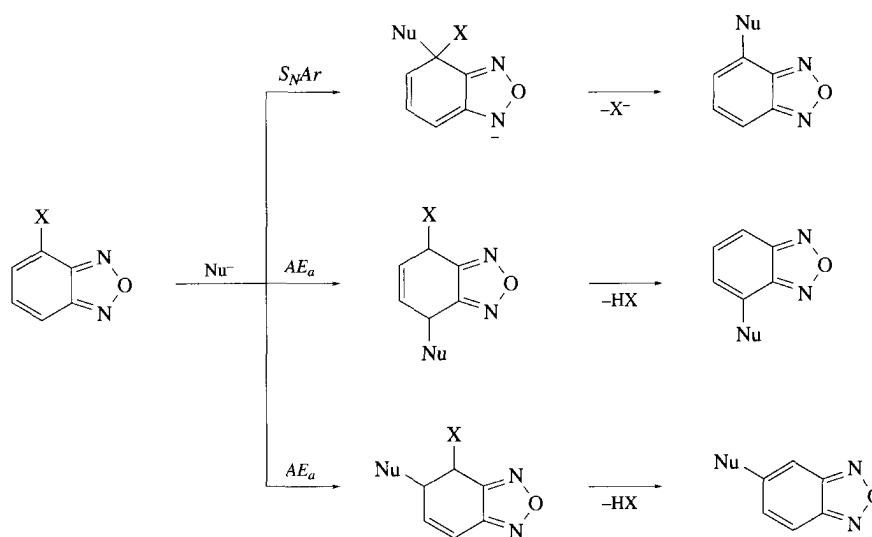
4.05.7.2.2 Reactions with nucleophiles

(i) Nucleophilic substitution reactions

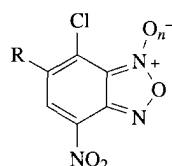
Halides are displaced by a variety of nucleophiles including alkoxides, phenoxides, thiolates, cyanide, and amines. 4-Halogenobenzofurazans yield either 4- or 5-substituted products resulting from normal *ipso* or *cine* reactions, and 5-halogeno derivatives react similarly. An addition-elimination (AE_a) mechanism has been invoked to explain the *cine* products, whereas *ipso* substitution can result from both AE_a and S_NAr pathways (Scheme 14) <81MI 405-02>.

Nucleophilic attack is greatly enhanced when the ring is activated by nitro substituents and the *N*-oxide moiety in benzofuroxans further increases reactivity. Thus the 7-chloro-4-nitro compounds (76) and (77) react rapidly with phenols, amines, and thiols to give the 4-substituted-7-nitro derivatives, and the 5,7-dinitro analogues (78) and (79) are even more reactive. The literature dealing with the applications of such nucleophilic substitutions has expanded greatly in the last decade (see Section 4.05.10). The strong fluorescence and the characteristic spectra shown by each of the resulting ethers, amines, and thioethers has led to the widespread use of benzofurazans (76) and (78) as fluorogenic reagents for analytical purposes <94MI 405-05>. Tyrosyl, cysteinyl, and amino residues in proteins can be labeled by this method, and such displacement reactions have also provided access to fluorescent probes incorporating a variety of biologically interesting molecules, including amino acids and nucleosides. The exceptional reactivity of these systems is illustrated by the observation that furoxan (79) undergoes S_NAr hydrolysis 10^4 times more rapidly than picryl chloride in aqueous solution <93JCS(P2)337>.

One of the nitro groups in furazan (78) can be substituted by chloride and azide, and displacement of sulfonyl groups has also been reported. Nucleophilic reactions in the homocyclic ring of benzofuroxans may be accompanied by deoxygenation of the *N*-oxide; 4-nitrobenzofuroxan with dialkylamines affords 4-dialkylamino-7-nitrobenzofurazans as the major product. Substitution reactions



Scheme 14



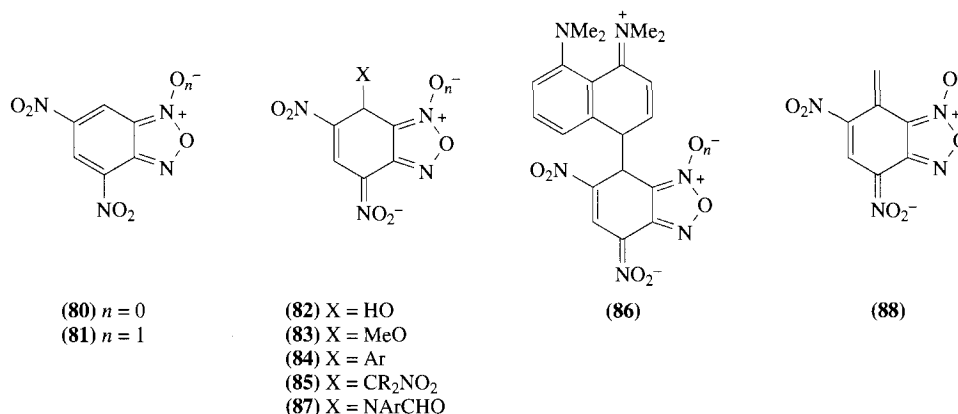
- (76) R = H, n = 0
 (77) R = H, n = 1
 (78) R = NO₂, n = 0
 (79) R = NO₂, n = 1

can take place even in the absence of a good leaving group. Displacement of hydrogen in 4-nitrobenzofuroxan by carbanions of the form ⁻CHClSO₂R occurs at C(5) and C(7) <90CJC2239>, and sulfonium ylides react at the 7-position of 4,6-dinitrobenzofuroxan <93SC1569>. Other synthetically valuable reactions include the conversion of benzofurazan itself to its 4-formyl derivative by reaction with LDA followed by DMF <87SZP661728>.

(ii) Meisenheimer complex formation

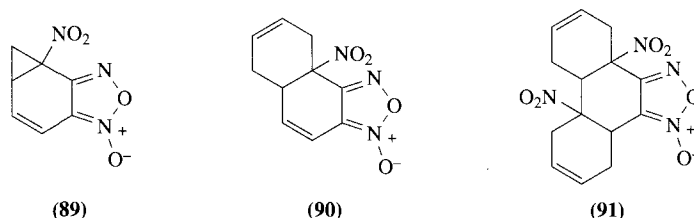
The 4,6-dinitro compounds (80) and (81) have been studied in particular detail <95MI 405-4>. Both are strongly electrophilic and readily form σ- (Meisenheimer) complexes. 4,6-Dinitrobenzofuroxan (81), which is often referred to as DNBF, is regarded as a 'superelectrophile', much more powerful than the *para*-nitrobenzenediazonium cation and common electron-deficient aromatics such as 1,3,5-trinitrobenzene (TNB). This neutral 10 π-electron heteroaromatic system undergoes facile σ-complexation in aqueous and methanolic solution in the absence of base, and it has been estimated that the resulting complexes (82) and (83) are ca. 10¹⁰ more stable thermodynamically than the corresponding adducts with TNB. Even weak nucleophilic carbon centres which do not add to TNB react quantitatively with DNBF under mild conditions. These include enols and several electron-rich aromatic and heteroaromatic substrates, for example, 1,3,5-trimethoxybenzene, phenols, anilines, thiophenes, pyrroles, and indoles, all of which form stable carbon-bonded σ-adducts (84). Nitroalkanes also react in the absence of base to afford (85), which may subsequently eliminate nitrous acid to give the 7-alkylidene analogue. Its electrophilic character is further illustrated by its reaction with 1,8-bis(dimethylamino)naphthalene, the so-called 'proton sponge,' yielding carbon-linked compound (86), and thus providing evidence for nucleophilic character in the latter reagent. Reaction with formanilide salts affords nitrogen-linked adducts (87) which provide access to 7-arylaminodnbf on hydrolysis <89SC2789>. It is also noteworthy that 7-methyl-DNBF is a strong carbon acid

($pK_a = 2.5$), but with a low reactivity which can be attributed to extensive delocalization of the negative charge as illustrated in formula (88) <92APO(27)119>. The chemistry of DNBf has been the subject of a review <95MI 405-04>.



4.05.7.2.3 Miscellaneous reactions and transformations involving homocyclic ring substituents

The 4,5- and 6,7-double bonds are sufficiently localized to undergo [3 + 2] and [4 + 2] cycloaddition reactions. Mesitonitrile oxide gives mixtures of regioisomeric 1 : 1 and 2 : 1 adducts depending on the substitution pattern <90JCS(P1)3277> and alkyl diazoacetates react similarly to afford pyrazolo derivatives <83CC990>. Diazomethane reacts with 4-nitrobenzofuroxan to yield the cyclopropa compound (89), presumably by loss of dinitrogen from the pyrazoline cycloadduct, but other diazo compounds and aryl azides lead to ring-opened products. Diels–Alder reactions occur for benzofuroxans activated by electron-withdrawing groups; thus butadiene forms 1 : 1 and 2 : 1 adducts (90) and (91) with 4-nitro- and 4,6-dinitrobenzofuroxans respectively.



As for the monocyclic 1,2,5-oxadiazoles discussed earlier in this section a wide range of transformations can be performed on substituents attached to the homocyclic ring of benzofurazans and their *N*-oxides, and numerous derivatives have been prepared by this approach. For example, 4-methylbenzofurazan can be brominated at the methyl group without affecting the carbocyclic ring, and 5-aminobenzofuroxan has been prepared from the 5-carboxylic acid in a four-stage sequence in which the key step is the Curtius rearrangement of the 5-azidocarbonyl compound. 4-Formylbenzofurazan provides a valuable starting material for the synthesis of various dihydropyridine derivatives some of which have notable biological activity (Section 4.05.10). 4,5-Diaminobenzofurazan undergoes the expected condensation reactions, affording furazanoquinoxalines and benzimidazole on reaction with 1,2-diones and formic acid respectively <90HCA902>. The chemistry of heterocyclic rings fused to 1,2,5-oxadiazoles is covered in later volumes of this work.

4.05.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING NITROGENS

Until 1995 the only *N*-substituted 1,2,5-oxadiazoles for which the chemistry had been examined in any depth were the furoxans, and the first section is therefore devoted to the principal reaction of their *N*-oxide function, i.e. deoxygenation to the furazan; other aspects of their chemistry

including cycloaddition reactions involving the $C=N^+-O^-$ unit are discussed in Section 4.05.5.2. However, the reactivity of some *N*-alkyl-1,2,5-oxadiazolium salts has also been investigated and a brief discussion of their chemistry is therefore included.

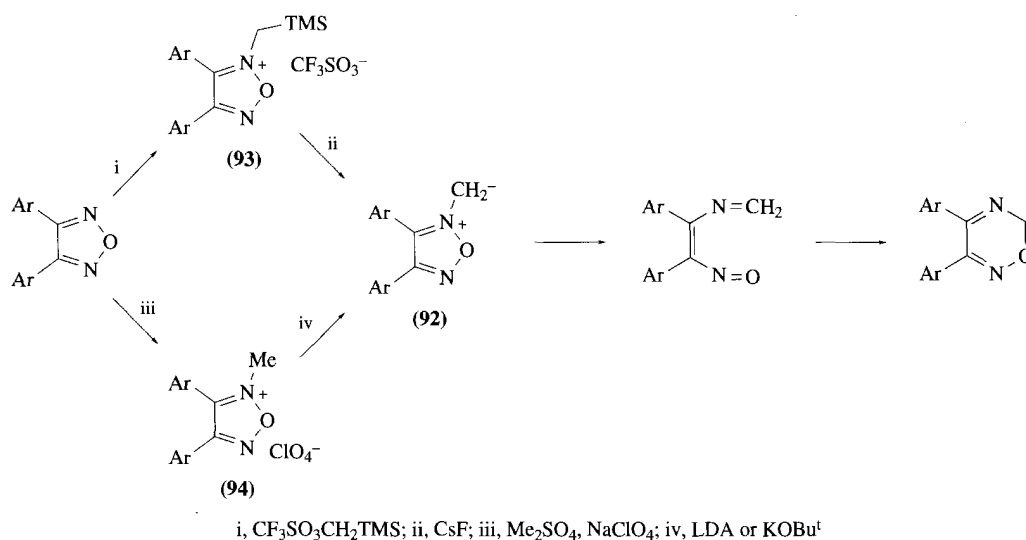
4.05.8.1 Deoxygenation of Furoxans and Benzofuroxans

The reduction of furoxans/benzofuroxans to furazans/benzofurazans has been the subject of detailed study over many years and has been discussed in previous reviews. It represents a valuable synthetic approach to the latter series, particularly in cases where the furoxan is more readily available (Sections 4.05.9.1.2 and 4.05.9.2.3). Many reducing agents result in cleavage of the heterocyclic ring, but reaction with tervalent phosphorus compounds, such as trialkyl and triaryl phosphites and phosphines, causes deoxygenation leaving the heterocycle intact. However, for strained analogues fragmentation products may also be formed; for example, acenaphthofuroxan (**11**) affords acenaphthofurazan (**16**) at room temperature, but on warming ring cleavage and further deoxygenation leads to 1,8-dicyanonaphthalene. Benzofuroxan has also been deoxygenated by heating with sodium azide in ethylene glycol or acetic acid, and by reaction with (1-methoxycarbonylethylidene)triphenylphosphorane <86T3631>.

4.05.8.2 Reactivity of *N*-Alkyl-1,2,5-oxadiazolium salts

Although the furazan ring is notably resistant to electrophilic attack quaternization of the nitrogen atoms can be achieved under forcing conditions (Section 4.05.5.1.2). The resulting 2-alkyl-1,2,5-oxadiazolium salts can be isolated but 3-unsubstituted analogues are susceptible to base-catalyzed hydrolysis; for example, treatment of the unsubstituted furazan (**1**) with triethyloxonium tetrafluoroborate affords the *N*-ethyl cation which is readily hydrolyzed to *N*-ethyl(hydroxyimino)acetamide (Scheme 6, R = H) <64JA1863>.

Of particular note is the report by Butler *et al.* of the generation of 3,4-diarylfurazan *N*-methanides (**92**) <95JCS(P1)1083>. These were formed (Scheme 15) as transient intermediates by desilylation of *N*-trimethylsilylmethyl-1,2,5-oxadiazolium salts (**93**) using caesium fluoride, and subsequently underwent rapid ring expansion to 6*H*-1,2,4-oxadiazines. Methanide (**92**) also resulted from treatment of *N*-methylfurazan salt (**94**) with base.



Scheme 15

4.05.9 SYNTHESSES

The principal methods for the construction of 1,2,5-oxadiazole frameworks were already well developed in 1984 when CHEC-I was published, and this section is therefore designed to update this coverage. Different approaches are generally required for furazans and furoxans, and furthermore the methods used for 3,4-fused arene analogues are also quite distinct. Separate sections are thus devoted to furazans, benzofurazans, furoxans, and benzofuroxans; unless otherwise stated the material included is cited in the reviews listed in the Introduction to this chapter.

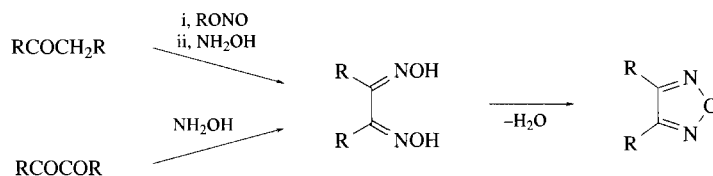
The stability of the heterocyclic ring, particularly to oxidation, allows a wide range of substituent group interconversions to be carried out thus providing access to numerous derivatives. Indeed, the preferred route to a particular compound may often be by manipulation of a readily accessible analogue, rather by building the substituent into the precursor. The reader is referred to Section 4.05.7 for illustrations of the synthetic scope such reactions afford for all the 1,2,5-oxadiazole systems under review.

4.05.9.1 Furazans

Although furazan ring formation by various routes has been reported the three most synthetically useful approaches involve the dehydrative cyclization of 1,2-dioximes, the deoxygenation of furoxans, and the Boulton–Katritzky rearrangement of other five-membered heterocyclic systems.

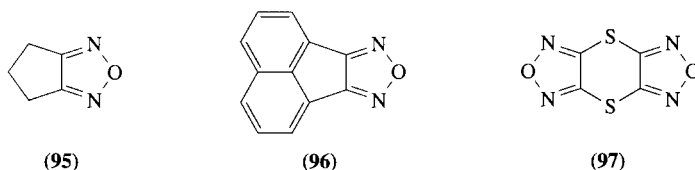
4.05.9.1.1 Dehydration of 1,2-dioximes

The ready accessibility of 1,2-dioximes (glyoximes) and the ease with which they are dehydrated has ensured that this is the most common route to furazans. The starting materials are usually prepared by oximation of the appropriately substituted 1,2-diketone or, more often, by α -nitrosation of an alkyl ketone followed by oximation of the resulting 1,2-dione monooxime (Scheme 16). 1,2-Dioximes can also be prepared by reduction of furoxans (Section 4.05.5.2.4) and, in cases where the furoxan is more readily available than the furazan, for example, by nitrile oxide dimerization, this furoxan $\rightarrow$ glyoxime $\rightarrow$ furazan sequence represents a viable synthetic strategy for symmetrically substituted derivatives.



Scheme 16

Various reagents have been employed for the dehydration step including sulfuric acid, aqueous ammonia, dicyclohexylcarbodiimide, phenyliodine(III) diacetate <82MI 405-01>, and alcoholic sodium hydroxide. Phosphorus oxychloride and thionyl chloride are also used, but in these cases 1,2,4-oxadiazoles may be formed as by-products. For cyclic 1,2-dione dioximes which are not susceptible to such Beckmann rearrangements thionyl chloride is a particularly mild and selective reagent. The value of this technique is illustrated by the preparation in near quantitative yields of the thermally labile trimethylenefurazan (**95**) by treatment of cyclopentane-1,2-dione dioxime with thionyl chloride in liquid sulfur dioxide <62BCJ722>, and of acenaphthofurazan (**96**) and *p*-dithi-inodifurazan (**97**) from the corresponding glyoximes and $\text{SOCl}_2/\text{CH}_2\text{Cl}_2$ or MeCN <73JOC1054, 91MI 405-01>.

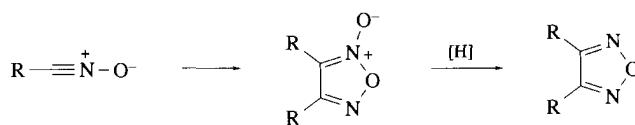


For furazans bearing one or more hydrogen substituents basic dehydrating agents must be avoided as the products are unstable under these conditions (see Section 4.05.5). The parent unsubstituted furazan, for example, was first synthesized by melting glyoxime with succinic anhydride and allowing the heterocycle to distill from the reaction mixture <64JA1863, 65JOC1854> and a similar approach proved successful for monosubstituted analogues: 3-methylfurazan has been prepared by heating propane-1,2-dione dioxime with phthalic anhydride <92KGS1101>, and adamant-1-ylfurazan is likewise formed by dehydration of adamantylglyoxime with acetic anhydride <87ZOR2571>. In contrast, disubstituted furazans are more robust and the full range of dehydrating conditions can be utilized. Treatment of glyoxime diacetates with sodium hydroxide similarly affords furazans, and 3-ferrocenyl-4-alkylfurazans have been prepared by this route <90ZOB2049>.

The glyoxime dehydration route is compatible with various substituents including not only alkyl, aryl, and heteroaryl but also acyl, carboxyl, and amino groups; for example, 3-amino-4-phenylfurazan is formed on heating α -(hydroxyimino)phenylacetamidoxime with sodium acetate in ethanol, and the same compound also results from treatment of benzoyl cyanide with hydroxylamine and sodium acetate in ethanol <87JCB(B)690>.

4.05.9.1.2 Deoxygenation of furoxans

An efficient route to symmetrically substituted furazans (Scheme 17) is provided by the deoxygenation of the corresponding furoxan, which can often be readily prepared via dimerization of the appropriate nitrile oxide (see Section 4.05.9.3.3). A wide range of substituents can be accommodated, but care must be taken to avoid overreduction and, in cases where the target furazan is thermally labile, ring-opened by-products may also be formed <95JHC371>. A variety of reagents have been employed including trialkyl and triaryl phosphites and phosphines, phosphorus pentachloride, or stannous chloride in acetic acid, and zinc/acetic acid.



Scheme 17

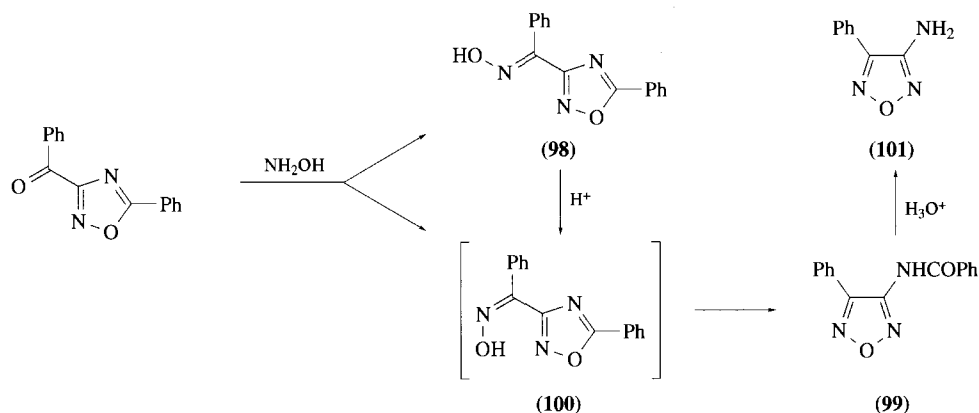
4.05.9.1.3 Rearrangements of 3-acyl-1-oxa-2-azole oximes

Furazans are formed via the Boulton–Katritzky rearrangement of the oximes of several classes of 3-acyl-1-oxa-2-azoles, including 1,2,4-oxadiazoles, isoxazoles, and furazans. These reactions have been intensively investigated over many years, and the literature comprehensively reviewed <81AHC(29)141, 90KGS1443>; the latter survey deals specifically with the exploitation of such rearrangements for furazan synthesis.

(i) 1,2,4-Oxadiazoles

The ease with which 3-(hydroxyiminoalkyl)-1,2,4-oxadiazoles rearrange to 3-amidofurazans has long been recognized <31G138> and this approach has been developed into an effective route to several furazan derivatives. The reaction proves to be strongly geometry dependent; (*E*)-oximes rearrange rapidly whereas the (*Z*)-isomers are generally stable. For example, oximation of 3-benzoyl-5-phenyl-1,2,4-oxadiazole affords a mixture of (*Z*)-oxime (**98**) and furazan (**99**), the latter resulting from *in situ* rearrangement of the (*E*)-oxime (**100**) (Scheme 18) <85JCR(S)190>. The utility

of this route is enhanced by the addition of acid which achieves (*Z*) → (*E*) oxime isomerization and also hydrolyzes the amide to provide access to amino analogues (**101**).

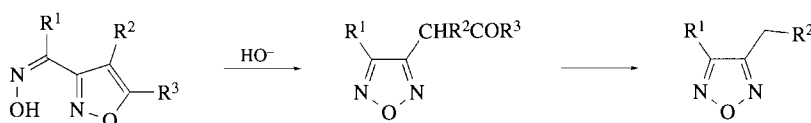


Scheme 18

1,2,4-Oxadiazole to furazan transformations are not limited to the oximes of keto substituents; amidoximes and hydrazidoximes <92KGS969> also rearrange readily. For example, (*Z*)-*N,N*-disubstituted amidoximes of 1,2,4-oxadiazole-3-carboxylic acids on treatment with acid isomerize even at room temperature to the thermodynamically more stable (*E*)-isomers, which then rearrange to diaminofurazans <91KGS822>.

(ii) Isoxazoles

The (*E*)-oximes of 3-acylisoxazoles are more stable than their 1,2,4-oxadiazole counterparts described above and do not generally react in the absence of a catalyst. With base, however, they undergo facile rearrangement to β -ketoalkylfurazans which may deacylate under the reaction conditions (Scheme 19). The corresponding (*Z*)-oximes can also provide a source of furazans provided the (*Z*) → (*E*) isomerization is facile, as is the case for *N,N*-disubstituted amidoximes. When the (*Z*) → (*E*) conversion barrier is high the rearrangement can sometimes be effected by heating in the presence of excess hydroxylamine.

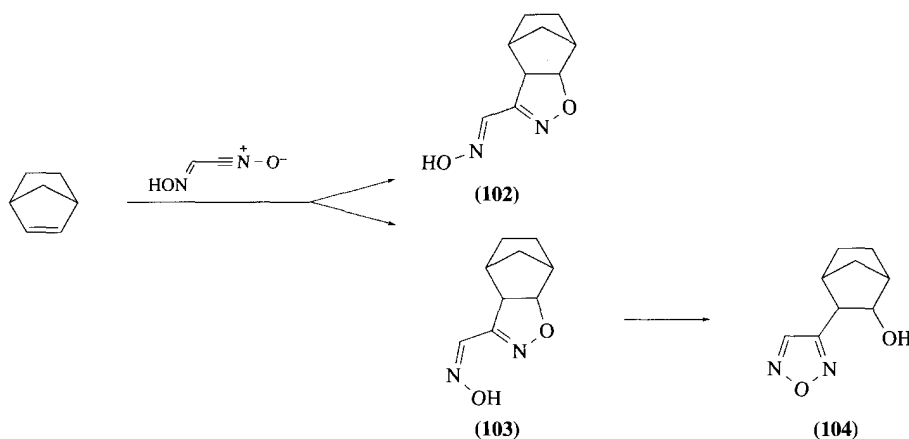


Scheme 19

Furazan formation by rearrangement of 2-isoxazoline oximes have also been reported <85T727, 91KGS827>. For example, hydroxyiminoacetonitrile oxide reacts with norbornene to afford isoxazoline (*E*)- and (*Z*)-oximes (**102**) and (**103**); the former is stable in alkali whereas the latter rearranges to furazan (**104**) (Scheme 20) <85T5181>.

(iii) Furazans and furoxans

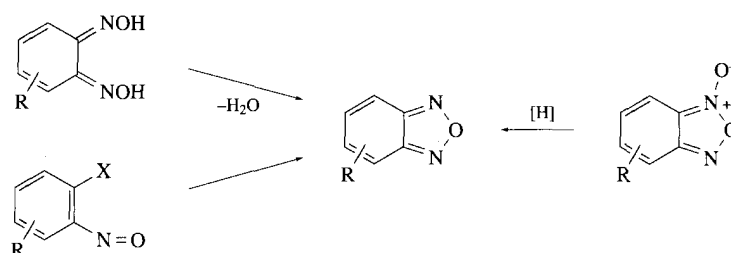
Boulton–Katritzky rearrangement of 3-acylfurazan oximes was discussed earlier (Section 4.05.5.1.4). Although forcing conditions are usually required thus limiting its synthetic utility, this approach has been used for the transformation of 4-aminofurazan-3-dialkylcarbamidoximes into the isomeric 4-dialkylaminofurazan-4-carboxamides <91KGS122>. Similarly 3,4-diacylfuroxan dioximes can also rearrange to furazans, but the process often affords complex mixtures of products and is again rarely of synthetic utility.



Scheme 20

4.05.9.2 Benzofurazans

The principal approaches to benzofurazans comprise the dehydration of *o*-quinone dioximes, the cyclization of *o*-disubstituted arenes, and the deoxygenation of benzofuroxans (Scheme 21). As for the monocyclic furazans these are long-established routes and have been covered in previous reviews <84CHEC-I(6)393, 84H(22)1571>.



Scheme 21

4.05.9.2.1 Dehydration of *o*-quinone dioximes

This route is compatible with a wide range of functionality in the homocyclic ring. Its utility is dependent on the availability of the appropriate dioximes, which are usually prepared by direct oximation of *o*-quinones or by reduction of the corresponding benzofuroxan (Section 4.05.5.2.4). Various dehydrating agents have been employed including thionyl chloride, sulfuric acid, acetic anhydride, isocyanates, and aqueous alkali. Alternatively, cyclization may be achieved by thermolysis of the diacetate or dibenzoate derivatives <84CHEC-I(6)393, 84H(22)1571>.

4.05.9.2.2 Synthesis from *o*-substituted nitrosoarenes

Various nitrosoarenes have been utilized as benzofurazan precursors including *o*-azido derivatives generated from the *o*-chloro analogues <66JCS(B)1004>, and 1-amino-2-nitrosoarenes which can be oxidized with ferricyanide or hypochlorite. Treatment of *o*-nitrosophenols with hydroxylamine also affords the furazan, presumably via an oximation-dehydration pathway involving the tautomeric *o*-quinone monooxime. Other related approaches involve the reduction of *o*-dinitroarenes with borohydride, and the thermolysis of *o*-nitroanilines and *o*-nitroacetanilides.

4.05.9.2.3 Deoxygenation of benzofuroxans

The partial reduction of benzofuroxans, discussed in Section 4.05.5.2.4, represents an effective route to numerous benzofurazans. The conversion may be achieved either directly by deoxygenation, for example, with sodium azide in ethylene glycol or acetic acid <75CI(M)243> or using phosphites, or in two stages via the dioxime with subsequent dehydration as described above.

4.05.9.2.4 Miscellaneous benzofurazan syntheses

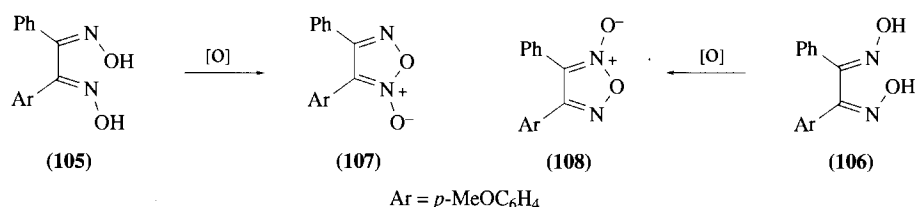
Boulton-Katritzky rearrangement of 7-nitrosobenzofuroxans affords 4-nitrobenzofuroxan (Equation (4); X = N, Y = O) <66JCS(B)1004>; similarly 3-methyl-7-nitroso-2,1-benzisoxazole, generated by phosphite deoxygenation of the nitro compound, yields 4-acetylbenzofurazan <71JCS(C)1193>. Benzofurazan is also formed in near quantitative yield on photolysis of 2,1,3-benzoselenadiazole *N*-oxide, the reaction presumably proceeding by initial cleavage of the N—Se bond, extrusion of selenium from the resulting 1-nitroso-2-(selenonitroso)benzene, followed by ring closure <76ACS(B)675>. Treatment of 1-nitronaphthalene with 4-amino-1,2,4-triazole in the presence potassium *t*-butoxide affords naphtho[1,2-*c*]furazan among other by-products <88JOC3978>.

4.05.9.3 Furoxans

Furoxans are not formed by direct oxidation of furazans, but they can readily be prepared by ring closure or cycloaddition pathways. The most synthetically useful routes are: the oxidative cyclization of 1,2-dioximes, the dehydration of α -nitroketoximes and, for symmetrically substituted furoxans, dimerization of nitrile oxides. For asymmetrically substituted analogues care must be taken in selecting the route in order to avoid formation of mixtures of 2- and 5-oxide isomers.

4.05.9.3.1 Oxidation of 1,2-dioximes

Monocyclic furoxans are most often prepared by oxidative cyclization of 1,2-dioximes. Diverse oxidizing conditions have been employed including hypohalite, ferricyanide, ceric ion, nitric acid and oxides of nitrogen, manganese dioxide <90IZV390>, lead tetraacetate, *N*-iodosuccinimide, and phenyliodine(III) bistrifluoroacetate. The parent unsubstituted furoxan which had proved so elusive for many years has been prepared by this approach using dinitrogen tetroxide as the oxidizing agent <94MI 405-01>. The ring closure can be accomplished stereospecifically thus providing access to the individual isomers for non-symmetrically substituted furoxans. For example, on ferricyanide oxidation (*E,Z*)- and (*Z,E*)-*p*-methoxybenzil dioximes (**105**) and (**106**) are converted exclusively to the corresponding furoxans (**107**) and (**108**) (Scheme 22); on the other hand the (*Z,Z*) and (*E,E*) dioximes give mixtures of the two products. Electrochemical oxidation has also been examined in detail and it is reported that furoxans are formed in high yield using a graphite or platinum anode and either aqueous or non-aqueous media <92MI 405-03>.



Scheme 22

This route is compatible with various functionality and by choosing the appropriate reagents amino-, halo-, and nitro-substituted furoxans can be prepared; illustrative examples include the conversion of cyclopentan-1,2-dione dioxime to the thermally labile trimethylenefuroxan using aqueous sodium hypochlorite <79JCR(S)314>, and of the parent glyoxime to 3,4-dinitrofuroxan by

initial nitration followed by oxidation with dinitrogen tetroxide <93MI 405-01>. This approach is suitable for constructing 1,2,5-oxadiazoles fused to other carbocyclic and heterocyclic systems. Hypobromite oxidation of α -hydroxylaminooximes also affords furoxans <75KGS748>.

4.05.9.3.2 Dehydration of α -nitroketoximes

Furoxan formation via nitrosation of alkenes was first reported towards the close of the nineteenth century and has since been developed into a valuable route for analogues not readily accessible by other means. It is particularly suitable for the conversion of cycloalkenes into fused furoxans; for instance, furoxans (**14**) and (**38**) have been prepared from cyclooctene and norbornene respectively <83JCS(P1)293>. Mixtures of isomers may be formed from non-symmetrical alkenes. The process (Scheme 23) involves initial reaction with dinitrogen trioxide to afford the 1-nitroso-2-nitro adduct (often isolated as the 'pseudonitrosite' nitroso dimer), followed by rearrangement to the α -nitroketoxime tautomer, and finally dehydrative cyclization with, for example, sulfuric acid or the sulfur trioxide–dimethyl formamide complex. A number of functional groups can be accommodated in addition to alkyl and aryl; nitrosation of crotonaldehyde, for example, affords 4-formyl-3-methylfuroxan which can be isomerized thermally to the 3-formyl-4-methyl compound <89JHC1345>, and similarly nitrosation of β -nitrostyrene yields the individual arylnitrofuroxan isomers via the 2-aryl-2-hydroxyimino-1,1-dinitroethane <92MI 405-04>. Terminal alkenes sometimes lead directly to nitrofuroxans; thus 3-methyl-4-nitrofuroxan is formed by nitrosation of propene. α -Nitrooximes are also intermediates on a route to carbohydrate furoxans involving reaction of α -tosyloxyketones with hydroxylamine in aqueous pyridine followed by addition of sodium nitrite to the resulting α -hydroxyiminopyridinium salt <72CC1117>.

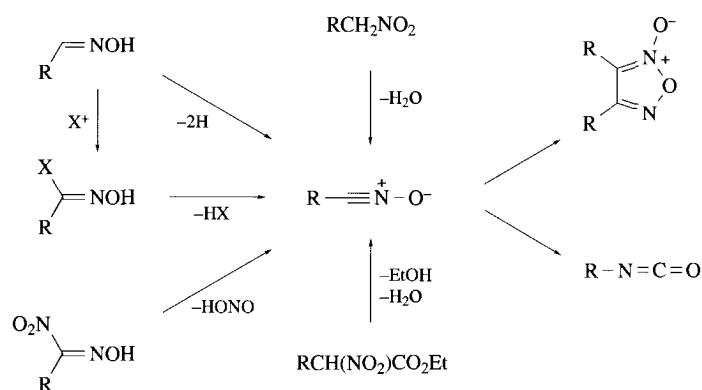


Scheme 23

4.05.9.3.3 Dimerization of nitrile oxides

The chemistry of nitrile oxides has been studied in great detail over many years and is currently the focus of renewed attention in view of the key role they play in the nitrile oxide-isoxazole/isoxazoline routes to natural products and analogues <B-88MI 405-02, 90H(30)719, 91MI 405-02>. Although their most characteristic and synthetically valuable reactions are 1,3-dipolar cycloadditions their tendency to undergo spontaneous 3 + 2 dimerization, which is usually regarded as an unwanted side-reaction, can be exploited for the preparation of furoxans (Scheme 24). This has been a very active area of research since the publication of CHEC-I and a much wider variety of functionalized nitrile oxides are now available. Under controlled conditions the yields are generally high but the rate of reaction varies markedly. Bulky substituents in particular slow the process; thus at room temperature a neat sample of acetonitrile oxide has a lifetime of less than one minute, whereas mesitonitrile oxide and adamantane-1-carbonitrile oxide can both be isolated and only dimerize on warming. The route is not suitable for formonitrile oxide (fulminic acid) which behaves anomalously and yields polymers rather than the parent furoxan, nor is it generally appropriate for bicyclic furoxans; a few examples of intramolecular dimerization have been reported <89IZV2081>, but difunctional nitrile oxides usually polymerize to polyfuroxans. Rearrangement to isocyanates <85JCS(P1)1181> competes with the bimolecular dimerization, with the former becoming dominant at elevated temperatures. The preparation of furoxans from nitrile oxides is therefore carried out in concentrated solution at ambient temperature. From a practical point of view the method is effectively limited to symmetrically disubstituted furoxans; combination of two nitrile oxides can be

used in principle to make asymmetrically substituted analogues, but in practice selectivity is low and mixtures of products result.



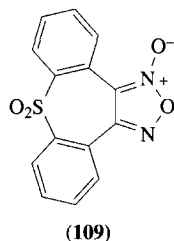
Scheme 24

The principal sources of nitrile oxides are oximes, hydroximoyl halides, and nitromethyl compounds. They have, however, also been identified as intermediates in various other reactions, and these could be used for the preparation of furoxans. In the following paragraphs the most preparatively useful methods are identified.

(i) From oximes and hydroximoyl halides

The route to diphenylfuroxan via benzonitrile oxide originally reported by Werner and Buss a century ago <1894CB2193> involving chlorination of benzaldoxime followed by base-mediated dehydrochlorination of the resulting benzohydroximoyl chloride continues to be a widely used method. Although hydroximoyl chlorides can be prepared from aldoximes and chlorine gas in an inert solvent this procedure is limited by the range of compatible substituents; alternative milder reagents now in widespread use include nitrosyl chloride and *N*-chlorosuccinimide. The dehydrohalogenation step, originally carried out with aqueous sodium bicarbonate or sodium hydroxide, is now usually performed by addition of triethylamine, the resulting triethylamine hydrochloride co-product being readily removed by filtration. Alternative hydrohalide scavengers include silver salts, molecular sieves <90H(31)1693>, potassium fluoride <91H(32)477>, and its dihydrate <93JCS(P1)2151>.

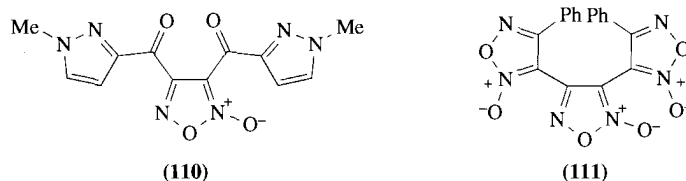
Some hydroximoyl halides are difficult to isolate in pure form and others are toxic, for example, as skin irritants, and it is therefore common practice to generate them *in situ* using NCS or NBS, and then to carry out the dehydrohalogenation-dimerization in one pot using triethylamine as base. For example, alkyl cyanate *N*-oxides, and hence dialkoxyfuroxans, can be formed by chlorination of formhydroximates followed by addition of triethylamine <93ACS1004>. Other reagents which allow one-pot halogenation-dehydrohalogenation-dimerization include sodium hypohalites <82S508>, 1-chlorobenzotriazole <90SC1373>, and chloramine-T <89S57>. The formation of dibenzothiepinofuroxan (**109**) by reaction of hypochlorite with 2,2'-sulfonylbis(benzaldoxime) represents a rare case of intramolecular nitrile oxide dimerization <891ZV2081>. Oxidation of aldoximes to nitrile oxides and thus furoxans has also been accomplished using mercury(II) acetate <92OPP91>, dimethyldioxirane <92NKK420>, and lead tetraacetate.



(109)

(ii) From nitrolic acids and their precursors

Closely related to the dehydrohalogenation of hydroximoyl halides described above is the elimination of nitrous acid from nitrolic acids ($\text{O}_2\text{NCR}=\text{NOH}$) which can occur on heating or by addition of base. Nitrolic acids are also likely intermediates in a variety of other preparations involving nitric acid and oxides of nitrogen. Aliphatic aldoximes yield nitrolic acids and subsequently furoxans on reaction with dinitrogen tetroxide, and the same reagent can be used to convert acetone to diacetylfuroxan. Of particular value is the formation of such diacyl derivatives from aliphatic and aromatic (carbocyclic and heterocyclic) methyl ketones by treatment with nitric acid. For example, di(2-thenoyl)furoxan and the pyrazole analogue (**110**) are formed on reaction of fuming nitric acid with 2-acetylthiophene and 3-acetyl-1-methylpyrazole, respectively <85ZOB1565, 91KGS833>; trimeric furoxan (**111**) is formed by dimerization of 4-phenylfuroxan-3-carbonitrile oxide derived from the corresponding nitrolic acid <93LA441>. In the case of nitric acid oxidation of acetophenone to dibenzoylfuroxan the mechanism has been investigated in some detail and benzoylformaldoxime and the corresponding nitrolic acid identified as key intermediates on the pathway <85JCS(P2)1643>.



(iii) From nitromethyl compounds

Although phenyl isocyanate/triethylamine-mediated dehydration of nitroalkanes to nitrile oxides and hence furoxans was originally reported by Mukaiyama *et al.* in 1960 <60JA5339> it was not until the 1980s that the full potential of the method was realised. The choice of dehydrating agents has also been extended to include diisocyanates, phosphorus oxychloride, chloroformate esters, diketene, thionyl chloride, tosyl chloride/potassium carbonate/18-crown-6 <86M1091>, nitric acid in acetic acid, acetyl chloride/acetic anhydride, and *p*-toluenesulfonic acid with <94JCR(S)116> or without microwave radiation <84BCJ2531>. The wide range of functionality which can be incorporated, and which makes this approach so valuable in nitrile oxide-based synthetic strategies, is illustrated by the following representative examples.

Bis(diethoxyphosphonyl)furoxan is formed on reaction of $\text{POCl}_3/\text{Et}_3\text{N}$ with diethyl nitromethylphosphonate <90S817>, secondary and tertiary nitroacetamides are converted to furoxan-3,4-dicarboxamides by treatment with thionyl chloride <89TL3193>, and dibenzoylfuroxan is similarly formed from β -nitroethylbenzene with acetyl chloride/acetic anhydride <86T3825>. Diethoxycarbonyl- and bisarenesulfonylfuroxans have likewise been prepared by this route, which is also particularly well suited for dialkylfuroxans for which the hydroximoyl halide approach is practically inconvenient. Nitromethyl compounds are sources of nitronate esters ($\text{RCH}=\text{NO}_2\text{R}'$) which can yield nitrile oxides by elimination of alcohol ($\text{R}'\text{OH}$) <84JOC4595, B-88MI 405-02>. Treatment of α -nitroacetophenone with tellurium tetrachloride and triethylamine at low temperatures affords dibenzoylfuroxan in high yield <90CL559>; in this case the reaction proceeds via initial conversion of the nitromethyl group to the hydroximoyl chloride and subsequent dehydrochlorination. Dehydration (conc. H_2SO_4 & oleum) of dinitromethane via its potassium salt to yield dinitrofuroxan has also been reported <93MI 405-03>.

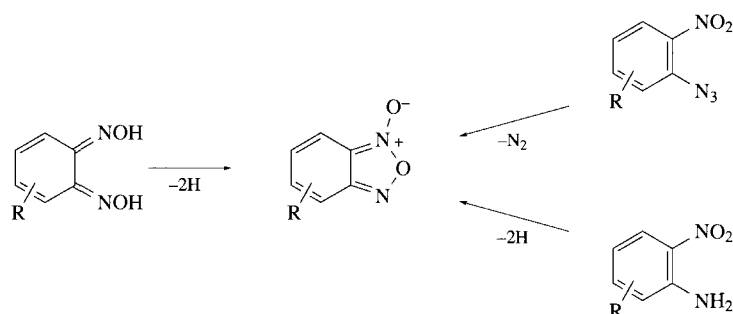
(iv) From miscellaneous sources

Of numerous other preparations for which nitrile oxides have been invoked as intermediates, one of the most synthetically useful is that developed by Shimizu *et al.* which employs alkyl esters of α -nitroalkanoic acids as precursors <87BCJ1948>. The method is suitable for aliphatic, amide, and ester derivatives, and involves thermolysis in an inert solvent to generate the nitrile oxide with concomitant expulsion of carbon dioxide and alkanol. Other reactions leading to furoxans via nitrile oxides include treatment of α -bromo- α -nitrotoluene with triphenylphosphine <84TL2029>, nitrosation

of diazo compounds stabilized by electron-withdrawing substituents, decarboxylation of 2-methyl-4-nitro-5(2*H*)-isoxazolone to afford bis(*N*-methylcarbamoyl)furoxan <92H(34)1511>, formation of bis-(alkoxycarbonyl)furoxans by addition of alcohols to tetranitroethene <83JOC5384>, and reaction of dinitrogen tetroxide with salts of substituted dinitromethanes <92MI 405-05>.

4.05.9.4 Benzofuroxans

The principal methods for forming the heterocyclic ring of benzofuroxans involve oxidation of *o*-quinone dioximes, thermolysis of *o*-nitroaryl azides, and oxidation of *o*-nitroanilines (Scheme 25). Ring chain tautomerism (Section 4.05.5.2.1) for the *N*-oxides of asymmetrically substituted benzofuroxans is more facile than for monocyclic analogues and mixtures of isomers may result. Benzofuroxans are also formed by Boulton–Katritzky rearrangement of 7-nitro-2,1-benzisoxazoles and 4(7)-nitrobenzofuroxans (Section 4.05.5.2.5).



Scheme 25

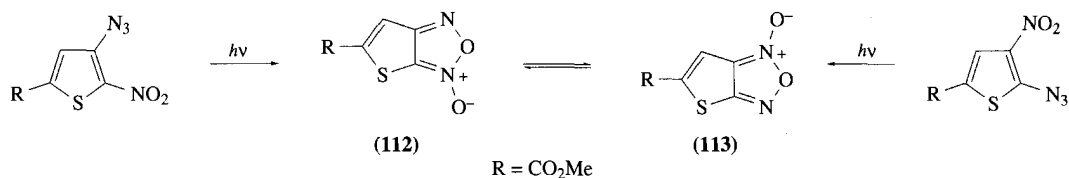
4.05.9.4.1 Oxidation of *o*-quinone dioximes

Benzofuroxans can be prepared by oxidation of *o*-quinone dioximes with, for example, ferricyanide or hypohalite in a process which closely parallels the formation of monocyclic furoxans from glyoximes. Its utility is restricted by the availability of the starting materials which are themselves often best made by reduction of the furoxan. However, it is a valuable approach when the parent quinone or its monooxime is accessible by other means. It was, for example, the route originally used for naphtho[1,2-*c*]furoxan, the first aromatic-fused derivative <1886CB176>, and it is the method of choice for acenaphthofuroxans (**11**). In other cases oxidation of *o*-nitroanilines or thermolysis of *o*-nitroaryl azides are more suitable.

4.05.9.4.2 Decomposition of *o*-nitroaryl azides

Thermolysis of *o*-nitroaryl azides provides a general route to benzofuroxans and hetero-substituted analogues <51OS(31)14>. Its popularity can be attributed both to its reliability and the ready availability of the azides, which can either be isolated or generated *in situ*, for example, from the *o*-nitrohaloarene and sodium azide under phase transfer conditions <83JCS(P2)461, 87S616>. As the reaction usually occurs at a temperature below that required for decomposition of the corresponding *meta* and *para* isomers it is deduced that the mechanism involves intramolecular displacement of dinitrogen by the oxygen of the adjacent nitro group. The ring closure can also be accomplished photolytically; for example, a mixture of thieno[2,3-*c*]furoxan isomers (**112**) and (**113**) is formed on photolysis of either 4-azido-5-nitro- or 5-azido-4-nitrothiophene-2-carboxylic acid esters (Scheme 26). Various substituents can be accommodated in the carbocyclic ring and a wide range of 1,2,5-

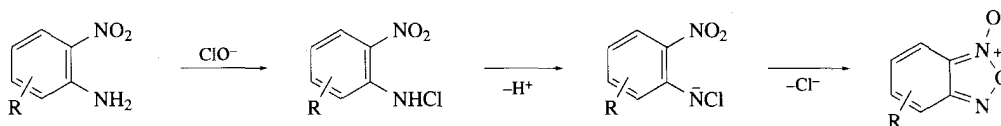
oxadiazoles fused to other heterocycles have been prepared by this approach including pyrido-, quinolino-, pyridazino-, pyrimidino-, imidazo-, thieno- and thiadiazolo-derivatives. Pyrido[2,3-*c*]furoxans are also formed on pyrolysis of 8-nitrotetrazolo[1,5-*a*]pyridines <90JOC3755>.



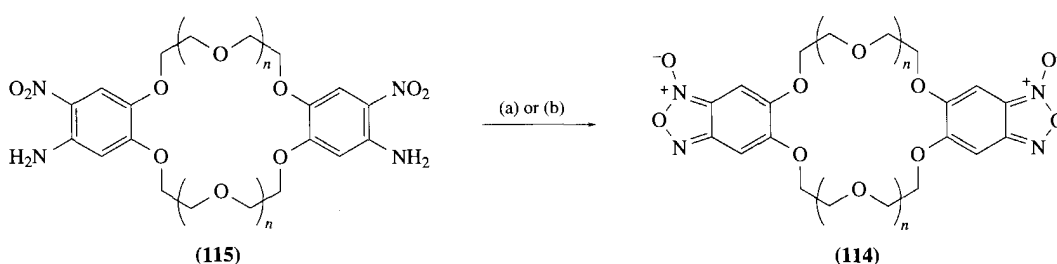
Scheme 26

4.05.9.4.3 Oxidation of *o*-nitroanilines

Oxidative ring closure of *o*-nitroanilines is a well-established method for the preparation of benzofuroxans <57OS(37)1>. Alkaline hypochlorite is the most commonly used reagent, but phenyl-iodine(III) diacetate and electrolysis on a graphite electrode in the presence of potassium iodide have also been employed <84MI 405-01>. It is particularly useful for cases where the azide decomposition approach described above is slow, for example, when steric factors inhibit the interaction of the nitro and azido moieties. Its scope, however, is restricted by the instability of some benzofuroxans under the alkaline oxidizing conditions. The mechanism (Scheme 27) of the hypochlorite reaction is believed to involve initial *N*-chlorination, deprotonation and loss of chloride to afford the furoxan, possibly via a singlet nitrene intermediate. The utility of *o*-nitroanilines as starting materials is illustrated by the synthesis of crown ether annelated benzofuroxans (114); the *o*-nitroaniline precursor (115) can be oxidized as shown in Scheme 28 either directly by treatment with hypochlorite <85ZC17>, or stepwise via the corresponding azide <85GEP226286>.



Scheme 27



(a) i, diazotization; ii, NaN₃; iii, AcOH, reflux
(b) NaOCl, KOH, heat

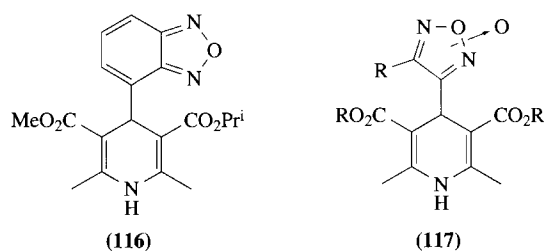
Scheme 28

4.05.10 APPLICATIONS

1,2,5-Oxadiazoles and their benzo derivatives find use in applications as diverse as pharmaceuticals, analytical reagents, propellants and explosives, starting materials in organic synthesis, and for polymer preparation and modification.

From a synthetic point of view the most significant targets have been quinoxaline di-*N*-oxides, prepared by ring expansion of benzofuroxans (Section 4.05.5.2.5). These reactions have been the subject of numerous patents since the mid-1970s in the search for novel antibacterial agents. Benzimidazoles are also accessible from benzofuroxans and their reduction provides a convenient route to *o*-quinone dioximes. Similarly reductive ring cleavage of monocyclic furazans and furoxans affords α,ω -diamines; thus hexamethylenediamine and dodecamethylenediamine can be prepared from the tetramethylene- and decamethylenefuroxans which are themselves readily accessible by nitrosation of cyclohexene and cyclododecene respectively (Section 4.05.9.3.2). Thermal cyclo-reversion of furoxans can provide access to nitrile oxides without the need for a co-reagent, and this approach has been exploited in the nitrile oxide/isoxazoline route to natural products and analogues (B-88MI 405-02, 90H(30)719, 91CHE(49)391). The corresponding reaction for bicyclic furoxans yields bis(nitrile oxides) which can be used to crosslink unsaturated polymers including natural rubber and polybutadiene. The same reaction provides a convenient route to diisocyanates suitable for polyurethane production (Scheme 10). Several examples of heat and hydrolysis resistant polymers incorporating furazan or furoxan units in the backbone have been described (75MI 405-01, 86MI 405-01).

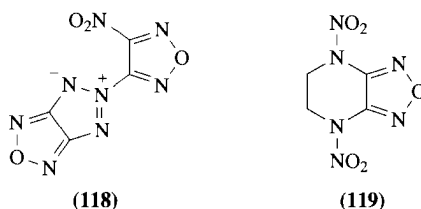
A wide spectrum of biological activity has been reported for compounds incorporating the 1,2,5-oxadiazole nucleus. For example, antibacterial, antihelmintic, and fungicidal activities have been described for a number of furoxans, some phenyl derivatives appear to have central muscle relaxant and anticonvulsant properties. Nitrobenzofuroxans inhibit nucleic acid, and protein biosynthesis. In addition to the various pharmaceutical effects summarized in CHEC-I a number of new applications have been identified and developed. Particular attention has been focussed on derivatives bearing dihydropyridine substituents as antihypertensive and antianginal agents. Ispradine (**116**) is a potent dihydropyridine calcium channel blocker and proves to be an effective peripheral and coronary vasodilator (90MI 405-02). Vasodilating and antiaggregatory activity has also been reported for the furoxan analogue (**117**) of Nefedipine (93MI 405-04). Several furoxancarboxamides and sulfonamides have been examined as potential nitric oxide donors (95BJP1605, 95JHC811); the corresponding furazans are not active. It has been established that these furoxans act as prodrugs and mimic the endogenous formation of NO following chemical reaction with sulfhydryl groups of low molecular weight thiols and proteins. For example, the cardiovascular action of 4-hydroxymethylfuroxan-3-carboxamide has been studied in depth and it has been shown that it exerts vasodilator action via the NO/cGMP pathway. Such compounds may therefore be regarded as nitrovasodilators. Steroidal furazans have been examined for their anabolic activity (85H(23)2931). The early literature dealing with the biochemical and pharmacological properties of benzofurazans and benzofuroxans has been reviewed (81MI 405-02). Agrochemical applications of furazans and furoxans as herbicides, plant-growth regulators and pesticides have also been described.



The ease with which halides are displaced by amines, thiols and phenols from 4-halo-7-nitro-benzofurazans (Section 4.05.7.2.2), taken with the characteristic fluorescence exhibited by the resulting derivatives, forms the basis of a powerful analytical technique. The applications of chloro compound (**76**), as such a fluorogenic reagent, were highlighted in CHEC-I and since then the fluoro analogue 4-fluoro-7-nitrobenzofurazan has become increasingly used on account of its favorable reactivity profile. The benzofurazan moiety proves to be well suited for sensitive detection of analytes by fluorimetry at the pmol and fmol level, and similar reagents for the detection of various other functional groups have also been developed (94MI 405-05). These include 4-hydrazino-7-nitro- and 4-dimethylaminosulfonyl-7-hydrazino-benzofurazans for carbonyl compounds, and alkylamino-benzofurazans for carboxylic acids (91MI 405-02, 92MI 405-06, 94MI 405-05). 4-Isothiocyanato derivatives have been used as a fluorogenic Edman reagent for the detection of peptides (93MI 405-05). These techniques have been used for applications as varied as detection of latent fingerprints on paper (87MI 405-01), of estrogens in urine, and as TLC staining reagents. The role of benzofurazans as

fluorogenic reagents in the biosciences has been the subject of several reviews <89MI 405-02, 94MI 405-05>.

Various nitro-furazans and furoxans can act as propellants and explosives. A notable example which has been studied in the search for suitable dense energetic compounds is the triazolofurazanylfurazan compound (**118**); it is comprised entirely of carbon, nitrogen, and oxygen atoms and it has the optimal composition for self-conversion to carbon monoxide and dinitrogen <93HAC521>. Bis-nitramine derivatives such as furazanopiperazine (**119**) also show explosive properties <86JPC4686>.



Several examples of crown ethers incorporating 1,2,5-oxadiazoles as subunits have been described (Section 4.05.7.1.4). Other applications of furazans and furoxans have been summarized in earlier reviews <81AHC(29)251, 84CHEC(6)393>.

4.06

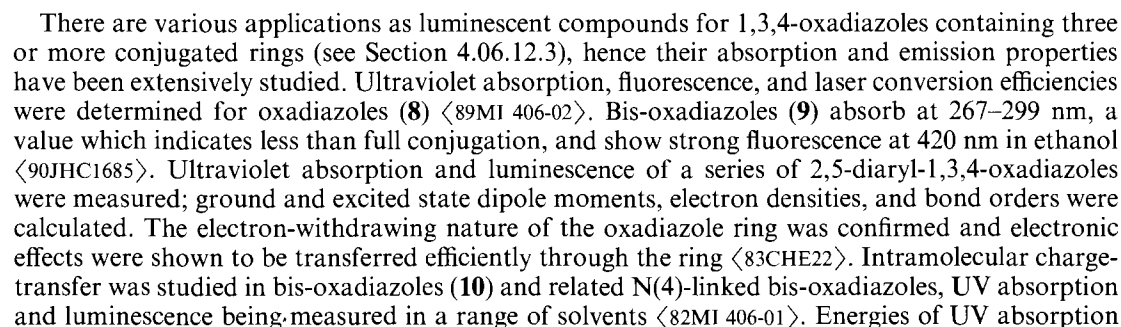
1,3,4-Oxadiazoles

JOHN HILL

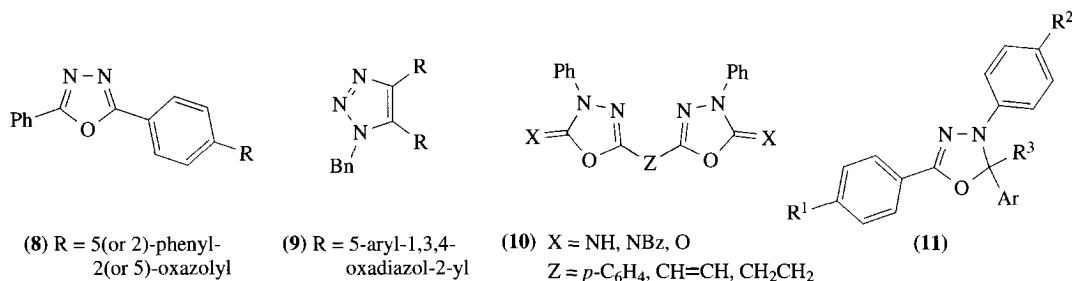
University of Salford, UK

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An example of a thermally stable neutral, fully conjugated molecule is 1,3,4-oxadiazole (**1**). Other conjugated systems are 1,3,4-oxadiazolium cations (**2**), exocyclic-conjugated mesoionic 1,3,4-oxadiazoles (**3**) and 1,3,4-oxadiazolines (**4**). Nonconjugated reduced systems include 2,3-dihydro-1,3,4-oxadiazole (Δ^2 -1,3,4-oxadiazoline (**5**)), 2,5-dihydro-1,3,4-oxadiazole (Δ^3 -1,3,4-oxadiazoline (**6**)), and 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazolidine (**7**)). The chemistry of 1,3,4-oxadiazoles is reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (84CHEC-I(6)427), which contains references to reviews of literature prior to 1965. Developments since the mid-1980s include the synthesis of (i) 1,3,4-oxadiazoles substituted with a wide variety of heterocyclic groups, (ii) a range of oxadiazoles fused to a second heterocyclic ring (e.g., Section 4.06.5.2), and compounds containing more than one oxadiazole ring. No significant new general routes to 1,3,4-oxadiazoles have been reported.



and fluorescence maxima of oxadiazoles (**11**) showed significant linear correlation with Hammett $\sigma\rho$ values, which is consistent with an increase in charge-transfer (and in dipole moment) in the excited singlet state relative to that in the ground state <82JPR246>.



4.06.3.2 NMR Spectroscopy

The chemical shift of the ring protons in 1,3,4-oxadiazole (δ (CDCl₃) 8.73 ppm) is lowered by alkyl substitution as in 2-methyl-1,3,4-oxadiazole (δ (CDCl₃) 2.58 (Me) and 8.53 ppm (C-5 proton)) and is increased by a sulfur substituent as in 2-methylthio-1,3,4-oxadiazole (δ (d₆-DMSO) 9.42 ppm (C-5 proton)) (see also <84CHEC-I(6)427>).

The chemical shifts for C-2 and C-5 in potassium salts of 2,5-di-(carboxyphenyl)-1,3,4-oxadiazoles occur at δ (¹³C) 164.5–164.8 ppm <84JCR(S)118>. Carbon-13 NMR Spectra (δ ppm for C-2 and C-5 respectively) have been reported for Δ^2 -1,3,4-oxadiazolin-5-ones (143.6–155.4 and 147.5–156.1), Δ^2 -1,3,4-oxadiazoline-5-thiones (158.4–161.7 and 174–179), 5-methoxy-1,3,4-oxadiazoles (159.7–160.8 and 166.1–166.6), and 1,3,4-oxadiazolium-2-olates (159.8–160.5 and 152.2–154.4) <82OMR(18)159>. It has been demonstrated that 4,5-diphenyl-1,3,4-oxadiazolium-2-olate shows ¹⁷O resonances (δ (H₂O) at 0 ppm) at δ (line width in Hz) 266 (430) and 181 (390) ppm for O-1 and exocyclic oxygen respectively. The latter value is closer to that expected for an enolate than for a carbonyl group <88HCA241>. The observed ¹⁵N nuclear shielding of 1,3,4-oxadiazole in diethyl ether is $+81 \pm 1$ ppm.

4.06.3.3 IR Spectroscopy

The infrared spectra of 1,3,4-oxadiazoles are characterized by bands at 1640–1560 ($\nu_{\text{C}=\text{N}}$), 1030–1020 ($\nu_{\text{C}-\text{O}}$), and 970 cm⁻¹ <84CHEC-I(6)427>. These bands occur at longer wavelengths in 2,5-dialkyl derivatives and at shorter wavelengths in Δ^2 -1,3,4-oxadiazoline-5-thiones. The thione structure of the latter is consistent with bands at 3450 and 3165 ($\nu_{\text{N}-\text{H}}$), 1538–1438 ($\nu_{\text{C}-\text{NH}}$) and 1350–1300 cm⁻¹ ($\nu_{\text{C}=\text{S}}$). A band is shown at 1785–1740 cm⁻¹ by Δ^2 -1,3,4-oxadiazolin-5-ones due to the C=O group. Amino-1,3,4-oxadiazoles are characterized by two bands ($\nu_{\text{N}-\text{H}}$) at >3200 and ca. 3100 cm⁻¹ and a band at 1670–1640 cm⁻¹, which is shifted to longer wavelength by substituents. A band is shown at 1710 or 1680 cm⁻¹ by Δ^2 -1,3,4-oxadiazolin-5-imines.

4.06.3.4 Mass Spectrometry

It has been shown that 2-amino-5-aryl-1,3,4-oxadiazoles generally undergo fragmentation to give significant ArCO⁺ and [M-HCNO]⁺ ions <82JIC277>, and 2-phenyl- Δ^2 -1,3,4-oxadiazolin-5-one (and 5-thione) lose CO₂ or COS respectively to give the ion PhC=N=NH⁺ <81OMS(16)29>. The mass spectra of some 4-substituted 2-aryl- Δ^2 -1,3,4-oxadiazoline-5-thiones have been described <81PJC599> and 4-acyl- Δ^2 -1,3,4-oxadiazolines were shown to fragment by six main pathways <84CHE498>.

4.06.3.5 Other Spectroscopic Methods

The crystal structures of 5-methyl-5-(2-methylprop-1-enyl)-2-phenyl-4-(4-phenylthiazol-2-yl)- Δ^2 -1,3,4-oxadiazoline (<90ZC26>) and the rubidium and silver salts of 2-phenyl- Δ^2 -1,3,4-oxadiazolin-5-one (<85JOC4461>) have been analyzed. A crystal study of bis-[2-(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl] ether produced bond lengths and angles and showed the rings to be nearly coplanar (<87AX(C)2166>).

Photoelectron spectra of 2,5-di-(fluoroalkyl)-1,3,4-oxadiazoles were studied and adiabatic and vertical ionization potentials were given (<89JGU2411>).

4.06.4 THERMODYNAMIC ASPECTS

It has been shown that 2-amino-1,3,4-oxadiazoles, Δ^2 -1,3,4-oxadiazolin-5-ones (cf. (4; X = O, R = H)), and Δ^2 -1,3,4-oxadiazoline-5-thiones (cf. (4; X = S, R = H)) are in tautomeric equilibrium with Δ^2 -1,3,4-oxadiazolin-5-imines (cf. (4; X = NH, R = H)), 2-hydroxy-1,3,4-oxadiazoles and 1,3,4-oxadiazole-2-thiols respectively, although the former are the predominant species. However, in each case, reaction with electrophilic reagents may lead to derivatives of either of the two tautomeric forms (see Sections 4.06.5.2 and 4.06.7.2 and 4.06.7.4).

"Aromaticity indices" based on a statistical evaluation of peripheral bond orders have been derived for five-ring heterocycles; a value of 50 for 1,3,4-oxadiazole compares with values of 43 and 66 for furan and thiophene respectively (<85T1409>). Somewhat in contrast, O—C, C—N, and N—N bond orders of 1.3124, 1.9062, and 1.3348 (MMX, EXE calculation) for 1,3,4-oxadiazole led to the conclusion that the molecule was not aromatic (<91H(32)2023>).

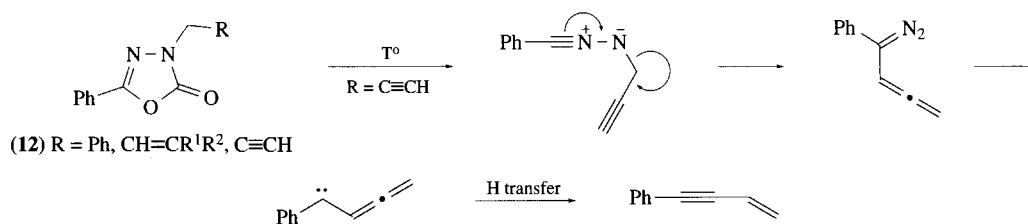
Apart from 1,3,4-oxadiazole (b.p. 150°C), its lower alkyl derivatives and some dihydro compounds, 1,3,4-oxadiazoles are generally solids. In synthesis, the common method of purification is by crystallization of the crude reaction product. A few oxadiazoles, for example, alkyl ethers and acetates derived from 2,5-dihydro-2-hydroxy-2,5,5-trialkyl-1,3,4-oxadiazoles (cf. (38)), have been purified by distillation under reduced pressure. In some cases, chromatography over silica gel has been used.

4.06.5 FULLY CONJUGATED RINGS; REACTIVITY OF RING ATOMS

Reactions at ring atoms consist mainly of electrophilic attack at nitrogen and cycloadditions. Examples of the reaction of 2-substituted 1,3,4-oxadiazoles with bifunctional compounds at both ring nitrogen and at the substituent, leading to cyclic systems, are included in Section 4.06.5.2 irrespective of where the initial point of attack took place. A few examples of nucleophilic attack at unsubstituted carbon are described, the more common nucleophilic attack at substituted carbon being included under reactions of the appropriate substituent (Sections 4.06.7.1–7.5).

4.06.5.1 Unimolecular Thermal Reactions

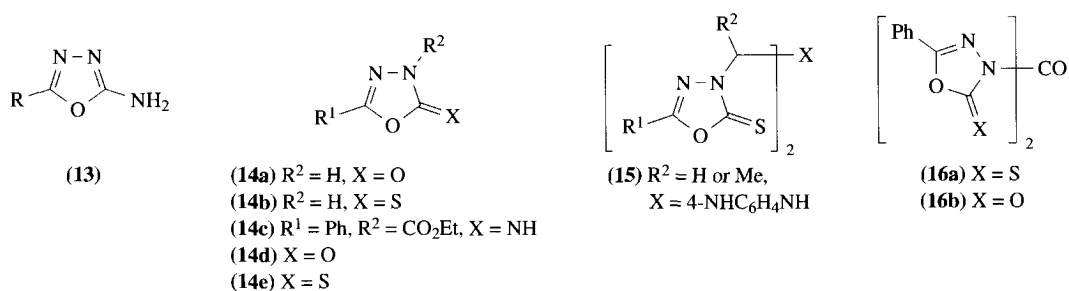
Most 1,3,4-oxadiazoles are thermally stable (unlike many Δ^3 -1,3,4-oxadiazolines, see Section 4.06.6.2) and high temperatures are needed to induce ring cleavage. At 700°C oxadiazolinones (**12**) lose carbon dioxide to form a nitrilimine which undergoes further reaction, with loss of nitrogen. For example, 4-phenylbut-1-en-3-yne was formed on heating oxadiazolinone (**12**; R = ethynyl) (Scheme 1) (<82JA2865>).



Scheme 1

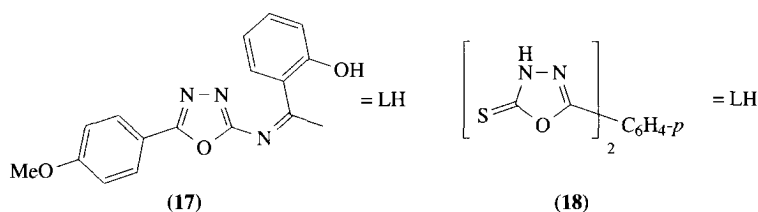
4.06.5.2 Electrophilic Attack at Nitrogen

Alkylation of oxadiazoles (**13**), (**14a**), and (**14b**) generally takes place at ring nitrogen, whereas acylation often occurs at the exocyclic heteroatom, particularly with amines (**13**) <84CHEC-I(6)427>. Exceptions occur, as in the acylation of amine (**13**; R = Ph) with ethyl chloroformate to give the imine (**14c**) <87EGP245196>. Sodium salts of oxadiazolinones (**14a**), formed by the action of sodium hydride, react with phosgene <89JHC231>, 1-chloro-3,3-dimethylbutan-2-one <85JAP(K)6004175>, and tin halides R_3SnX <86USP4582828> to give *N*-substituted oxadiazoles (**14d**; $R^2 = COCl$), (**14d**; $R^2 = CH_2COCMe_3$), and (**14d**; $R^2 = SnR_3$) respectively. Many examples of Mannich amino-alkylation of oxadiazolinethiones (**14b**) have been reported, including the formation of bis-oxadiazoles (**15**) using *p*-phenylenediamine with formaldehyde or acetaldehyde <82JIC776>. The latter two aldehydes react with thiones (**14b**) to give *N*-hydroxyalkyl derivatives (**14e**; $R^2 = CH_2OH$ or $CH(Me)OH$). Acylation of thione (**14b**; $R^1 = Ph$) with trichloromethyl chloroformate yielded bis-oxadiazole (**16a**) <89JAP(K)01283278>. A similar acylation of oxadiazolinone (**14a**; $R^1 = Ph$) with phosgene/triethylamine gave the bis-oxadiazolinone (**16b**).



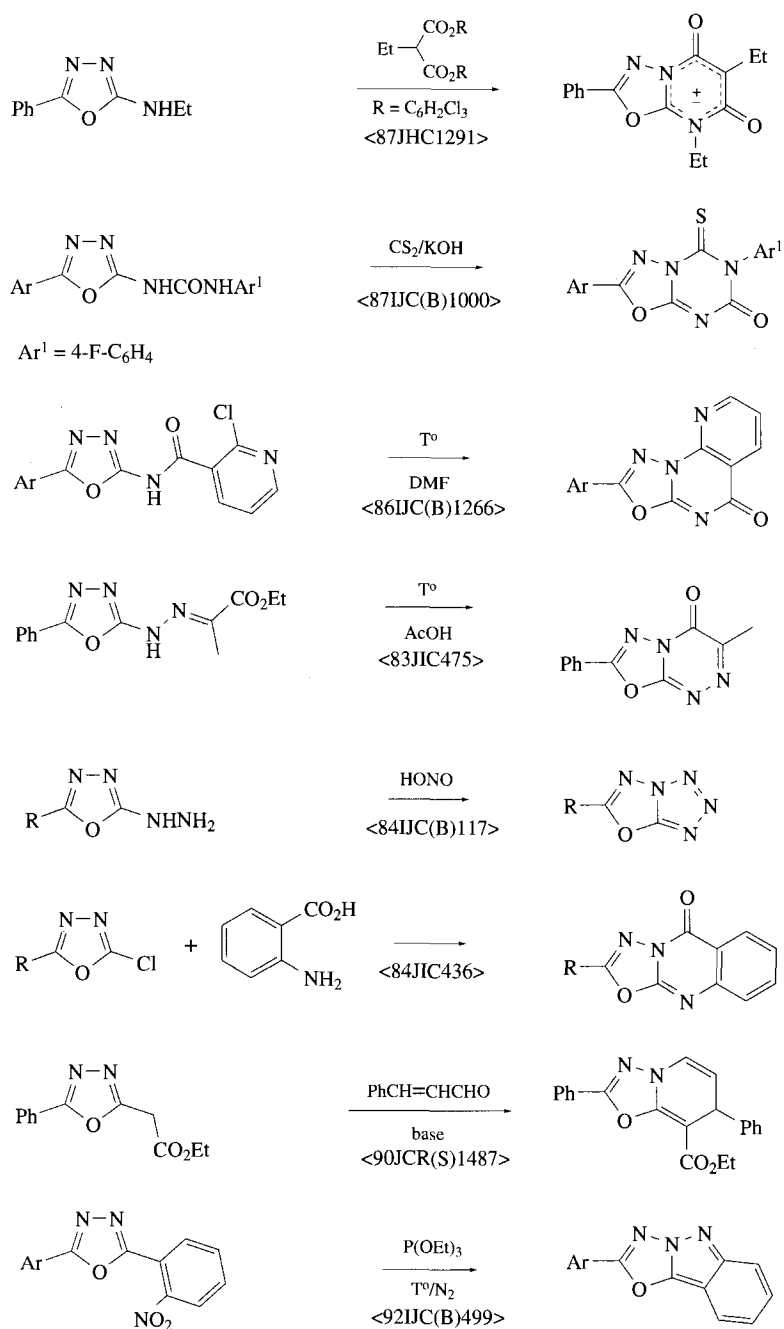
Many examples of the cyclization of substituted 1,3,4-oxadiazoles to form a second heterocyclic ring have been described. A selection, illustrating different types of reactions, and of heterocyclic products, is shown in Scheme 2.

Many examples of metal complexes have been reported in which bonding between the metal ion and oxadiazole ring nitrogen probably exists (e.g., as indicated by their IR spectra). For example, imine (**17**) forms complexes $ML_2(H_2O)_2$ ($M = Mn, Co, Ni$, and Cu) and ML_2 ($M = Zn, Cd, Hg$, and Pb) <84MI 406-01>. Oxadiazolinethiones readily form complexes which, in the case of the bis-thione (**18**) are polymeric; $CuL_{0.5}SO_4 \cdot 3 H_2O$, $ZnL_{0.5}SO_4 \cdot H_2O$, $CdL_{0.5}(OAc)_2 \cdot H_2O$ and $HgL_{0.5}Cl_2$ <85JIC(A)238>. Simple oxadiazolinethiones (**14b**) form complexes $CpTiCl_nL_{(3-n)}$ ($n = 0-2$, $Cp =$ cyclopentadienyl, and $LH = (14b)$) <85BCJ2395>. Similar complexes are formed by zirconium(IV) <85JOM(279)395>.



4.06.5.3 Nucleophilic Attack at Unsubstituted Carbon

Nucleophilic attack at substituted ring carbon is probably the most common reaction of 1,3,4-oxadiazoles. However, few examples have been reported of nucleophilic attack at unsubstituted carbon since such compounds (**19a**) are relatively uncommon. The mechanism of the well-known conversion of 2-amino-oxadiazoles (in aqueous alkali) into triazoles has been studied in the case of the reaction where (**19a**; $R^1 = NHPh$) is converted to (**20**). This proceeds via the anion of semicarbazide $PhNHCONHNHCHO$ and is initiated by hydroxide attack at C-5 <84JCS(P2)537>. A similar nucleophilic attack by hydroxide on oxadiazole (**19a**; $R^1 = 5$ -pyrazolyl) was followed by cyclization to the pyrazolo-triazine (**21**). Hydrolytic cleavage of 2-aryl-1,3,4-oxadiazoles to aroylhydrazides allows use of the former as "protected hydrazides." Oxadiazole (**19a**; $R^1 = 4$ -

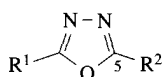
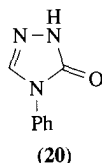


Scheme 2

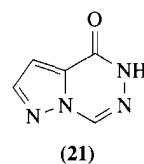
hydroxyphenyl) was iodinated and then methylated. Subsequent hydrolytic cleavage in hydrochloric acid yielded 3,5-diiodo-4-methoxybenzoylhydrazide, not available by direct iodination of the hydrazide (<85OPP230>).

4.06.5.4 Reactions with Electron-Deficient Species

Reactions of 1,3,4-oxadiazoles at ring atoms with radicals or with electron-deficient species are uncommon. Diazoalkanes $\text{R}^1\text{R}^2\text{CN}_2$ reacted with oxadiazolinethiones (**22a**; $\text{R} = \text{H}$) to give *N*-alkyl

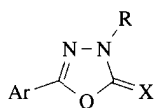
(19a) $R^2 = H$ (19b) $R^1 = Ar^1$, $R^2 = 4-F-C_6H_4CH=N$ (19c) $R^2 = NCS$ (19d) $R^1 = R^2 = CF_3$ (19e) $R^1 = R^2 = CO_2Me$ 

(20)



(21)

derivatives (**22a**; $R = CHR^1R^2$; e.g., $R^1 = R^2 = Ph$) which were oxidized by acidic permanganate to oxadiazolinones (**22b**; $R = CHR^1R^2$) (81PJC599).

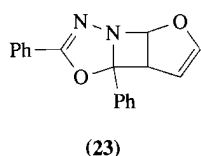
(22a) $X = S$ (22b) $X = O$

4.06.5.5 Cyclic Transition State Reactions with a Second Molecule

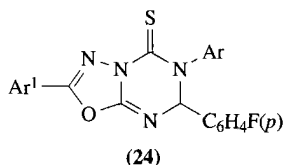
For convenience, all reactions which are formally cycloadditions to the oxadiazole ring (or to the ring and a side chain), including those which may be stepwise but where no evidence for the mechanism is provided, are shown in structures (**23**)–(**32**).

Irradiation of 2,5-diphenyl-1,3,4-oxadiazole in the presence of furan led regioselectively to the [2 + 2] adduct (**23**). Oxadiazole-imines (**19b**) undergo a thermal [4 + 2] cycloaddition with aryl isothiocyanates $ArNCS$ to give oxadiazolo-triazines (**24**) (88MI 406-01). The oxadiazolyl isothiocyanates (**19c**) reacted in a similar manner with cyanides RCN to give triazines (**25**) (83IJC(B)1177). Oxadiazoles (**19d**) and (**19e**) undergo Diels-Alder cycloaddition with alkynes $R^3C\equiv CR^4$ to give adducts (**26**) which were not isolated as loss of nitrogen to give furans (**27**) occurred during the reaction. Cyclopropene reacted similarly to give, in this case, a γ -pyran (**28**), the reaction involving cleavage of the cyclopropane ring after cycloaddition. Cyclopentene and oxadiazole (**19d**) reacted to give the bis-adduct (**29**). In this case, the initial cycloadduct (**30**) probably decomposes to a carbonyl ylide (**31**) which reacts with a second cyclopentene molecule. Other strained cycloalkenes behaved similarly (88TL3231). This reaction was exploited for the synthesis of "spacer molecules" such as (**32**) by the coupling of two molecules of cycloalkene (**33**) on reaction with oxadiazole (**19d**) (91TL1889).

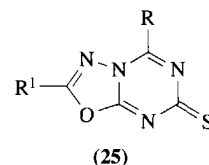
Although oxazoles form cycloadducts with singlet oxygen, no such reaction occurs with 1,3,4-oxadiazoles.



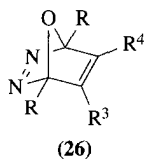
(23)



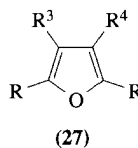
(24)



(25)

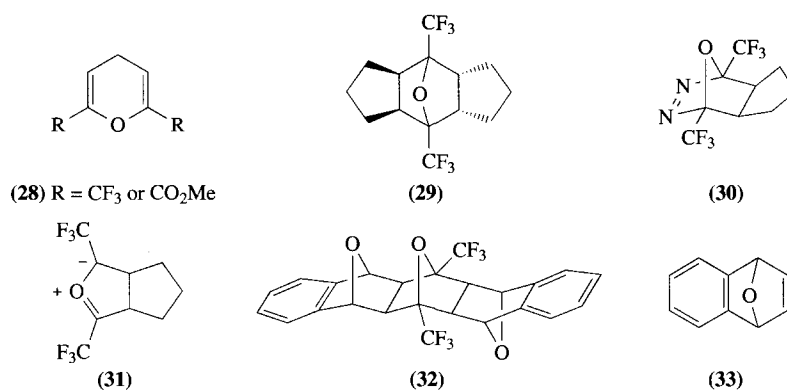


(26)



(27)

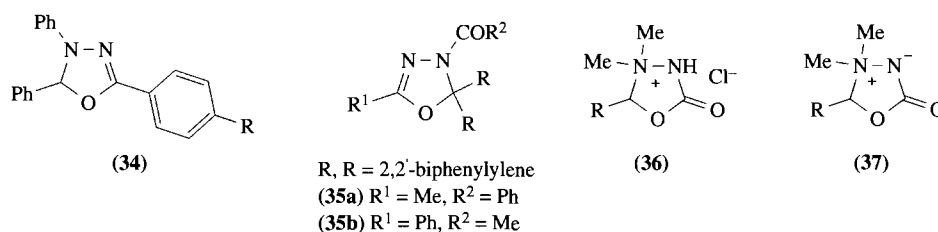
e.g. $R = CF_3$ or CO_2Me , $R^3, R^4 = (CH_2)_6$
or $R = CF_3$, $R^3 = H$, $R^4 = NMe_2$



4.06.6 REACTIVITY OF NONCONJUGATED RINGS

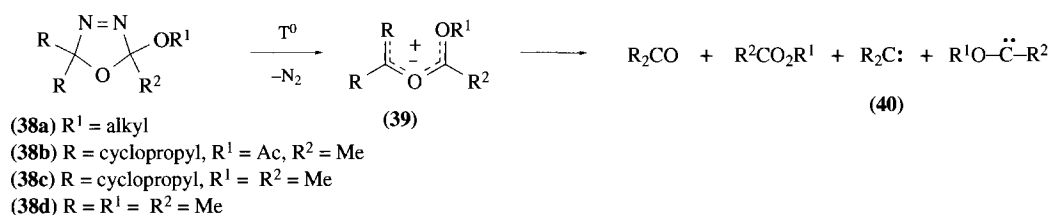
4.06.6.1 2,3-Dihydro-1,3,4-oxadiazoles (Δ^2 -1,3,4-Oxadiazolines)

Rate constants, higher when R is an electron-withdrawing group, have been determined for the hydrolytic cleavage of oxadiazolines (34) to benzaldehyde and hydrazides 4-R-C₆H₄CONHNHPh <81ZC450>. Thermolysis of the 4-acyloxadiazoline (35a) gave the isomer (35b) and not a diacylhydrazone as had been previously reported <85T5187>. The oxadiazolium cation (36; R = Me or Bu) was deprotonated by base to give the cyclic aminimide (37), which cleaved to aldehyde RCHO and isocyanate Me₂NN=C=O (isolated as a dimer) on heating. The aminimide (37; R = Me) reacted with nucleophiles NuH to form hydrazides NuCONHNMe₂ (e.g., Nu = OEt, NR¹R²) <86TL6319>.

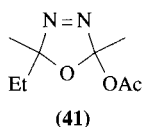


4.06.6.2 2,5-Dihydro-1,3,4-oxadiazoles (Δ^3 -1,3,4-Oxadiazolines)

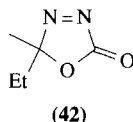
Interest in Δ^3 -1,3,4-oxadiazolines is largely concerned with their fragmentation on UV irradiation or particularly on heating. Loss of nitrogen from oxadiazolines (38a), usually on heating below 100°C, yields a carbonyl ylide (39), which typically fragments to give carbenes and carbonyl compounds (Scheme 3). At high concentrations, carbene products may react with the oxadiazoline to give azines such as (R₂C=N)₂ and R₂C=NN=C(OR¹)R² formed from carbene (40) and oxadiazoline (38a) <84JOC343, 92JA8751>. The carbonyl ylide (39) may also cyclize to an epoxide and/or undergo hydrogen transfer to give a hemiacetal such as AcOCH(Me)OC(Et)=CH₂ from (41) <89CJC1753>. The reaction has been used to prepare dicyclopropyl ketone from (38b) and dicyclopentylcarbene (40; R = cyclopentyl) from (38c).



Scheme 3



Ultraviolet irradiation of oxadiazoline (**38d**) at 333.6 nm (or irradiation using benzophenone as a triplet sensitizer) gave 2-diazopropane and methyl acetate. A triplet biradical intermediate formed by cleavage of the C(OMe)—N bond was postulated <90TL863>. Oxadiazolinone (**42**) underwent nucleophilic attack at the carbonyl group by methyllithium to give acetate (**41**) after treatment of the product with acetyl chloride <89CJC1753>.



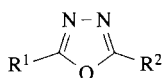
4.06.7 REACTIVITY OF SUBSTITUENTS ON CARBON

The most common reaction of 2- or 5-substituted 1,3,4-oxadiazoles is attack at ring carbon by a nucleophile. This may lead to displacement of the substituent (e.g., of Cl or SR) or to opening of the oxadiazole ring. The latter may be followed by a variety of reactions such as recyclization to a different heterocyclic ring. Changes in the substituent itself, even when involving a nucleophile, may take place without affecting the ring.

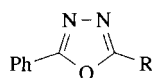
4.06.7.1 C-Linked Substituents

Bromination of the phenyl group in 5-(4-nitrophenyl)-2-phenyl-1,3,4-oxadiazole in the presence of potassium bromate yielded *o*- (16%), *m*- (14%), and *p*-bromo (26%) products, together with low yields of dibromo products <84JCR(S)382>. Similar results were obtained on nitration of 2,5-diphenyl-1,3,4-oxadiazole with fuming nitric acid to give dinitro products. The ratio of *o*-: *m*-: *p*-nitration was 1:1:2.

Nitroaryl-1,3,4-oxadiazoles were reduced to aminoaryl derivatives using hydrazine or hydrogen/palladium. Oxidation (potassium permanganate/pyridine) of 2,5-di-(*m*- or *p*-tolyl)-1,3,4-oxadiazoles (**43a**) gave the corresponding dicarboxylic acids (**43b**) <84JCR(S)118> and oxidation with chromium trioxide/acetic anhydride yielded diacetoxymethyl derivatives (**43c**), which underwent acid hydrolysis to dialdehydes (**43d**) <90JPS(A)3647>. Lithiation with butyllithium of the methyl group in oxadiazole (**44a**), followed by reaction with isoamyl nitrite, yielded the oxime (**44b**) <84JMC1201>.



- (43a) $R^1 = R^2 = 3\text{- or }4\text{-MeC}_6\text{H}_4$
 (43b) $R^1 = R^2 = 3\text{- or }4\text{-C}_6\text{H}_4\text{CO}_2\text{H}$
 (43c) $R^1 = R^2 = 3\text{- or }4\text{-(AcO)}_2\text{CHC}_6\text{H}_4$
 (43d) $R^1 = R^2 = 3\text{- or }4\text{-C}_6\text{H}_4\text{CHO}$
 (43e) $R^1 = \text{Me}, R^2 = \text{CH}_2\text{Cl}$
 (43f) $R^1 = \text{Me}, R^2 = \text{CH=CHAr}$
 (43g) $R^2 = \text{CH}_2\text{CO}_2\text{Et}$
 (43h) $R^2 = \text{C(CO}_2\text{Et)=NNHAr}$
 (43i) $R^2 = \text{CH}_2\text{Ac}$



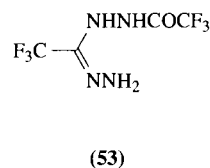
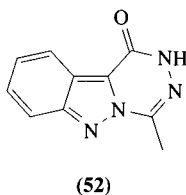
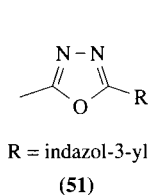
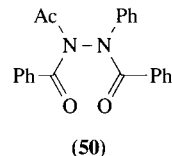
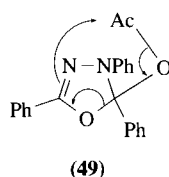
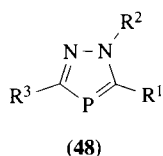
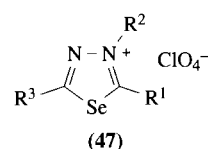
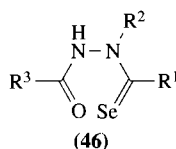
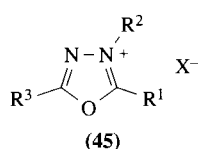
- (44a) $R = \text{Me}$
 (44b) $R = \text{CH=NOH}$
 (44c) $R = \text{CH}_2\text{Cl}$
 (44d) $R = \text{CS}_2^-\text{NHEt}_3^+$
 (44e) $R = \text{CS}_2\text{Me}$
 (44f) $R = \text{CSNR}^1\text{R}^2$
 (44g) $R = \text{C(SMe)=C(CN)}_2$

Oxidation of the chloromethyloxadiazole (**44c**) with sulfur and triethylamine in dimethylformamide below 50°C gave the salt (**44d**) which formed a carbodithioate (**44e**) (λ_{max} 533 nm) on reaction with methyl iodide. Below 35°C (**44c**) reacted with sulfur and an amine $R^1R^2\text{NH}$ to give a thioamide (**44f**) which was also obtained by treating salt (**44d**) with the amine <89JPR243>. Dithioester (**44g**), also formed directly when chloro compound (**44c**) was treated with sulfur and methyl iodide, yielded thioamides (**44f**) on treatment with amines.

Condensation of ester (**44e**) with the anion of malononitrile gave the alkene (**44g**) <91JPR35>. Oxadiazole (**43e**) and triethyl phosphite gave a methane phosphate which underwent a Wittig reaction with aldehydes ArCHO to form alkenes (**43f**). When the alkyl side chain contained an active methylene group, as in (**43g**), reaction with arenediazonium salts ArN_2X yielded arylhydrazones (**43h**) <88LA909>.

Ethyl 1,3,4-oxadiazole-2-carboxylates react with ammonia (or amines) or hydrazine to give the corresponding amides or hydrazides respectively <85JPR109>. Amides were also formed from amines and 1,3,4-oxadiazole-2-carbonylazides <91EGP290425>. The decarboxylation of 5-amino-1,3,4-oxadiazole-2-carboxylic acids and esters has been studied and rate constants were measured <87JHC1457>. Oxadiazol-2-ylacetones (**43i**) were obtained from the corresponding ethylene acetals using hydrogen bromide/acetic acid, anhydrous formic acid, or strongly acidic ion exchange resin <82M793>.

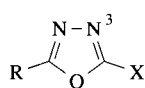
Further examples of nucleophilic attack on oxadiazolium salts leading to ring cleavage and subsequent recyclization to a different heterocycle have been described. Salt (**45**; $\text{X} = \text{OAc}$ or ClO_4) reacted with hydrogen selenide (or HSe^-) to give hydrazide (**46**) which cyclized to the selenadiazolium salt (**47**) in perchloric acid/acetic anhydride <85JGU2318>. Treatment of salts (**45**) with tris-(trimethylsilyl)phosphane in the presence of potassium fluoride gave diazaphospholes (**48**) in 20–30% yield <86TL4415>. On heating, oxadiazolium salt (**45**; $\text{X} = \text{OAc}$, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Ph}$) ring opened to triacylhydrazine (**50**). Acyl transfer in intermediate adduct (**49**) was postulated <83CHE1246>. Nucleophilic attack by propoxide led to ring opening of oxadiazole (**51**) with subsequent recyclization to the indazolo-triazine (**52**) <84JHC91>. Ring opening of oxadiazole (**19d**) with hydrazine yielded hydrazone (**53**) which cyclized to a 1-aminotriazole on heating in acetic acid <89JOC1760>.



4.06.7.2 N-Linked Substituents

It has been shown that 2-amino-oxadiazoles (**54a**) generally *N*-alkylate at position 3 and acylate at the 2-amino group (see also Section 4.06.5.2). In the presence of triethylamine, benzoyl chloride gives exclusively the 2-benzoylamido product, but with benzoyl chloride alone, significant amounts of the 3-benzoyl product (**55a**) are formed, particularly when R is an electron-withdrawing group <89JOU2002>. Treatment of oxadiazole (**54a**; $\text{R} = \text{Me}$) with trimethylsilyl chloride and triethylamine gave 60% of the silyl derivative (**55b**) <89EGP271906>. A similar silylation of (**54a**; $\text{R} = \text{Ph}$) yielded a mixture of silyl derivatives which gave the oxadiazolinimine (**55c**) on reaction with 2,4-dinitrofluorobenzene <89EGP273438>. Products (**54b–e**) were formed when amino-oxadiazoles (**54a**) reacted with aldehydes (R^1CHO) <88JIC357>, thiocyanate <87IJC(B)1000>, carbon disulfide/methyl iodide <91MI 406-01>, or methyl isothiocyanate/alkyl halide (R^1X) <84JHC1377> respectively. With ethyl acetoacetate, an enamine (**54f**) was produced <83IJC(B)815>. Amine (**54a**) and diphenyl chlorophosphate gave the phosphoramidate (**54g**) <81MI 406-01>, whereas with (**56**) an imine derivative (**57**)

was produced <84JGU1523>. Diamine (**54a**; R = NH₂) reacted with nitrous acid to give a mono-diazonium salt which coupled with 2-naphthol to form an azo dye <86MI 406-01>.



(54a) X = NH₂

(54b) X = N=CHR¹

(54c) X = NHCSNH₂

(54d) X = N=C(SMe)₂

(54e) X = N=C(SR¹)NHMe

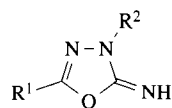
(54f) X = NHC(Me)=CHCO₂Et

(54g) X = NHP(O)(OPh)₂

(54h) X = NHHNH₂

(54i) X = N₃

(54j) X = NHCH(R¹)Z

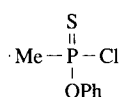


(55a) R² = COPh

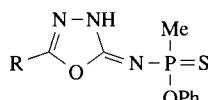
(55b) R¹ = Me, R² = TMS

(55c) R¹ = Ph, R² = 2,4-dinitrophenyl

(55d) R¹ = CO₂Et, R² = Ph

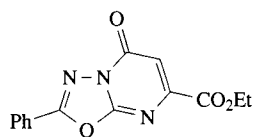


(56)

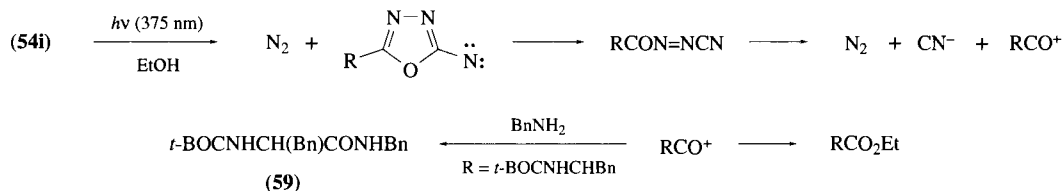


(57)

Hydrazines (**54h**) form hydrazones with carbonyl compounds and yield azides (**54i**) on treatment with nitrous acid. Azide (**54i**; R = Ph) reacted with diethyl fumarate, with loss of nitrogen, to give the oxadiazolo-pyrimidinone (**58**) <83JIC475>. Azides (**54i**) have been used as photochemical acylating agents, irradiation in ethanol producing the acyl ion RCO⁺ which, in the absence of stronger nucleophiles, forms an ester (Scheme 4). Irradiation of aminoalkyloxadiazolyl azides (e.g., (**54i**; R = t-BOCNHCHBn)) in the presence of amines leads to amino-amides, as in the formation of the amino acid derivative (**59**). This reaction has been extended to the synthesis of peptides <83JA902>.

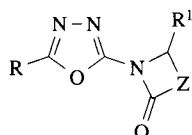


(58)



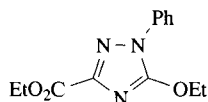
Scheme 4

Addition at the imine group of *N*-oxadiazolylimines (**54b**; R¹ and R generally aryl or hetaryl) occurs to give adducts (**54j**; Z = CN, P(O)(OEt)₂, and SP(S)Ph₂) with reagents HCN, (EtO)₂POH, and Ph₂PS(SH), respectively <88JIC357, 88PS(37)129>. Cycloadducts (**60a**) and (**60b**) were formed on reaction with chloroketene (ClCH₂COCl/NEt₃) <88ABC621> and thiolacetic acid <84MI 406-02> respectively. Oxadiazolinimine (**55**; R² = CO₂R) was hydrolyzed in 10% hydrochloric acid and ethanol to the corresponding oxadiazolinone (**62**; R² = CO₂R) <89EGP268944>, whereas imine (**55d**) was converted into triazole (**61**) on heating in ethanol <85EGP226883>.

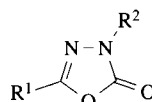


(60a) Z = -CH(Cl)-

(60b) Z = -CH₂S-



(61)



(62a) R² = H

(62b) R¹ = Ar, R² = COR

(62c) R² = Ar

(62d) R¹ = CF₃, R² = H

(62e) R¹ = Ph, R² = COCl

(62f) R¹ = Ph, R² = CON(Me)NH₂

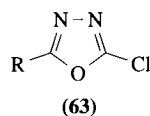
(62g) R² = CH₂C(R)=NNHPh

(62h) R¹ = Ar, R² = Me

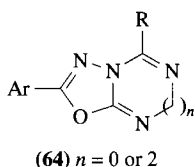
(62i) R¹ = Ph, R² = CO₂Et

4.06.7.3 O-Linked Substituents

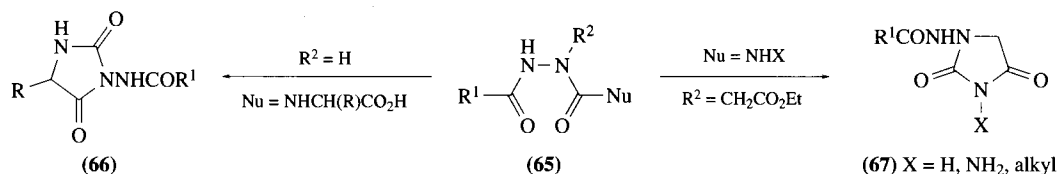
Most reactions of oxadiazolinones (**62**) involve nucleophilic attack at the carbonyl group. This is typically followed by opening of the ring, often with subsequent recyclization to a different heterocycle. Simple nucleophilic displacement occurred on conversion of oxadiazolinone (**62a**; $R^1 = R$) into chloro-oxadiazole (**63**) on treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride <84JIC436> or with thionyl chloride <90AP(323)595>.



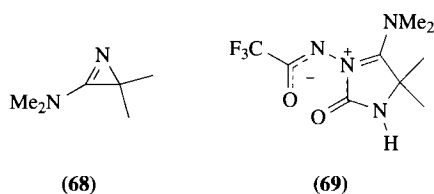
Nucleophilic attack on oxadiazolinone (**62b**) by diamino compounds $NH_2(CH_2)_nNH_2$ ($n = 0$ or 2) led to oxadiazolotriaza heterocycles (**64**) <91H(32)237>. Nucleophilic attack followed by ring opening occurred when oxadiazolinones (**62c**) were treated with amines R^2R^3NH , yielding semi-carbazide derivatives $R^1CONHN(Ar)CONR^2R^3$ <82JHC823>.



Ring opening on attack by nucleophile NuH on an oxadiazolinone (**62**) leads to an intermediate (**65**) which may recyclize. When the nucleophile was an amino acid, cyclization to hydantoin (**66**) occurred <90JHC739>, and when R^2 was a CH_2CO_2Et group, cyclization to hydantoin (**67**) (Scheme 5) took place. Ring opening with subsequent recyclization also occurred when oxadiazolinone (**62d**) reacted with azirine (**68**) to give the stabilized azomethine imine dipole (**69**) <85C354>.

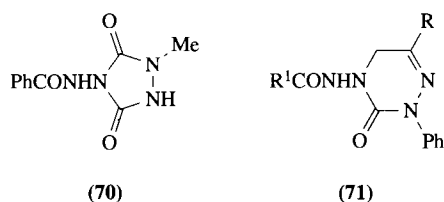


Scheme 5

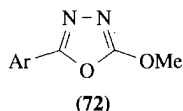


Other examples of nucleophilic attack leading to ring opening/recyclization are the formation of triazolidinedione (**70**) from oxadiazolinone (**62e**) and methylhydrazine, presumably via intermediate (**62f**) <89JHC231>, and the conversion of phenylhydrazones (**62g**) into triazinones (**71**) in the presence of base <92JHC959>.

The thermal rearrangement of methyl ethers (**72**) to 4-methyloxadiazolin-5-ones (**62h**) has been

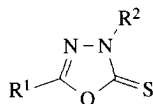


shown to involve the transfer of a methyl group from one molecule to another in an ionic process $\langle 92\text{CC132} \rangle$. Oxadiazolinones (**62i** = L) form the following complexes; $[\text{MnL}_2(\text{NCS})_2]_n \cdot \text{MeOH}$ ($n = 2$ or 3), $[\text{CoL}(\text{MeOH})(\text{NCS})_2]$, $[\text{CoL}_2(\text{NCS})_2] \cdot \text{MeOH}$, and $[\text{ZnL}(\text{MeOH})(\text{NCS})_2]$. Bonding of the metal ion to the ring carbonyl group (ν_{CO} shift of $15\text{--}40\text{ cm}^{-1}$ on complexation) is likely $\langle 84\text{ZC336} \rangle$.



4.06.7.4 S-Linked Substituents

The linear correlation of $\text{p}K_{\text{a}}$ data for 2-aryloxadiazolinethiones (**73e**) with Hammett substituent σ_{x} values excludes the presence of the thiol tautomer (**74a**; $\text{R}^1 = m\text{-}$ or $p\text{-X-C}_6\text{H}_4$) in equilibrium with the more stable (from HMO calculations) thioamide tautomer (**73e**), from which ionization occurs $\langle 83\text{H}(20)2211 \rangle$. Salts have been formed from amines and oxadiazolinethiones (**73**; $\text{R}^2 = \text{H}$). Alkylation of the latter, usually in the presence of base, typically gives *S*-alkyl derivatives (**74b**), whereas acylation (and Mannich alkylation, see Section 4.06.5.2) generally leads to substitution at N-4. However, the kinetic product from thiones (**73a**) and benzoyl chloride (below -50°C) is the *S*-benzoyl derivative (**74c**) which irreversibly forms the 4-benzoyl derivative (**73f**) on heating $\langle 85\text{H}(23)2065 \rangle$. The sodium salt of thione (**73b**) reacted with phosgene and dimethylamine to give the *S*-acyl derivative (**74d**) $\langle 85\text{USP4500539} \rangle$. Treatment of thione (**73c**) with epichlorhydrin, followed by addition of sodium hydroxide, gave the oxadiazolinone (**75**), presumably by rearrangement of the *S*-alkyl intermediate (**74e**) $\langle 89\text{JOU1384} \rangle$.



(73a) $\text{R}^1 = 4\text{-R-C}_6\text{H}_4$, $\text{R}^2 = \text{H}$

(73b) $\text{R}^1 = \text{cyclopropyl}$, $\text{R}^2 = \text{H}$

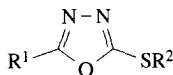
(73c) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$

(73d) $\text{R}^1 = \text{ArCH}_2\text{O}$, $\text{R}^2 = \text{H}$

(73e) $\text{R}^1 = m\text{-}$ or $p\text{-X-C}_6\text{H}_4$, $\text{R}^2 = \text{H}$

(73f) $\text{R}^1 = 4\text{-R-C}_6\text{H}_4$, $\text{R}^2 = \text{COPh}$

(73g) $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{CH}_2\text{NHNH}_2$



(74a) $\text{R}^2 = \text{H}$

(74b) $\text{R}^2 = \text{alkyl}$

(74c) $\text{R}^1 = 4\text{-R-C}_6\text{H}_4$, $\text{R}^2 = \text{COPh}$

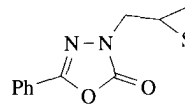
(74d) $\text{R}^1 = \text{cyclopropyl}$, $\text{R}^2 = \text{CONMe}_2$

(74e) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{Cl}$

(74f) $\text{R}^2 = \text{CH}_2\text{C}(\text{R})=\text{NNH}_2$

(74g) $\text{R}^2 = \text{Me}$

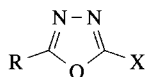
(74h) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Et}$



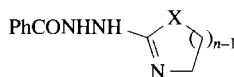
(75)

Displacement of sulfur occurs readily, particularly from *S*-alkyl derivatives and sulfones, as shown in the following transformations: (i) (**74a**; $\text{R}^1 = \text{R}$) is transformed to (**54h**) using hydrazine $\langle 83\text{JIC475} \rangle$; (ii) (**74g**; $\text{R}^1 = \text{R}$) is transformed to (**76b**) using amine HNR^1R^2 $\langle 85\text{RRC257} \rangle$; (iii) (**76a**) is transformed to (**76c**) or (**54i**) using sodio diethyl malonate $\langle 90\text{H}(31)1115 \rangle$ or sodium azide $\langle 83\text{JA902} \rangle$ respectively. Nucleophilic displacement of SO_2Me in sulfone (**76a**; $\text{R} = \text{Ph}$) on reaction with amines $\text{NH}_2(\text{CH}_2)_n\text{XH}$ was followed by a cyclization/ring opening sequence to give products (**77**) $\langle 84\text{CPB5040} \rangle$. Nucleophilic attack leading to a ring opening/recyclization sequence, although less common than with oxadiazolinones (Section 4.06.7.3), is illustrated by the following two types of reaction. Thione (**73d**), on heating with methyl anthranilate, gave the quinazoline (**78**) $\langle 85\text{MI406-01} \rangle$ and intramolecular nucleophilic attack in the hydrazone (**74f**) led to the triazole (**79**) $\langle 82\text{JOC2757} \rangle$. Intramolecular attack at the thione group in oxadiazolinethione (**73g**) resulted in cyclization to triazolooxadiazole (**80**) $\langle 84\text{JCED477} \rangle$.

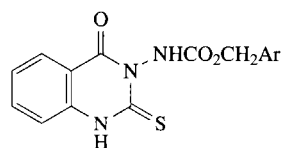
The "oxadiazolythio" portion of *S*-benzoate (**74c**) is a good leaving group and reaction with aniline to form benzanilide and thione (**73a**) is rapid at room temperature. The diester formed from thione (**73a**) and isophthaloyl chloride similarly reacts with diamines, under these mild conditions, to give polyamides $\langle 85\text{JPS(A)2727} \rangle$.

(76a) X = SO₂Me(76b) X = NR¹R²(76c) X = CH(CO₂Et)₂

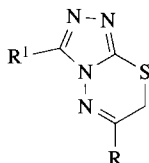
(76d) X = H

(76e) X = NHR¹

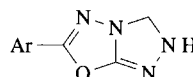
(77) X = O, n = 3; X = S, n = 2



(78)

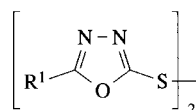


(79)



(80)

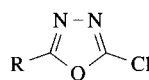
Oxadiazolinethiones (73; R² = H) are oxidized by bromine to disulfides (81) <91JIC108> and *S*-methyl derivatives (74g; R¹ = R) are oxidized to sulfones (76a) <83JA902>. Heating in the presence of Raney nickel converts thiones (73; R¹ = R, R² = H) into oxadiazoles (76d) <84JHC91>.



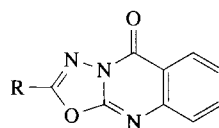
(81)

4.06.7.5 Halogen Substituents

Chlorooxadiazoles (82) react with amino compounds R¹NH₂ (R¹ = NH₂, NHPh, alkyl, or aryl), secondary amines R¹R²NH and azide ion to give products of nucleophilic displacement (76e), (76b), and (54i) respectively <84MI 406-03, 90AP(323)595>. Reaction with anthranilic acid resulted in nucleophilic displacement with subsequent cyclization to oxadiazoloquinazolone (83) <84JIC436>.



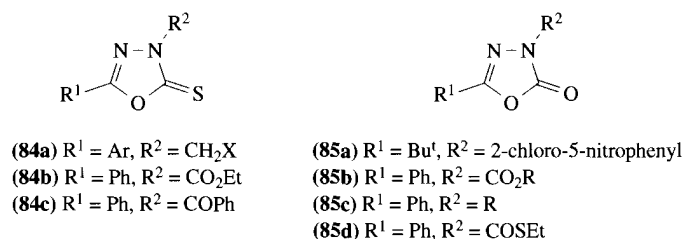
(82)

(83) R = Ph, PhOCH₂

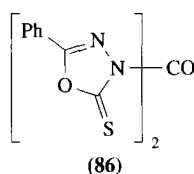
4.06.8 REACTIVITY OF SUBSTITUENTS ON NITROGEN

Nucleophilic displacement of chlorine in oxadiazolinethione (84a; X = Cl) (obtained from hydroxy compound (84a; X = OH) by thiols RSH, amines R¹R²NH, or hydrazine leads to products (84a; X = SR, NR¹R², and NHNH₂, respectively) <81JIC1173, 84JCED477>. The nitro group in oxadiazolinone (85a) was reduced to an amino group by iron powder and acetic acid <88EUP258773>. On heating in pyridine 3-methyl-2,5-diphenyl-1,3,4-oxadiazolium perchlorate was demethylated to give 2,5-diphenyl-1,3,4-oxadiazole <87UKZ1207>. A variety of alkyl esters (85b; R = alkyl) were decarboxylated to give the corresponding 4-alkyl derivatives (85c; R = alkyl) on heating at 200°C;

heating the thiolate ester (**85d**) at 300°C or the thione (**84b**) at 230°C gave mainly the thioether (**74h**) <91BSF71>.



The imide (**86**) (see (**16a**) in Section 4.06.5.2) is a reactive acylating reagent under mild conditions. Reaction with aniline or phenol yields diphenylurea $(\text{PhNH})_2\text{CO}$ or diphenyl carbonate $(\text{PhO})_2\text{CO}$ respectively. With benzoic acid, 2-phenyl-4-benzoyl-1,3,4-oxadiazoline-5-thione is formed, hence reaction of (**86**) with benzoic acid and nucleophiles NuH ($\text{Nu} = \text{NHPh}, \text{OPh}, \text{SPh}$) yields amide PhCONHPh , ester PhCO_2Ph , and thioester PhCOSPh respectively. With diamines $\text{R}(\text{NH}_2)_2$, (**86**) forms polyureas $[-\text{CONHRNH}-]_n$ <89BCJ539>.



4.06.9 RING SYNTHESIS FROM ACYCLIC PRECURSORS

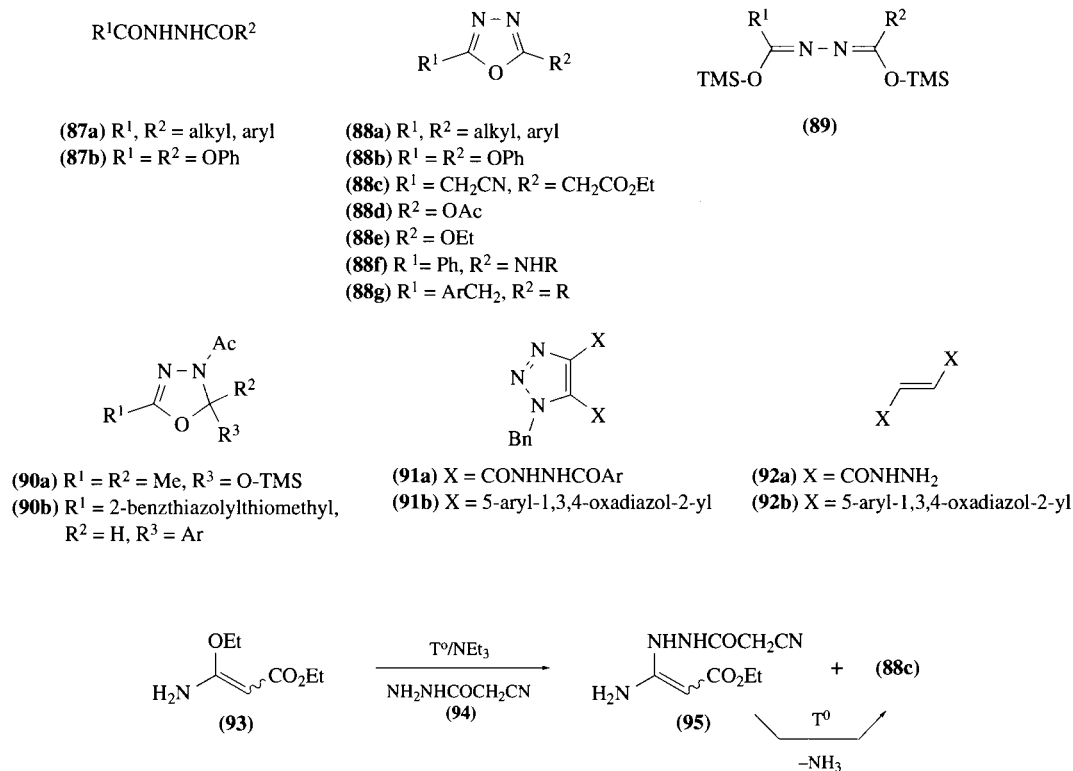
This section includes both new syntheses and variations on previously described syntheses <84CHEC-I(6)427>. The synthesis of interesting or novel oxadiazoles by established routes is also described. Unlike the arrangement in CHEC-I, reactions of two compounds which lead to a 1,3,4-oxadiazole are described in Section 4.06.9.2 (“two-bond cyclizations”), even though the final stage of the reaction may be a “one-bond cyclization” of an intermediate which was not isolated.

4.06.9.1 Cyclization with Formation of One Bond

Variations on the main route to 2,5-disubstituted 1,3,4-oxadiazoles (**88**) by cyclodehydration of 1,2-diacylhydrazines (**87a**), include the use of chlorosulfonic acid <83MI 406-01> or phenyl dichlorophosphite <82RRC935> in dimethylformamide. A nonaqueous, nonacidic, route to oxadiazoles (**88a**) involves treatment of hydrazine (**87a**) with hexamethyldisilazane and tetrabutylammonium fluoride, the last step presumably being fluoride-catalyzed cyclization of intermediate bis-silyl ether (**89**) <86SC1665>. In a related reaction, 1,1,2-triacetylhydrazine with trimethylsilyl chloride/triethylamine gave the oxadiazolinyl silyl ether (**90a**) <84IZV694>. Cyclodehydration ($\text{PCl}_5/\text{POCl}_3$) of diester (**87b**) gave the diphenoxyoxadiazole (**88b**) and “double” cyclization (POCl_3) of triazoles (**91a**) gave the triazole-bis-oxadiazoles (**91b**) <90JHC1685>. A “one-pot” reaction of fumaric acid dihydrazide (**92a**) and a substituted benzoic acid ArCO_2H in polyphosphoric acid yielded 1,2-di-oxadiazolylenes (**92b**) <88MI 406-02>.

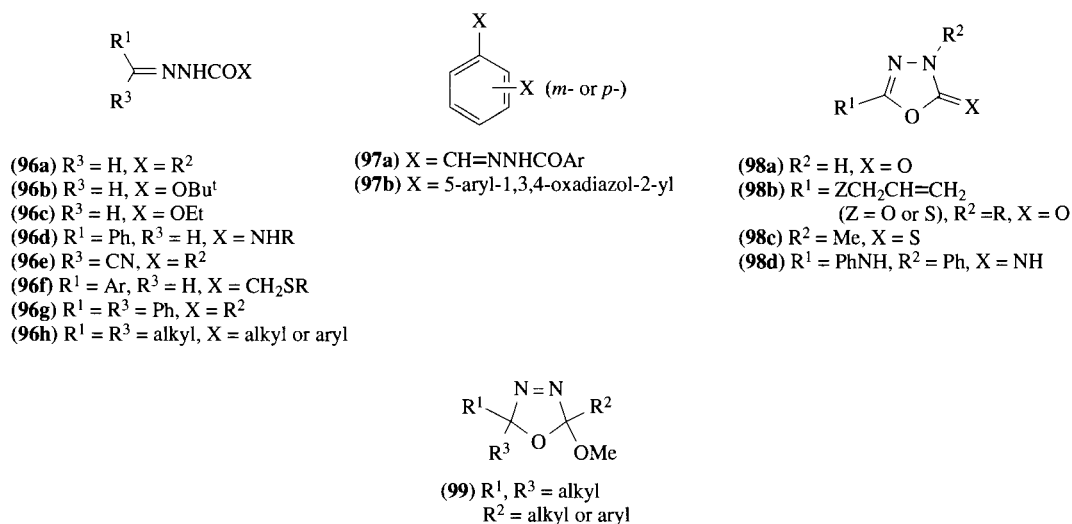
The malonate derivative (**93**) reacted with acylhydrazine (**94**) to give a mixture of diacylhydrazine monoenamine (**95**) and oxadiazole (**88c**), (Scheme 6) which was also formed from (**95**) on heating <88LA909>.

Oxidation of acylhydrazones (**96a**), derived from aldehydes, has been developed into a useful route to disubstituted oxadiazoles (**88a**). The use of solid potassium permanganate with acetone as solvent was claimed to give higher yields than the use of other oxidizing agents (e.g., halogens) <87JJC(B)890>. An “improved synthesis” of bis-oxadiazolylbenzenes (**97b**) involved oxidation of bis-hydrazones (**97a**) with lead tetraacetate <86S411>. Acylhydrazones (**96b**) were oxidized by iodosobenzene diacetate to oxadiazolinones (**98a**), with acetates (**88d**) also being formed in some cases. A similar oxidation of ethyl esters (**96c**) gave oxadiazolyl ethers (**88e**) <86JHC945>. Acylhydrazones



Scheme 6

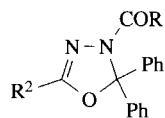
(96a) underwent electrolytic oxidation in methanol to form oxadiazoles **(88a)**, whereas the ketone derived acylhydrazones **(96h)** cyclized to Δ^3 -oxadiazolines **(99)**. Initial oxidation and deprotonation to cation $[\text{R}^1\text{R}^3\text{CN}=\text{NCOR}^2]^+$ was proposed <92JOC1375>. Oxidative cyclization ($\text{FeCl}_3/\text{AcOH}$) of semicarbazones **(96d)** yielded amino-oxadiazoles **(88f)** <82IJC(B)321>.



The cyanohydrazones **(96e)**, on heating in dimethyl sulfoxide, cyclized with loss of HCN to give unsymmetrical 2,5-disubstituted oxadiazoles **(88a)** <84S146>.

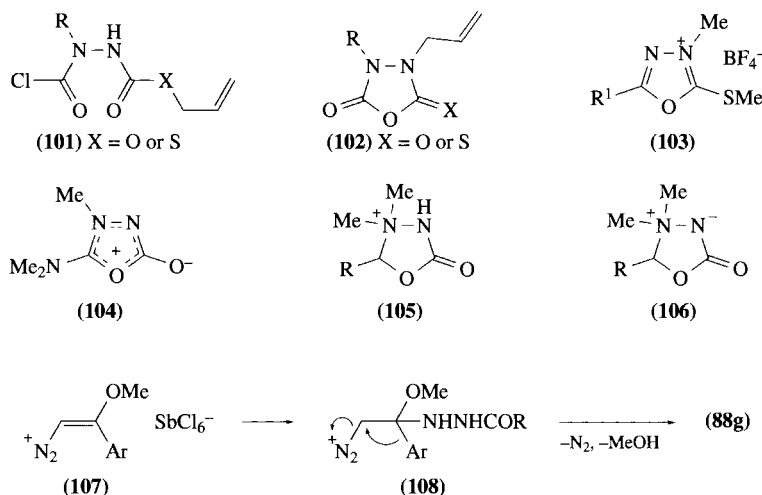
Nonoxidative cyclization of acylhydrazones in acetic anhydride yields 4-acetyloxadiazolines, as in the conversion of hydrazone **(96f; R = 2-benzthiazolyl)** into oxadiazoline **(90b)** <89MI 406-03>. Hydrazones derived from tetra-*O*-acetyl-D-arabinose cyclized ($\text{Ac}_2\text{O}/\text{ZnCl}_2$) to oxadiazoles pos-

sessing a chiral substituent <88CAR(182)19>. Benzophenone acylhydrazones (**96g**) cyclized on reaction with acid chlorides RCOCl to oxadiazolines (**100**) <85T5187>.



(100) R, R² = Me or Ph

Allyl esters (**101**), on treatment with diisopropylamine, formed oxadiazolinones (**102**), probably via Claisen rearrangement of an initially formed oxadiazolinone (**98b**) <88JOC38>. In a variation of the main route to Δ^2 -oxadiazoline-5-thiones (from dithiocarbazates $\text{RCONHNHCS}_2^- \text{M}^+$ (M = K or NH_4)), dithioates $\text{R}^1\text{CONHN}(\text{Me})\text{CS}_2\text{R}^2$ cyclized, on treatment with triethylamine, to oxadiazolinethiones (**98c**), which formed oxadiazolium salts (**103**) on reaction with trimethyl-oxonium tetrafluoroborate <88S690>. Acid-catalyzed cyclization of cyanosemicarbazide $\text{PhN}(\text{CN})\text{NHCONHPh}$ yielded the oxadiazolinimine (**98d**) <91EGP287255> and the isocyanate $\text{Me}_2\text{NCON}(\text{Me})\text{NCO}$ cyclized on heating to give the isosydnone (**104**) <86JOC3858>. A rare cyclization to a 1,3,4-oxadiazole, which involves C—N bond formation, occurred on heating hydrazide $\text{Me}_2\text{NNHCO}_2\text{CH}(\text{Cl})\text{R}$. The product (**105**) gave the aminimide (**106**) on treatment with base <86TL6319>. Acylhydrazides RCONHNH_2 add to alkenediazonium salts (**107**) at -20°C . Loss of nitrogen from adducts (**108**) leads to oxadiazoles (**88g**) in moderate yields (Scheme 7) <85CB4026>.

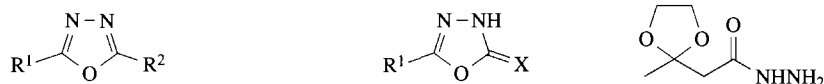


Scheme 7

4.06.9.2 Cyclization with Formation of Two Bonds

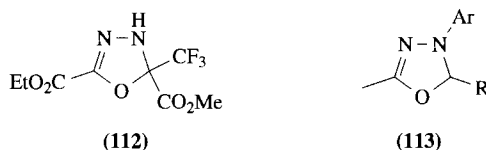
Important routes to monosubstituted oxadiazoles (**109a**), amino-oxadiazoles (**109b**), oxadiazolinones (**110a**), and oxadiazolinethiones (**110b**) involve reaction of hydrazides $\text{R}^1\text{CONHNH}_2$ with triethyl orthoformate, cyanogen bromide, phosgene, or carbon disulfide (or CSCl_2) respectively. Reaction of hydrazide (**111**) with triethyl orthoformate, or with CS_2/KOH , allowed the synthesis of oxadiazolymethyl ketones (**109c**) and (**110c**) respectively after hydrolysis (see Section 4.06.7.1) of the acetal group <82M793>. An alternative to cyanogen bromide is phenyl cyanate (PhOCN), which reacted with hydrazides $\text{R}^1\text{CONHNH}_2$ to give amino-oxadiazoles (**109b**; e.g., R^1 = 4,6-dimethyl-2-pyrimidinyl) <85PHA17>. From oxadiazole-2-carbohydrazides (**109d**) bi-oxadiazolyls (**109e**) and (**109f**) were prepared using cyanogen bromide <85JPR109>, or thiophosgene <90EUP364396> respectively. It has been shown that *o*-aminobenzoylhydrazine reacted (i) with 1,1'-carbonyl-bis-imidazole (a variation of the use of phosgene) to give oxadiazolinone (**110d**) <83H(20)571>, and (ii) with 1,3-dicyclohexylcarbodiimide and an isothiocyanate RNCS to give amino-oxadiazole (**109g**) <84JHC1807> (a variation of the oxidative cyclization of acyl-thiosemicarbazides to amino-oxadiazoles <84CHEC-I(6)427>). A variation of the reaction of acylhydrazines and carbon disulfide,

forming oxadiazolinethiones (**110b**), is the reaction of thiosemicarbazide RNHCSNHNH_2 with carbon oxysulfide and benzyl chloride, which yields amino-oxadiazolyl thioethers (**109h**) <91IJC(B)430>.



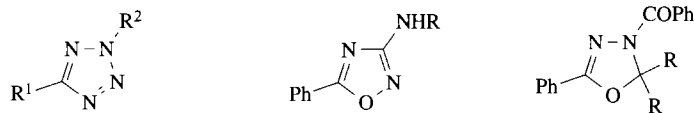
- (109a) R² = H
 (109b) R² = NH₂
 (109c) R¹ = CH₂Ac, R² = H
 (109d) R² = CONHNH₂
 (109e) R² = 5-amino-1,3,4-oxadiazol-2-yl
 (109f) R² = 5-mercapto-1,3,4-oxadiazol-2-yl
 (109g) R¹ = *o*-aminophenyl, R² = NHR
 (109h) R¹ = NHR, R² = SBn
 (109i) R¹ = Me, R² = OEt
 (109j) R¹ = Ph, R² = CH₂Ac
 (109k) R¹ = F₂NCF₂, R² = 5-F₂NCF₂-1,3,4-oxadiazol-2-yl
 (109l) R¹ = Ph, R² = NHR
 (110a) X = O
 (110b) X = S
 (110c) R¹ = CH₂Ac, X = S
 (110d) R¹ = *o*-aminophenyl, X = O
 (111)

Whereas trifluoromethyl ketones undergo cycloaddition with diazoalkanes PhC(R)N_2 to give Δ^3 -oxadiazolines <84CHEC-I(6)427>, ketoester $\text{CF}_3\text{COCO}_2\text{Me}$ reacts with diazoacetate $\text{N}_2\text{CHCO}_2\text{Me}$ to give Δ^2 -oxadiazoline (**112**) <88IZV127>. It has been shown that 1,3-dipolar cycloaddition of aldehydes RCHO to nitrilimines $\text{ArN}^-\text{—N}=\text{C}^+(\text{Me})$ (obtained on dehydrochlorination of chlorohydrazone MeC(Cl)=NNHAr) gave Δ^2 -oxadiazolines (**113**) <83JIC961>. The electrochemical reduction of fluorourethane EtOCONHF in acetonitrile yielded nitrene $\text{EtOCON}\dot{\text{N}}$, which underwent 1,3-dipolar cycloaddition with the nitrile group to form oxadiazole (**109i**) in low yield <84CJC768>.



4.06.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Two variations of the useful route to oxadiazoles (**109**) via loss of nitrogen from 3-acyltetrazoles (**114a**) are (i) the reaction of tetrazole (**114b**) with diketene to give the oxadiazolylmethyl ketone (**109j**) <76CPB2549>, and (ii) the reaction of oxalyl chloride with the sodium salt of tetrazole (**114c**) (prepared from $\text{F}_2\text{NCF}_2\text{CN}$ and NaN_3) to give the bi-oxadiazolyl (**109k**) <90JFC(47)333>. Ultraviolet irradiation of 1,2,4-oxadiazoles (**115**) gave 1,3,4-oxadiazoles (**109l**) <88JHC931>. On heating 3,3-dialkyl-*N,N'*-dibenzoyldiaziridines rearrange to oxadiazolines (**116**) <86CB2963>.



- (114a) R² = COR
 (114b) R¹ = Ph, R² = H
 (114c) R¹ = CF₂NF₂, R² = H

(115) R = H or Me

(116)

4.06.11 REVIEW OF RING SYNTHESIS

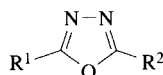
No important new general routes to 1,3,4-oxadiazoles have been reported since the mid-1980s. The major routes (as emphasized in both CHEC-I, and in the preceding two sections, 4.06.9.1 and 4.06.9.2) are (i) the formation of oxadiazoles by cyclodehydration of diacylhydrazines

$R^1\text{CONHNHCOR}^2$, (ii) the formation of oxadiazoles by oxidation of acylhydrazones $\text{RCH}=\text{NNHCOR}'$, and (iii) the formation of oxadiazolinones, oxadiazolinethiones, and amino-oxadiazoles by the action on hydrazides RCONHNH_2 of phosgene, carbon disulfide (or thiophosgene), and cyanogen bromide respectively.

4.06.12 APPLICATIONS

4.06.12.1 Biologically Active 1,3,4-Oxadiazoles

Bactericidal and/or fungicidal activity was reported for oxadiazoles (**117a**), amino-oxadiazoles (**117b**) <88JIC807> and oxadiazolinethiones (**118a**) <88IJC(B)542>. The tin derivative (**118b**) is an effective fungicide and antimicrobial activity is shown by thione (**118c**) <82IJC(B)321>. Anti-inflammatory, sedative, and analgesic properties were reported for diaryloxadiazoles (**117c**) <84FES414>. Amino-oxadiazoles (**117d**) show analgesic activity and amino-oxadiazoles (**117e**) exhibit both antiinflammatory and antiproteolytic properties <89JPS999>. Anticonvulsant and nervous system depressant activity was reported for amino-oxadiazoles (**117f**), where R is a quinazolin-3-yl group <91PHA290>. Amino-oxadiazoles (**117g**) show local anaesthetic activity <83JIC575>. The oxadiazolinone (**118d**) is an orally active antiallergic agent, for example in the treatment of asthma and allergy disease, and is claimed to be more potent than sodium cromoglycate <84JMC121>.



(**117a**) $R^1 = \text{Ar}$, $R^2 = \text{CH}_2\text{CONHCONHR}$

(**117b**) $R^1 = \text{ArOCH}_2$, $R^2 = \text{NHCOR}$

(**117c**) R^1 and $R^2 =$ trimethoxy- or 3,4-methylenedioxy-phenyl

(**117d**) $R^1 = 2\text{-pyridyl}$, $R^2 = \text{NR}_2\cdot\text{HCl}$

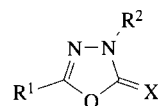
(**117e**) $R^1 = 4\text{-biphenyloxy-methyl}$, $R^2 = \text{NHAr}$

(**117f**) $R^1 = \text{Ar}$, $R^2 = \text{NHCH}_2\text{CONHR}$

(**117g**) $R^1 = \text{Ar}$, $R^2 = \text{NHCO}(\text{CH}_2)_n\text{NRR}'\cdot\text{HCl}$
($n = 2$ or 3)

(**117h**) $R^1 = \text{cyclopropyl}$, $R^2 = \text{SCONMe}_2$

(**117i**) $R^1 = R^2 = 4\text{-X-C}_6\text{H}_4$ ($\text{X} = \text{F}$ or NO_2)



(**118a**) $\text{X} = \text{S}$, $R^1 = \text{hetarylOCH}_2$, $R^2 = \text{H}$

(**118b**) $\text{X} = \text{O}$, $R^1 = 1\text{-methylcyclopropyl}$, $R^2 = \text{Sn}(\text{Ph})_3$

(**118c**) $\text{X} = \text{S}$, $R^1 = 5\text{-chloro-2-phenylindol-3-ylamino}$, $R^2 = \text{H}$

(**118d**) $\text{X} = \text{O}$, $R^1 = 3\text{-chlorobenzo[b]thiophen-2-yl}$, $R^2 = \text{H}$

(**118e**) $\text{X} = \text{O}$, $R^1 = 4\text{-cyclohexylphenoxy}$, $R^2 = \text{H}$

(**118f**) $\text{X} = \text{O}$, $R^1 = 2,4\text{-dichlorophenoxy-methyl}$, $R^2 = \text{Bn}$

(**118g**) $\text{X} = \text{O}$, $R^1 = \text{Bu}^t$, $R^2 = 2,4\text{-dichloro-5-isopropoxyphenyl}$

(**118h**) $\text{X} = \text{O}$, $R^1 = \text{OMe}$, $R^2 = o\text{-methoxyphenyl}$

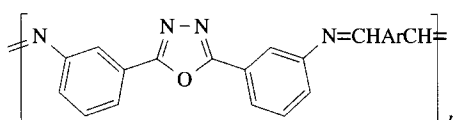
(**118i**) $\text{X} = \text{O}$, $R^1 = \text{MeNH}$
 $R^2 = 2,3\text{-dihydro-2,2,4-trimethylbenzofuran-7-yl}$

Examples of the many oxadiazolinones which show herbicidal activity (weed killers) are (**118e**), (**118f**), and "oxadiazon" (**118g**), which is the subject of many regular reports in the literature. Insecticidal activity is shown by oxadiazolinones (**118h**), (**118i**), (the latter is an aphicide), and oxadiazole (**117h**).

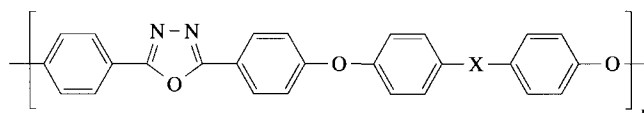
4.06.12.2 Polymers

It has been shown that 2,5-di-(3-aminophenyl)-1,3,4-oxadiazole reacts with aldehydes $\text{Ar}(\text{CHO})_2$ ($\text{Ar} = m\text{-}$ or $p\text{-phenylene}$) to give heat resistant polyazomethines (**119**), which are insulators, convertible into semiconductors by doping with iodine <92JPS(A)1369>. Polyazomethines having an alternative structure were prepared from aromatic diamines and oxadiazole-dialdehydes <90JPS(A)3647>. The activating effect of the oxadiazole ring in 4-fluoro- and 4-nitrophenyl-1,3,4-oxadiazoles allows nucleophilic displacement of these substituents. Thus 2,5-diaryloxadiazoles (**117i**) react with bis-phenols to give high MW polyethers (**120**) <92MM2021>.

A development in the synthesis of macromolecular scintillators is the radical co-polymerization of alkenes with the fluorescent co-monomer 2-*t*-butyl-5-(4'-vinyl-4-biphenyl)-1,3,4-oxadiazole <89MI 406-04>. Basic initiators cause ring opening of 2-phenyl-1,3,4-oxadiazolin-5-one with subsequent anionic polymerisation to form *N*-benzamido-1-nylon $[-\text{N}(\text{NHCOPh})\text{CO}-]_n$ <90PB583>.

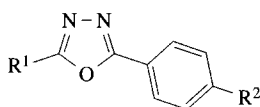


(119)

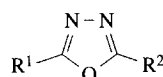
(120) eg. X = CMe₂, C(CF₃)₂

4.06.12.3 Luminescent Compounds, Dyes, and Photosensitive Materials

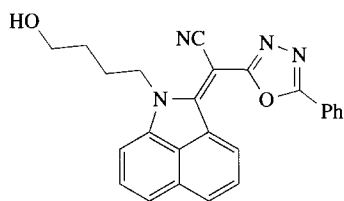
When part of an extended conjugated system, 2,5-disubstituted-1,3,4-oxadiazoles often fluoresce. This makes them potentially useful as laser dyes, optical brighteners, and scintillators. For example, oxadiazole **(121a)** <84GEP(O)3245202> and 1,4-bis-(5-phenyl-1,3,4-oxadiazol-2-yl)naphthalene <83GEP(O)3126464> are fluorescent whiteners on polyester. Applications of oxadiazole **(121b)** include use as a laser dye, a blue-emitting phosphor, a wide range of applications as a scintillator, and as an electron-transport layer in a thin-film electroluminescent device <91CL285>. Azo dyes (e.g. **(122a)**) find use in electrophotographic photoconductors and the use of the light-fast benzindole dye **(123)** in thermal-transfer recording sheets has been reported <92MIP9205032>. An example of a bright blue emitter in electroluminescent devices is 1,3-bis-[5-(*p*-dimethylaminophenyl)-1,3,4-oxadiazol-2-yl]benzene <92MI 406-01>.



(121a) R¹ = OEt, R² = 4'-benzoxazol-2-ylstyryl
(121b) R¹ = 4-*t*-butylphenyl, R² = Ph



(122a) R¹ = R² = 2,4-C₆H₃X₂ (X = 2-hydroxy-3-phenylcarbamoyl-1-naphthaleneazo)
(122b) R¹ = Et, R² = 4-(4-propylcyclohexyl)-phenyl
(122c) R¹ = Cl₃C, R² = 2-(benzofuran-2-yl)ethenyl
(122d) R¹ = N₃, R² = 4-(5-azido-1,3,4-oxadiazol-2-yl)butyl
(122e) R¹ = R² = 2,4,6-trinitrophenyl
(122f) R¹ = R² = 3-formyl-2-hydroxyphenyl



(123)

Oxadiazoles used as liquid-crystal components include **(122b)** <83JAP(K)58144378>. Trichloromethyloxadiazoles, in particular **(122c)** <84EUP118766>, yield a radical and HCl on irradiation. This makes them useful in photosensitive compositions (e.g., lithographic printing plates and photoresists) where image formation is acid-catalyzed or involves radical-initiated polymerization. The diazide **(122d)** (λ_{max} 240 nm) is a contrast enhancing material for deep UV lithography in microelectronic devices <89EGP268537>.

4.06.12.4 Other Applications

It is reported that 2,5-dipicryl-1,3,4-oxadiazole **(122e)** is an initiating explosive <88USP43262> and 2,5-dimethyl-1,3,4-oxadiazole has been used to extract aromatic hydrocarbons from mixtures with alkanes. A use of 4,4'-carbonylbis-(2-phenyl-5-oxo-1,3,4-oxadiazole) **(16b)** is as a blowing agent

for foaming thermoplastic compositions (e.g., polycarbonate) <85USP4500653>. Two molecules of dialdehyde (**122f**) react with two molecules of ethylenediamine or *o*-phenylenediamine to give a macrocycle which is potentially able to bind divalent metal cations, but has the disadvantage of insolubility <93JOC2628>.

4.07

1,2,3-Thiadiazoles

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4.07.1 INTRODUCTION

4.07.1.1 Background

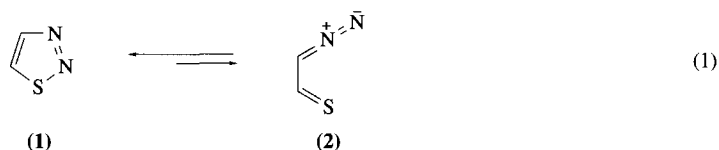
Chemists have been interested in 1,2,3-thiadiazoles since the late nineteenth century, but it was Hurd and Mori's synthesis of 1,2,3-thiadiazoles in 1955 that ushered in the modern era of research on this heterocycle <55JA5359>. Most of the 1,2,3-thiadiazole literature has dealt with thermal and photochemical reactions. However, exciting discoveries since the mid-1980s have expanded the knowledge of the thiadiazole ring. Modifications to syntheses have been developed, more extensive theoretical studies have been conducted, significant biological activity has been found and x-ray structures of simple 1,2,3-thiadiazoles are now available. Even with the surge of interest in thiadiazoles, of the four possible isomers, 1,2,3-thiadiazoles still account for the fewest literature citations. The gaps of our knowledge in this area are closing, but this isomer remains a fertile area of scientific endeavor.

4.07.1.2 Reviews

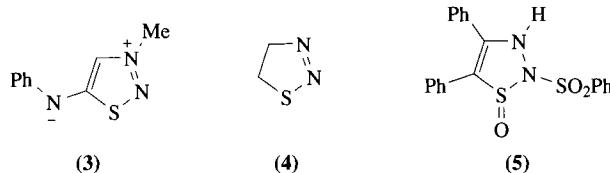
The 1,2,3-thiadiazole literature was extensively reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)447>. It covered the literature up to 1981 and cited many excellent previous references to 1,2,3-thiadiazoles. A further review on the chemistry of 1,2,3-selenadiazoles and 1,2,3-thiadiazoles, while comparing and contrasting these heterocycles, focused more on the former <90HAC1>. Another short review of 1,2,3-thiadiazoles addressed their rearrangement products <92PHC(4)128>. This review (second edition) covers the 1,2,3-thiadiazole literature up to the early part of 1994. It includes some references to CHEC-I when no reference to a particular subject is available between 1982 and 1994.

4.07.1.3 Possible Structures

The 1,2,3-thiadiazole (1) possesses three contiguous heteroatoms in a five-membered ring and exists as a remarkably stable neutral aromatic compound. It is isomeric with the ring opened α -diazothioketone (2) (Equation (1)) but although there is evidence that it reacts through this intermediate, all structural methods, including x-ray diffraction, point to (1) as the structure for a 1,2,3-thiadiazole.



1,2,3-Benzothiadiazoles have been extensively studied and their chemistry reviewed (84CHEC-1 (6)447). Fully aromatic mesoionic compounds such as (3) continue to be synthesized and studied but no review focusing on such systems has appeared. Very few examples of nonaromatic 1,2,3-thiadiazole derivatives such as (4) (93JOC82) and (5) exist and the area has not been reviewed.

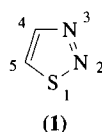


4.07.2 THEORETICAL METHODS

4.07.2.1 *Ab initio* Studies

Bond angles and lengths obtained from *ab initio* calculations on 1,2,3-thiadiazole (1) are presented in Table 1 (91JOM(405)309) and can be compared to values obtained for 4-phenyl-1,2,3-thiadiazole obtained by x-ray diffraction (Section 4.07.3.1). *Ab initio* calculations were also carried out for the ring protonated at N(2) and N(3). These calculations reveal that N(2) is the preferred site of protonation by almost 9 kcal/mol. This parallels the preferred site of metal coordination to 1,2,3-thiadiazoles found in several studies.

Table 1 Calculated molecular dimensions for 1,2,3-thiadiazole (1).



Bond lengths (nm)		Bond angles (°)	
S—N2	0.1676	C5—S—N2	102.8
N2—N3	0.1245	S—N2—N3	101.7
N3—C4	0.1375	N2—C3—C4	114.2
C4—C5	0.1346	N3—C4—C5	113.6
S—C5	0.1699	C4—C5—S	107.7

Frontier molecular orbital calculations have been employed successfully to predict reactions by examining the LUMO for nucleophilic substitution reactions and the HOMO for electrophilic reactions. Although these calculations have become quite routine, they unfortunately have not been applied to 1,2,3-thiadiazoles.

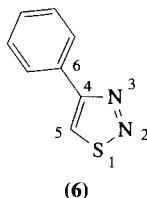
4.07.3 EXPERIMENTAL STRUCTURAL METHODS

4.07.3.1 X-ray Diffraction

Although x-ray diffraction methods remain the definitive structure proof, very few x-ray studies on 1,2,3-thiadiazoles exist and no structures have been published for 4,5-dialkyl substituted, nonionic 1,2,3-thiadiazoles. Recently 4-phenyl-1,2,3-thiadiazole and both the free and manganese cyclopentadienyldicarbonyl complex of 1,2,3-benzothiadiazole have been studied by x-ray diffraction (91JOM(405)309). The bond lengths and bond angles are listed in Table 2 for 4-phenyl-1,2,3-thiadiazole (6). The N(2)—N(3) and C(4)—C(5) bond lengths suggest nearly double bond character and the bond lengths of S—N(2) and S—C(5) indicate partial double bond character for both sulfur bonds suggesting that the ring is fully aromatic. Both the thiadiazole and benzene ring are essentially

flat but the torsional angle between both rings was not shown. The distance between C(4) and C(6) (0.1469 nm) is as expected for an sp^2-sp^2 carbon-carbon bond, perhaps indicating that the rings are skewed and that there is little conjugation between the two rings.

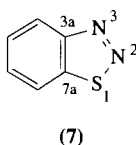
Table 2 Molecular dimensions for 4-phenyl-1,2,3-thiadiazole (6).



Bond lengths (nm)		Bond angles (°)	
S—N2	0.1666	C5—S—N2	93.2
N2—N3	0.1286	S—N2—N3	111.2
N3—C4	0.1378	N2—N3—C4	114.4
C4—C5	0.1363	N3—C4—C5	112.2
C5—S	0.1670	C4—C5—S	109.0
C4—C6	0.1469		

The bond lengths and bond angles found for benzo-1,2,3-thiadiazole (7) by x-ray are listed in Table 3. These values are quite close to those published for a substituted benzo-1,2,3-thiadiazole <84CHEC-I(6)447>. They are also quite similar to the values found for 4-phenyl-1,2,3-thiadiazole (6).

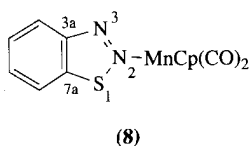
Table 3 Molecular dimensions for 1,2,3-benzothiadiazole (7).



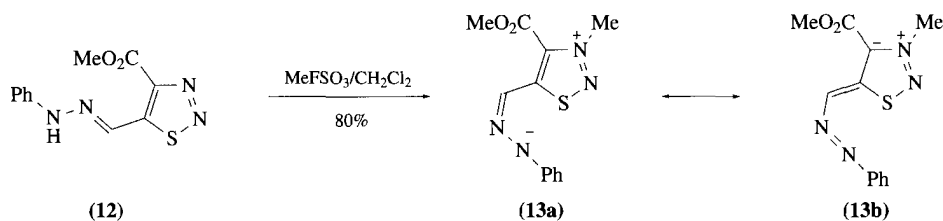
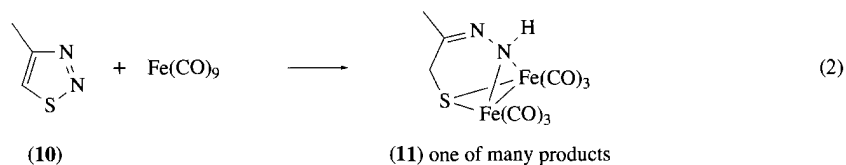
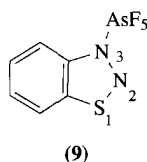
Bond lengths (nm)		Bond angles (°)	
S—N2	0.1706	C7a—S—N2	92.6
N2—N3	0.1279	S—N2—N3	112.7
N3—C3a	0.1384	N2—N3—C3a	113.4
C3a—C7a	0.1397	N3—C3a—C7a	114.2
C7a—S	0.1708	C3a—C7a—S	107.1

The bond lengths and angles for the manganese complex of 1,2,3-benzothiadiazole (8) are shown in Table 4. In compound (8) the thiadiazole ligand is intact and the manganese is bound to the nitrogen atom adjacent to the sulfur. *Ab initio* calculations show that N(2) is the preferred site of protonation (Section 4.07.2.1). Tables 2, 3, and 4, the structures of the free ligands and that of the complex with manganese show the heterocycle is essentially unaltered. The authors note, 'Whatever effect the metal may have upon the subsequent chemistry of the 1,2,3-thiadiazole is not reflected by any measurable structural changes upon coordination' <91JOM(405)309>.

The x-ray structure of 1,2,3-benzothiadiazole complexed with AsF₅ (9) shows that the arsenic binds at N3 <86CJC849>. When Fe₂(CO)₉ reacted with (10) one of the products was (11), for which x-ray diffraction revealed the unusual feature of the nitrogen and sulfur joined by an iron atom (Equation (2)) <89OM2961>. The mesoionic structure (13) is formed by methylation of 1,2,3-thiadiazole (12). It can best be described as a resonance hybrid of structures (13a) and (13b) and this was corroborated by the x-ray data (Scheme 1) <91JHC477>.

Table 4 Molecular dimensions for the thiadiazole portion of 1,2,3-benzothiadiazole · MnCp(CO)₂ (8).

Bond lengths (nm)		Bond angles (°)	
S—N2	0.1716	C7a—S—N2	92.7
N2—N3	0.1284	S—N2—N3	112.9
N3—C3a	0.1373	N2—N3—C3a	112.8
C3a—C7a	0.1417	N3—C3a—C7a	115.0
C7a—S	0.1705	C3a—C7a—S	106.5
N2—Mn	0.1970	S—N2—Mn	119.1

**Scheme 1**

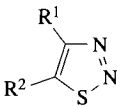
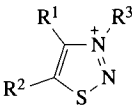
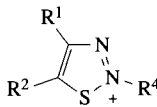
4.07.3.2 Proton NMR Spectroscopy

Proton NMR chemical shifts of 1,2,3-thiadiazoles give another indication as to the aromatic character of these compounds. Compiled in Table 5 are a number of examples of proton chemical shifts for ring substituted 1,2,3-thiadiazoles.

4.07.3.3 Carbon-13 NMR Spectroscopy

Carbon-13 NMR is often a more useful tool than ¹H NMR for the elucidation of heterocyclic structures in which there are few or no ring protons. For symmetrically substituted 1,2,3-thiadiazoles the carbon adjacent to the nitrogen atom is expected to have a lower field chemical shift than the carbon atom adjacent to the sulfur atom, as exemplified in a previous review (84CHEC-1(6)447). Several examples that follow this rule are illustrated in Table 6. A number of 4- and 5-substituted 1,2,3-thiadiazoles were studied by ¹³C NMR spectroscopy and the incremental effects of substituents

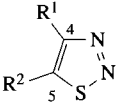
Table 5 Proton NMR spectral data for ring hydrogens of 1,2,3-thiadiazoles^a.

					
<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>δ</i> (Proton) for ring hydrogens	<i>Solvent</i>
				4	5
AB centered					
H	H			at	8.80
Me	H				8.20
H	Me			8.35	
H	Ph			8.70	
Ph	H				8.60
Ph	H	Me			9.93
Ph	H		Me		10.17

^aCited previously <84CHEC-I(6)447>.

on the C(4) and C(5) carbons of the 1,2,3-thiadiazole ring were tabulated <91BSB623>. With this more extensive body of data available it is possible to more accurately predict the chemical shift of ring carbons. In the case of mono-substituted 1,2,3-thiadiazoles the substituted carbon usually has a lower field chemical shift than the unsubstituted carbon.

Table 6 Carbon-13 NMR spectral data for ring carbons of 1,2,3-thiadiazoles.

					
<i>R</i> ¹	<i>R</i> ²	<i>Carbon-13 NMR (CDCl₃)</i> <i>for ring carbons</i> (ppm)		<i>Ref.</i>	
		4	5		
H	H	147.3	135.8	84CHEC-I(6)447	
Ph	H	163.9	130.9	84CHEC-I(6)447	
H	Ph	144.2	152.2	91BSB623	
Ph	Ph	157.5	150.8	84CHEC-I(6)447	
-(CH ₂) ₄ -		157.8	147.4	84CHEC-I(6)447	
-(CH) ₄ -		156.2	138.8	86CJC849	

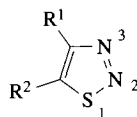
4.07.3.4 Nitrogen-15 NMR Spectroscopy

There are very few references to the ¹⁵N NMR of 1,2,3-thiadiazoles. The ¹⁵N NMR spectra of 15 monosubstituted 1,2,3-thiadiazoles have been published <93JHC301> and selected data are given in Table 7.

4.07.3.5 IR and UV Spectroscopy

Characteristic infrared absorptions for 1,2,3-thiadiazoles are: 1560–1475, 1350–1280 cm⁻¹ (ring skeletal); 1265–1200, 1190–1175, 1150–950 cm⁻¹ (ring breathing and CH in-plane deformations); and 910–890, 705–670 cm⁻¹ (CH out-of-plane deformations) <84CHEC-I(6)447>.

Simple 1,2,3-thiadiazoles show three absorption bands in the UV: 211–217 (ϵ_{max} 4380–5300), 249–253 (1460–2100), 290–294 (195–245) nm <84CHEC-I(6)447>.

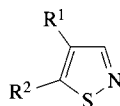
Table 7 Nitrogen-15 NMR spectral data for ring nitrogen of 1,2,3-thiadiazoles.

<i>R</i> ¹	<i>R</i> ²	Solvent	Nitrogen-15 NMR for ring nitrogens (ppm)	
			2	3
H	H	DMSO- <i>d</i> ₆	409.9	436.0
H	Et	CDCl ₃	403.7	434.5
H	CHO	CDCl ₃	427.2	438.4
Ph	H	DMSO- <i>d</i> ₆	411.2	433.3
Bu ^t	H	DMSO- <i>d</i> ₆	410.4	439.4
CHO	H	DMSO- <i>d</i> ₆	417.0	438.95

4.07.4 THERMODYNAMIC ASPECTS

4.07.4.1 Melting and Boiling Points

The parent compound, 1,2,3-thiadiazole (**1**), is a yellow liquid and its boiling point is 157°C at atmospheric pressure. When 1,2,3-thiadiazoles are heated above 200°C they usually decompose (Section 4.07.5). The melting and boiling points for a selection of substituted 1,2,3-thiadiazoles are presented in Table 8.

Table 8 Melting and boiling points for 1,2,3-thiadiazoles^a.

<i>R</i> ¹	<i>R</i> ²	<i>mp/bp</i> (mm) °C	<i>R</i> ¹	<i>R</i> ²	<i>mp/bp</i> (mm) °C
Ph	H	75–77	4-NO ₂ C ₆ H ₄	4-NO ₂ C ₆ H ₄	185.0–186.5
H	C ₆ H ₅	46–48, 90–100(0.2)	4-ClC ₆ H ₄	H	130.0–137.5
Ph	Ph	92–94	4-MeOC ₆ H ₄	Ph	81.5–82.5
—(CH ₂) ₁₀ —		29–32	Ph	4-MeOC ₆ H ₄	56.5–58.0

^aFound in <85JMC442>.

4.07.4.2 Solubility

No systematic study of the solubility characteristics of 1,2,3-thiadiazoles has been undertaken but most are freely soluble in methylene chloride and chloroform. The parent 1,2,3-thiadiazole (**1**) is soluble in alcohol, ether, and water. In contrast, a number of 1,2,3-thiadiazoles have been recrystallized from various alcohols and ethers <85JMC442, 88JHC1873>.

4.07.4.3 Chromatography

No systematic study of 1,2,3-thiadiazoles by TLC or GC has appeared, but as long as the temperatures for GC analysis are below 200°C (the approximate decomposition temperature for 1,2,3-thiadiazoles) this method should be satisfactory. Most simple thiadiazoles are isolated by distillation, and more complex structures are quite amenable to column chromatography <85JMC442, 88JHC1873>.

4.07.4.4 Aromaticity

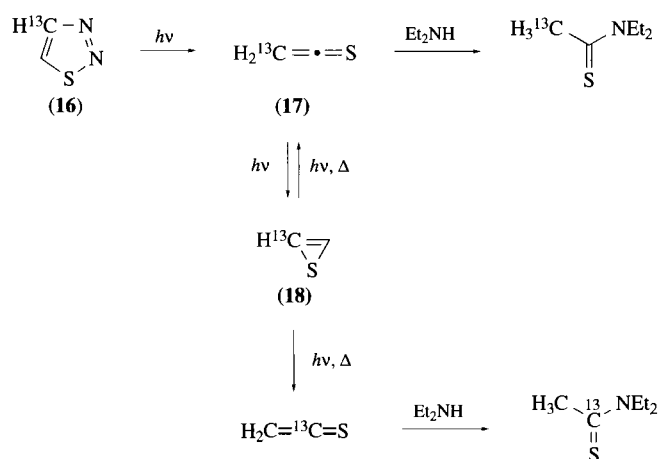
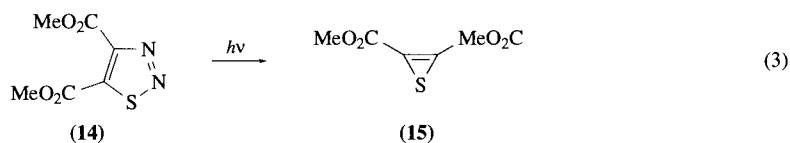
Rings incorporating $[4n + 2]$ π -electrons are aromatic according to the Hückel definition and on this basis 1,2,3-thiadiazoles can be considered as aromatic. This is supported by ^{13}C and ^1H NMR chemical shifts. In 1990, the aromaticities of some 5- and 6-membered ring heterocycles including 1,2,3-thiadiazole were studied by computational methods <90JPR885> and found to correlate well with their chemical natures.

4.07.5 REACTIVITY OF FULLY CONJUGATED RINGS

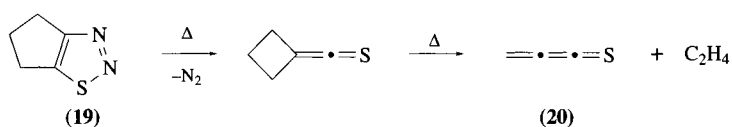
4.07.5.1 Thermal and Photochemical Reactions

4.07.5.1.1 Fragmentations

Upon photolysis of 1,2,3-thiadiazoles nitrogen is extruded and thiirenes can be formed, but their lifetime is fleeting as they rearrange to thioketenes. With the thought that electron withdrawing substituents would stabilize a thiirene, bis(carbomethoxy)-1,2,3-thiadiazole (**14**) was irradiated (10 K, 265 nm) in an argon matrix to form almost exclusively bis(carbomethoxy)thiirene (**15**), as determined by IR (Equation (3)). Upon further irradiation, (**15**) underwent fragmentation instead of forming a ketene <83ZN(B)1208>. Irradiation (247 nm) of ^{13}C labeled 1,2,3-thiadiazole (**16**) in Et_2NH yields the label scrambled *N,N*-diethyl thioacetamides. From the ^{13}C distribution in the products, it was deduced that fragmentation led primarily to the thioketene (**17**), and in a secondary photochemical reaction thiirene (**18**) was produced (Scheme 2) <92ACS482>. The pyrolysis of 1,2,3-thiadiazole (**19**) formed propadienethione (**20**) (Scheme 3) <88JA789, 90CPL(168)1>. Other workers also formed heterocumulenes by photolysis of substituted thiadiazoles <91CB2617>.

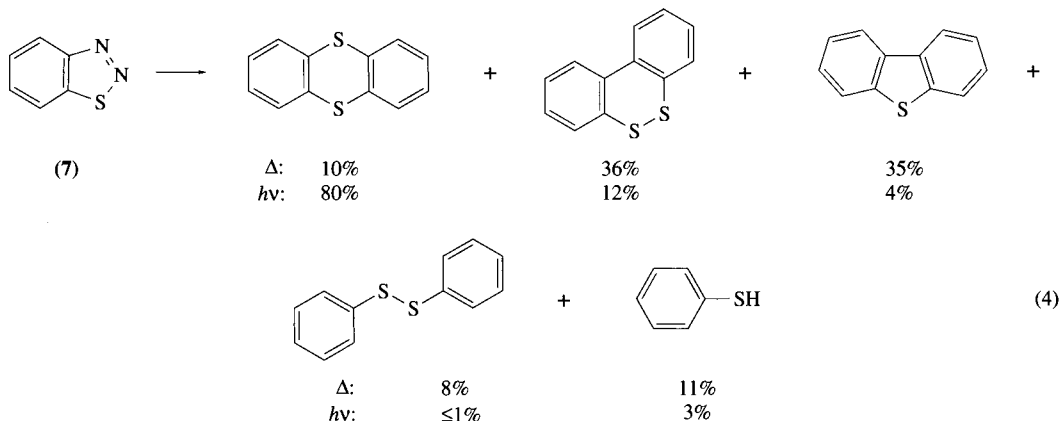


Scheme 2

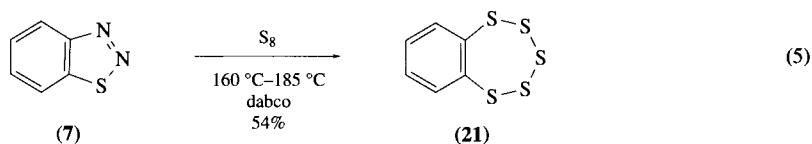


Scheme 3

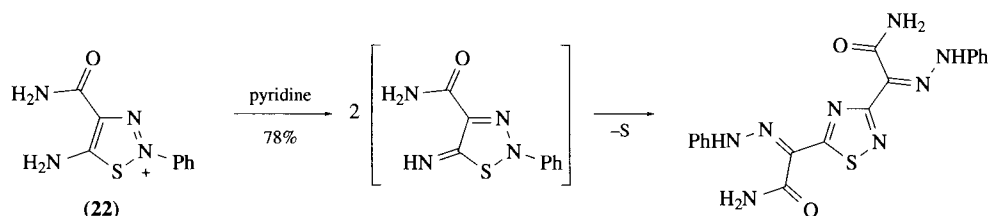
Unlike simple 1,2,3-thiadiazoles, 1,2,3-benzothiadiazoles do not form thioketenes on thermolysis or photolysis. Instead they yield many products, depending on the conditions (Equation (4)). The mechanisms of these reactions have been extensively studied ^[84CB107].



1,2,3-Benzothiadiazole (7), when heated in the presence of sulfur, first lost nitrogen and then reacted with sulfur to form benzopentathiepin (21) (Equation (5)) ^[84JOC1221]. This method has been extended to the synthesis of several heterocyclic ring compounds fused to pentathiepin starting from the corresponding 1,2,3-thiadiazolo heterocycle ^[85JA3871].

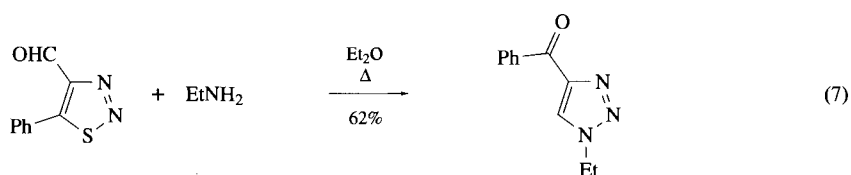
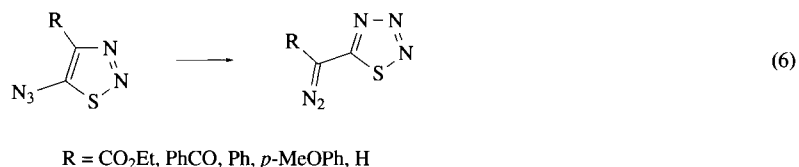


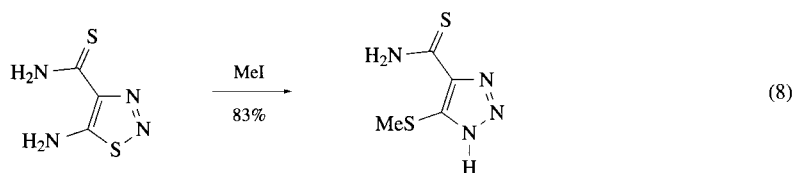
The 1,2,3-thiadiazole salt (22) when heated in pyridine affords a reactive intermediate that dimerizes with the extrusion of sulfur (Scheme 4) ^[86JPR741].



Scheme 4

L'abbé has studied the rearrangement reactions of 1,2,3-thiadiazoles to differently substituted 1,2,3-thiadiazoles ^[83CC588]. He also studied many 5-azido-1,2,3-thiadiazoles that rearranged to 1,2,3,4-thiadiazoles (Equation (6)) ^[88BSB163]. He even found that 1,2,3-thiadiazole-4-carboxaldehydes, upon treatment with amines, underwent thermal rearrangement to 1,2,3-triazoles (Equation (7)) ^[93JCS(P1)1719]. Others have found that methylation of 1,2,3-thiadiazole-4-carbothioamides yield 1,2,3-triazoles (Equation (8)) ^[90IZV938].





4.07.5.2 Electrophilic Attack at Aromatic Ring

1,2,3-Thiadiazoles are weak bases and form a deliquescent hydrochloride salt which is decomposed by water. No successful attempts to halogenate 1,2,3-thiadiazoles have appeared <84CHEC-I(6)447>.

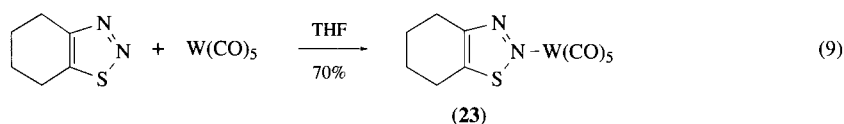
4.07.5.2.1 Electrophilic attack at nitrogen

There are several examples of alkyl halides reacting with 1,2,3-thiadiazoles at nitrogen to yield salts or mesoionic compounds <84CHEC-I(6)447>. Similarly, with Meerwein's reagent several substituted thiadiazoles yielded various 2- and 3-methylated 1,2,3-thiadiazoles (Table 9) <93JHC301>. The isomer ratios were determined by integrating the methyl singlets in the ^1H NMR spectra and the compounds were further studied by ^{15}N NMR spectroscopy (Section 4.07.3.4).

Table 9 Product distribution for the methylation of 1,2,3-thiadiazoles with Meerwein's reagent.

R^4	R^5	A (%)	B (%)
H	H	4	96
H	Cl		100
Ph	H	81	19
Bu ^t	H	87	13
CO ₂ Me	H	8	92

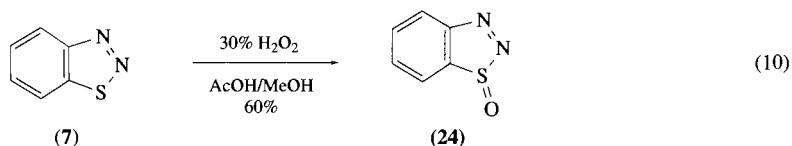
There are few examples of metal complexes reacting with 1,2,3-thiadiazoles to form stable products; one case involves the formation of the 2-substituted derivative (**23**) with tungsten pentacarbonyl (Equation (9)) <83CB230>. Reaction of simple 1,2,3-thiadiazoles with peracid occurs preferentially at N3 to give an *N*-oxide <84CHEC-I(6)447>.



4.07.5.2.2 Electrophilic attack at sulfur

Although electrophilic attack by peracids proceeds first at N(3) in simple 1,2,3-thiadiazoles, the sulfur can be oxidized by an excess of reagent to give an *N,S,S*-trioxide <84CHEC-I(6)447>.

However, reaction of 1,2,3-benzothiadiazole (**7**) with 30% hydrogen peroxide in mixture of acetic acid and methanol for 45 days afforded (**24**) in 60% yield (Equation (10) <90CJC1950>). Oxidation of (**7**) with a variety of other oxidizing agents (*m*-chloroperoxybenzoic acid, 30% hydrogen peroxide, hydrogen peroxide in methylene chloride–acetic acid mixtures, etc.) was unsuccessful.



4.07.5.3 Nucleophilic Attack at Aromatic Ring

There are few clear examples of reactions involving nucleophilic attack at the 1,2,3-thiadiazole ring. The chlorine in 5-chloro-1,2,3-thiadiazole is displaced by methoxide ion <74JHC343> and there is evidence that the fragmentation of 4,5-diphenyl-1,2,3-thiadiazole resulting from reaction with butyl lithium is initiated by attack at sulfur <71OPP163>.

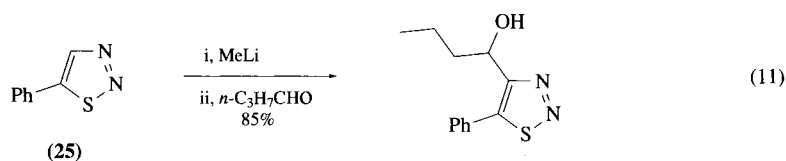
4.07.6 REACTIVITY OF NONCONJUGATED RINGS

Little is known about the reactivity of nonconjugated 1,2,3-thiadiazoles since few of these compounds are known (Section 4.07.1.3).

4.07.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4.07.7.1 Reactions at Hydrogen

Ring protons of 1,2,3-thiadiazoles are known to undergo rapid deuterium exchange under basic conditions, yet to date there have been no published estimates or experiments to determine the pK_a of these protons. Few attempts have even been made to metalate and alkylate this heterocycle. One study <85S945> found that metalation of 5-phenyl-1,2,3-thiadiazole (**25**) with methyl lithium gives 4-lithio-5-phenyl-1,2,3-thiadiazole, which is stable and reacts with aldehydes and ketones in high yields (Equation (11)). Also, treatment of 4-phenyl-1,2,3-thiadiazole with lithium diisopropylamide, in the presence of TMS-Cl, affords 4-phenyl-5-trimethylsilyl-1,2,3-thiadiazole.

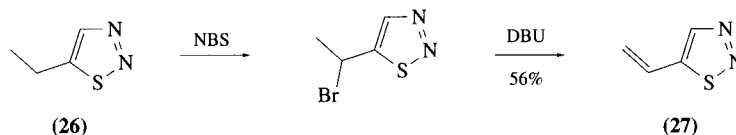


4.07.7.2 Reactions at C-linked Substituents

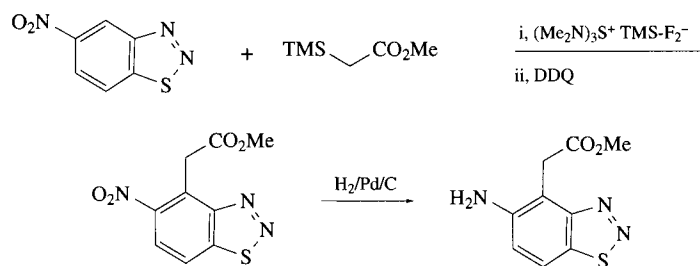
Benzylic positions are easily brominated, and this is the case for alkyl substituted 1,2,3-thiadiazoles. Thus 5-ethyl-1,2,3-thiadiazole (**26**) was readily brominated and subsequent elimination afforded the vinyl thiadiazole (**27**) (Scheme 5) <86LA1334, 86LA1344>. To prevent polymerization of the vinyl thiadiazole hydroquinone was added during the elimination step.

The naphthalene-like, aromatic structure of 1,2,3-benzothiadiazole imparts stability to the system which survives exposure to 20% potassium hydroxide at 150°C or 27% sulfuric acid at 200°C. It is not oxidized by potassium permanganate, potassium ferricyanide, chromic acid and dilute nitric acid <B-61MI 407-01>. Electrophilic substitution occurs in the benzo ring, predominantly at the 4-position. Chlorine in the 6-position is displaced by a variety of nucleophiles <75SST670>.

Nitro-substituted 1,2,3-benzothiadiazoles undergo an interesting reaction with methyl (trimethylsilyl)acetate (Scheme 6) <86JOC1704>. The benzothiadiazole is also stable to the conditions used to reduce the nitro group to the amine.



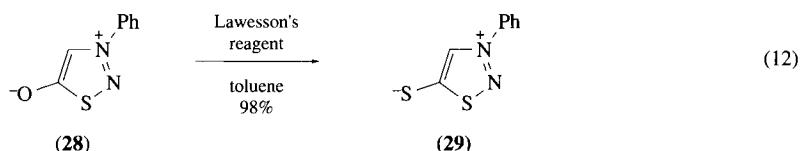
Scheme 5



Scheme 6

4.07.7.3 Reactions at O-linked Substituents

Mesoionic compounds (Section 4.07.1.3) are fully aromatic and usually have an exocyclic heteroatom, bearing a charge, attached to the ring. A new one-step method for converting the exocyclic oxygen of 3-phenyl-1,2,3-thiadiazolium-5-olate (28) into the exocyclic sulfur of 3-phenyl-1,2,3-thiadiazolium-5-thiolate (29) makes use of Lawesson's reagent (Equation (12)) <88BCJ2977>.



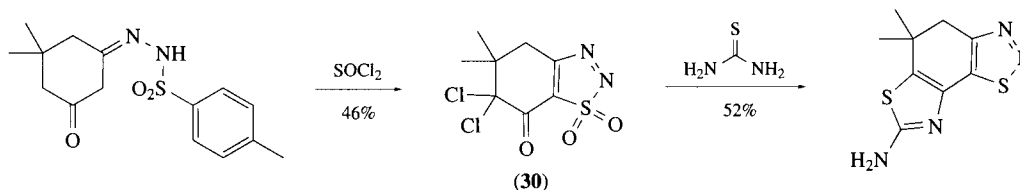
4.07.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

4.07.8.1 Substituents Attached to Nitrogen

The most familiar examples of 1,2,3-thiadiazoles bearing substituents on nitrogen are mesoionic compounds (Section 4.07.1.3) but little is known about the reactivity of such substituents.

4.07.8.2 Substituents Attached to Sulfur

Normally following the Hurd and Mori procedure a tosylhydrazone is converted with thionyl chloride to the corresponding thiadiazole. In one case under these conditions, the dioxide (30) was isolated <91PS(60)175> and subsequently deoxygenated with thiourea (Scheme 7).

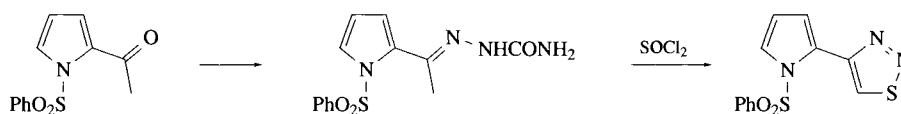


Scheme 7

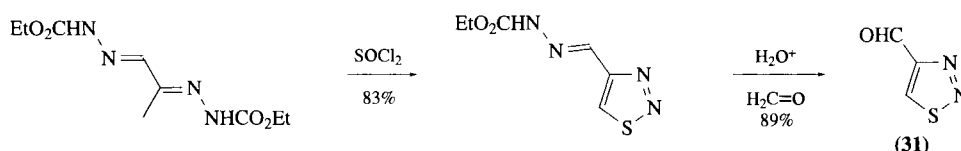
4.07.9 SYNTHESIS

4.07.9.1 From Hydrazones and Thionyl Chloride: Four Atoms Plus One Atom

A simple and elegant synthesis of 1,2,3-thiadiazoles from alpha-methylene ketones was developed in 1955 by Hurd and Mori (Section 4.07.11.1) <55JA5359>. This method has stood the test of time and continues to be the method of choice when a number of diverse 1,2,3-thiadiazoles are synthesized <85JMC442>. One can also produce heterocyclic substituted 1,2,3-thiadiazoles <90MI 407-01> under these conditions, as long as in the case of pyrrole a suitable protecting group is employed (Scheme 8). Furthermore, the useful starting material 4-formyl-1,2,3-thiadiazole (**31**) is available on large scale by this procedure (Scheme 9) <92SL95>. Both the mechanism <82JCS(P1)1223> and the regiochemistry <93H(36)33> of the Hurd and Mori reaction have been studied.

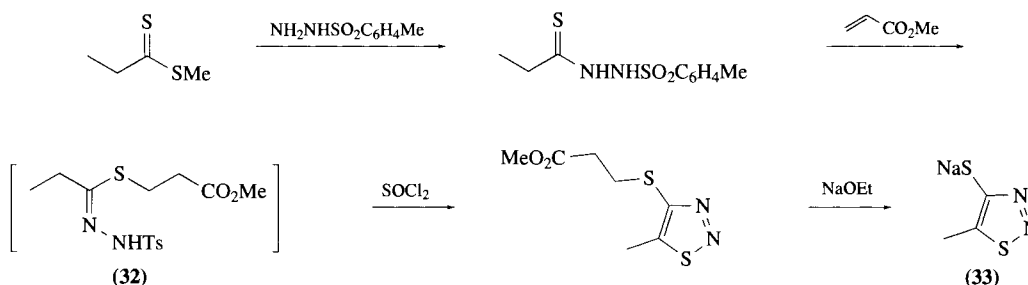


Scheme 8



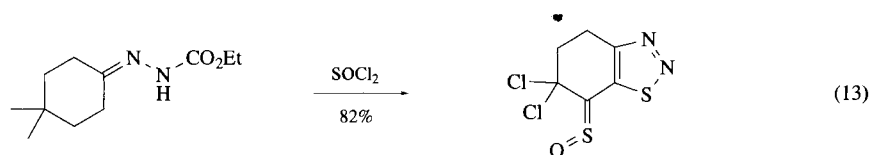
Scheme 9

The previously unreported 1,2,3-thiadiazole-4-thiolate (**33**) was synthesized by an extension of Hurd and Mori's cyclization procedure <88JHC1873> in which methyl dithiopropionate was converted to intermediate (**32**). This was cyclized with thionyl chloride to the 1,2,3-thiadiazole and the protecting group removed to give thiolate (**33**) (Scheme 10).



Scheme 10

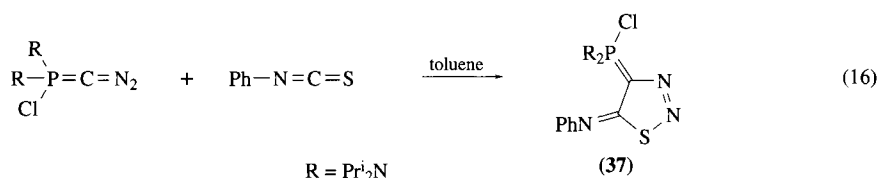
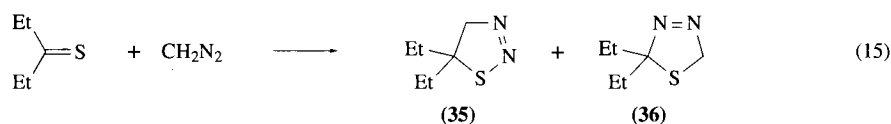
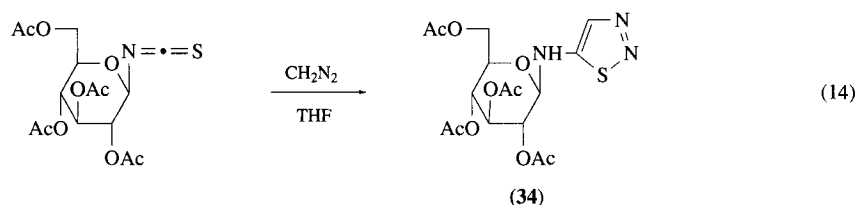
This method is also useful for the functionalization of substituents at C(5) during 1,2,3-thiadiazole formation (Equation (13)). The ratio of thiadiazoles and their sulfine derivatives is a function of both the acyl and alkylidene groups of the hydrazone starting materials <84JOC4773>.



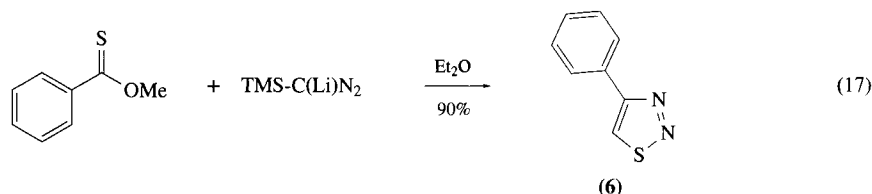
4.07.9.2 Dipolar Cycloaddition Reactions: Three Atoms Plus Two Atoms

Pechmann and Nold utilized the reaction of diazomethane with phenyl isothiocyanate for one of the earliest syntheses of a 1,2,3-thiadiazole <84CHEC-I(6)447>. This method continues to be used <82MI 407-01> for the synthesis of 5-amine substituted 1,2,3-thiadiazoles (**34**), and 4,5-disubstituted

1,2,3-thiadiazoles (Equation (14)) <88SUL155>. Thioketones were reacted with diazomethane to form 1,2,3-thiadiazolines and 1,3,4-thiadiazolines <89TL7045>. Depending on the solvent, different ratios of (35):(36) are produced (Equation (15)). This reaction has been studied in further detail by semiempirical calculations <93JOC82> and the higher ratio of 1,2,3-thiadiazoline products in more polar solvents can be explained by the higher dipole moment of the transition structure. The nonaromatic 1,2,3-thiadiazole derivative (37) was also formed by a cycloaddition route (Equation (16)) <92BSF367>.

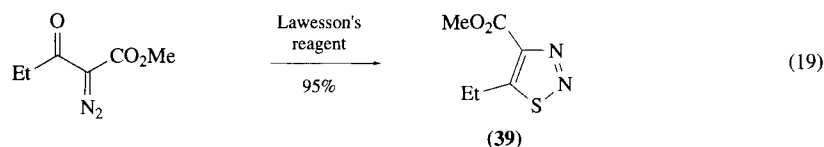
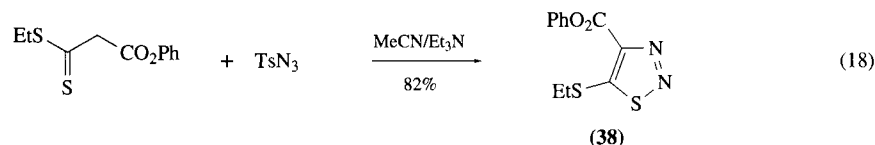


A very similar reaction to that of Pechmann and Nold but which probably does not proceed through a dipolar cycloaddition manifold is the formation of 1,2,3-thiadiazole (6) via a thionoester and lithium trimethylsilyldiazomethane (Equation (17)) <86H(24)589>. Lithium trimethylsilyldiazomethane also reacts with thioketones to produce 1,2,3-thiadiazoles <87H(26)1467>.



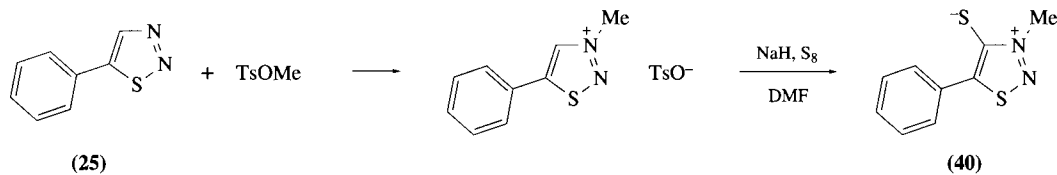
4.07.9.3 From Diazocarbonyl Compounds

Wolff's synthesis of 1,2,3-thiadiazoles from diazoketones is also one of the earliest methods for forming this ring. Others have used this method with minor modifications to produce an array of 1,2,3-thiadiazoles. For example, thiadiazole (38) was formed by a diazotransfer reaction on the dithiomalonate precursor (Equation (18)) <86SC917> and the 1,2,3-thiadiazole (39) was obtained from a diazoketone with Lawesson's reagent (Equation (19)) <86JOC4075>; see also <89T7329, 92S1150>.



4.07.9.4 Mesoionic Compounds

Mesoionic compounds are often synthesized from the parent 1,2,3-thiadiazole. For example, (40) was synthesized from 5-phenyl-1,2,3-thiadiazole (Scheme 11) <83CPB1746>.

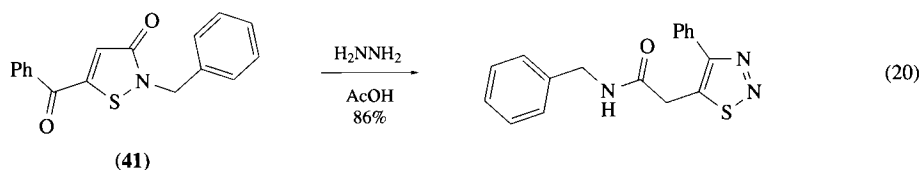


Scheme 11

4.07.10 SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

4.07.10.1 Synthesis From Other Heterocycles

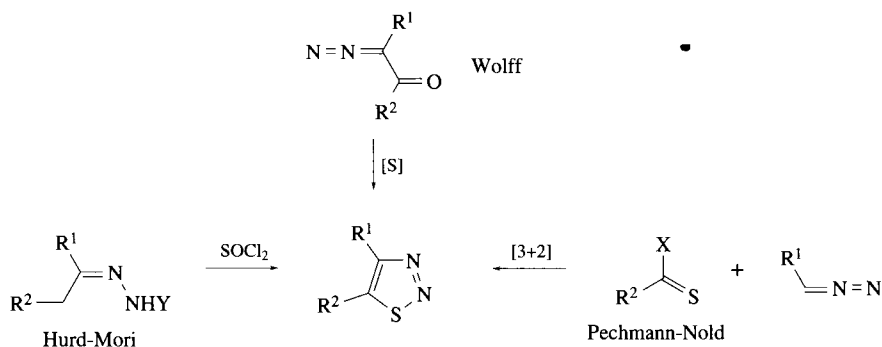
A number of examples of the transformation of other heterocycles into 1,2,3-thiadiazoles were collected in the first edition <84CHEC-1(6)447>. Few other examples have since appeared; one interesting case is the reaction of isothiazolone (41) with hydrazine to form a 1,2,3-thiadiazole (Equation (20)) <84JHC1679>.



4.07.11 SYNTHESIS OF 1,2,3-THIA DIAZOLES AND A CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

4.07.11.1 Comparison of Literature Methods

Scheme 12 shows synthesis of 1,2,3-thiadiazoles by the Wolff, Hurd–Mori and Pechmann–Nold methods. Pechmann's and Wolff's are the oldest of the methods. The Pechmann–Nold synthesis involves the [3 + 2] cycloaddition of diazo-compounds to isothiocyanates or thiocarbonyl compounds (modified Pechmann synthesis). The use of thiocarbonyl compounds in the [3 + 2] cycloaddition step has broadened the scope of this reaction and made the starting materials more readily accessible. Wolff's method requires the synthesis of diazoketones that are treated with a thionating reagent to produce 1,2,3-thiadiazoles. With the development of new methods of diazotransfer reactions, the diazoketone precursors have become easily attainable and with further attention to the thionating reagents, this reaction is also useful for the synthesis of 1,2,3-thiadiazoles.



Scheme 12

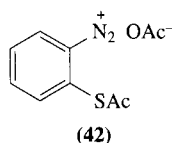
Although introduced over 40 years ago, Hurd and Mori's synthesis of 1,2,3-thiadiazoles remains the most widely used for the synthesis of 1,2,3-thiadiazoles. The simplicity of the method has contributed to its popularity. A variety of ketones and aldehydes have been converted into their corresponding hydrazones (tosyl and acyl), and thioamides have been converted into thio-carbazone esters. The carbonyl derivatives are then treated with thionyl chloride to yield 1,2,3-thiadiazoles in high yields. When one is faced with the task of synthesizing new 1,2,3-thiadiazoles, Hurd and Mori's method should always receive attention.

4.07.11.2 Comparison of New Methods

No new method for the synthesis of 1,2,3-thiadiazoles has appeared since that of Hurd and Mori. The most significant modification of this method since 1985 is Lee's synthesis of 4-thiasubstituted 1,2,3-thiadiazoles <88JHC1873>. A very interesting modification of Pechmann and Nold's method is the substitution of lithium trimethylsilyldiazomethane for diazomethane in the formation of 1,2,3-thiadiazoles <86H(24)589>. It is important to note that substitution of reagents here also changes the mechanism of the reaction.

4.07.11.3 1,2,3-Benzothiadiazoles

1,2,3-Benzothiadiazoles can be obtained by diazotization of *o*-aminothiophenols although yields tend to be variable. Thermal decomposition of the diazonium acetate (**42**) provides a modification which gives benzothiadiazole in good yield <78SST431>. Benzothiadiazoles can also be obtained, again in variable yields, by reaction of aromatic amines with S₂Cl₂ and treatment of the resulting benzothiazothiazolium salt with nitrous acid <70JCS(C)2250>. Diazo oxides on treatment with P₂S₅ also give benzothiadiazoles <B-61MI 407-01>.



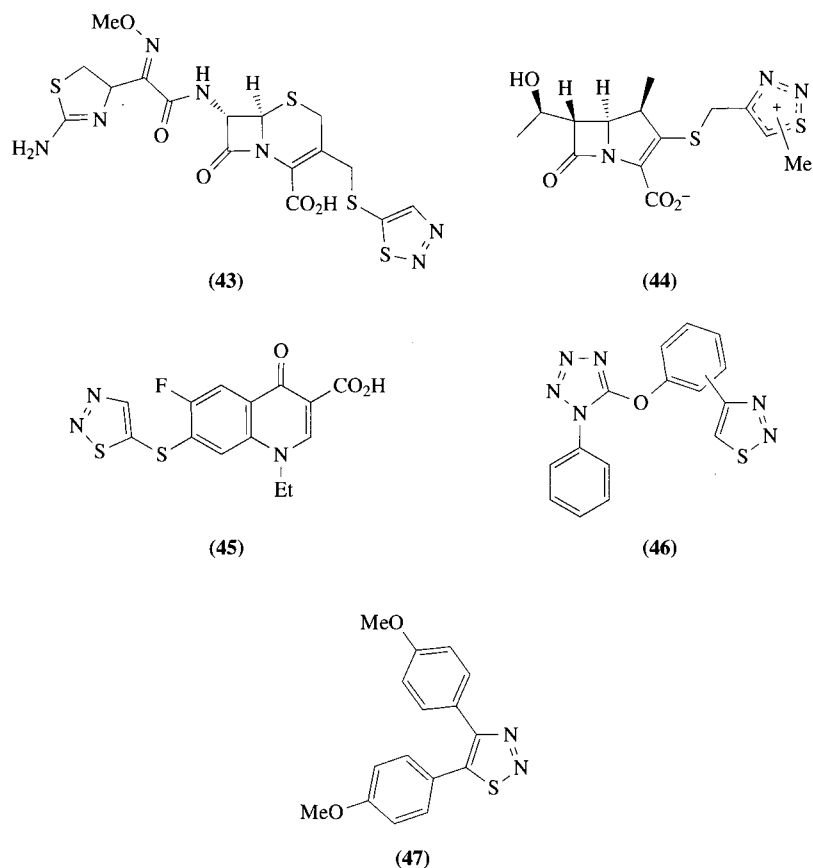
4.07.12 IMPORTANT COMPOUNDS AND APPLICATIONS

4.07.12.1 Antibiotics

A traditional template for antibiotics is the β -lactam ring and many novel entities have been produced by varying the attached appendages. Thiadiazole (**43**), a β -lactam derivative, was active against Gram-negative bacteria and showed activity against Gram-positive organisms including *Staphylococcus aureus* <83JAN179>. Others have taken the backbone of (**43**) and modified the methyl oxime to a 4-pyridone derivative forming another cepham antibiotic with broad antibacterial activity <91AAC104>. Carbapenems (**44**) similarly exhibited strong antimicrobial activity <92JOC4243>. The 1,2,3-thiadiazole ring has also been appended to the quinolone antibiotic template affording the quinolone (**45**) which is more potent than nalidixic acid but slightly less potent than pefloxacin <89JHC1141>. A simple 1,2,3-thiadiazole derivative (**46**) is as potent as penicillin G in an *in vitro* inhibition zone assay <90PJS417>.

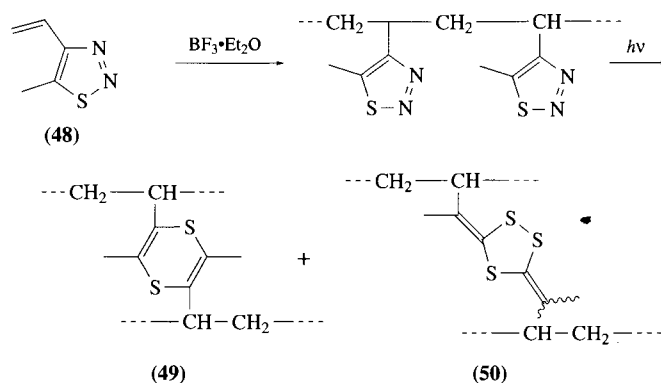
4.07.12.2 Cardiovascular Agents

In order to ameliorate the atherosclerotic complications of cardiovascular diseases, various means of inhibiting platelet aggregation have been investigated. Several 1,2,3-thiadiazoles were synthesized by the Hurd and Mori's method as collagen-induced inhibitors of platelet aggregation <85JMC442>, the most potent being compound (**47**).



4.07.12.3 Polymers

As detailed in Section 4.07.5.1, 1,2,3-thiadiazoles undergo facile photochemical fragmentation with extrusion of nitrogen. This property of 1,2,3-thiadiazoles has been utilized as a new type of photo-cross-linking of polymers ^[82CC481, 86LA1353]. The 4-vinyl-1,2,3-thiadiazole (**48**) was polymerized by a cationic chain process, and under these conditions the 1,2,3-thiadiazole remained intact (Scheme 13). Upon irradiation ($\lambda \geq 230$ nm, CH_2Cl_2 , RT) of the polymer the thiadiazole ring underwent fragmentation and the resulting diradical crosslinked affording subunits (**49**) or (**50**) in the final product (Scheme 13).



Scheme 13

4.08

1,2,4-Thiadiazoles

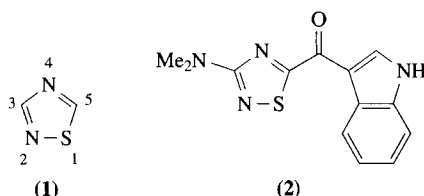
DAVID J. WILKINS and PAUL A. BRADLEY
Knoll Pharmaceuticals, Nottingham, UK

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4.08.1 INTRODUCTION

1,2,4-Thiadiazole (**1**) was first prepared and characterized in 1955 but products containing this ring system were described as early as 1821. A natural product containing the 1,2,4-thiadiazole nucleus was not reported until 1980. Dendrodoine (**2**) is a cytotoxic material isolated from the marine tunicate *Dendrodoa grassularia* [84CHEC-I(6)463].



The information published prior to 1980 was obtained from the extensive reviews by Kurzer [65AHC(5)119, 82AHC(32)285] and the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) [84CHEC-I(6)463]. For the period 1980–1993, a CAS on-line search was used to obtain the majority of literature references.

1,2,4-Thiadiazole is classified as a π -excessive sulfur-containing heteroaromatic compound [84CHEC-I(6)463]. The 1,2,4-thiadiazole nucleus is numbered as in (1). The double bonds in the partially reduced rings are designated Δ^2 , Δ^3 , Δ^4 , respectively (Figure 1) and these compounds are called thiadiazolines. The fully reduced ring is termed a thiadiazolidine.

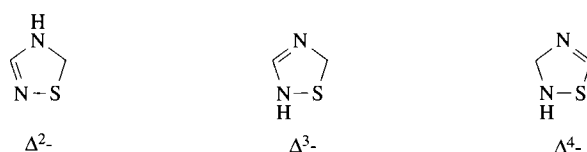


Figure 1 1,2,4-Thiadiazole nucleus showing partially reduced rings (thiadiazolines).

4.08.2 THEORETICAL METHODS

The 5-position of the nonprotonated 1,2,4-thiadiazole system was calculated to be the most reactive in nucleophilic substitution reactions using a simple molecular orbital method with LCAO approximation <84CHEC-I(6)463>.

1,2,4-Thiadiazole has been subjected to AM1 calculations <90JPR885>. The results were used to predict the degree of aromatic character of the heterocycle. Some energetic and magnetic parameters were also calculated. Electrostatic potentials at N-2 and N-4 have been calculated for 3,5-dimethyl-1,2,4-thiadiazole; the results for this compound and other 5-substituted 3-methyl-1,2,4-thiadiazoles were then used to predict binding to cortical muscarinic receptors <90JMC2052>.

4.08.3 EXPERIMENTAL STRUCTURAL STUDIES

4.08.3.1 Molecular Spectra

X-ray crystallographic techniques have greatly aided progress in deducing the chemistry of 1,2,4-thiadiazoles. The structures of a number of 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines have been determined by x-ray techniques, and are listed in Table 1.

The bond lengths and angles determined by double resonance modulation microwave spectroscopy are shown in Figure 2 <84CHEC-I(6)463>.

Table 1 X-ray crystal data for 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines.

Compound	Ref.
5-(<i>N</i> -Methylthiocarbamoylimino)-4-phenyl-3-phenylamino-4 <i>H</i> -1,2,4-thiadiazoline	81AX(B)1419
2-Ethyl-4-phenyl-5-phenylimino-1,2,4-thiadiazolidin-3-thione	86BCJ987
5-(1-Imino- <i>N</i> -methylethylamino)-3-methyl-1,2,4-thiadiazole	81AX(B)180
3,4-Dimethyl-5-thioformyl-4 <i>H</i> -1,2,4-thiadiazoline	81AX(B)1449
5-[(1-Aminoethylidene)amino]-3-chloromethyl-1,2,4-thiadiazole	81AX(B)185
3-Cyano-1,2,4-thiadiazole-5-carboximidate	84CB2681
5-Imino- Δ^3 -1,2,4-thiadiazoline	81JHC1309
3,5-Bis(diphenylamino)-1,2,4-thiadiazole	85AX(C)1329
4-Ethyl-5-ethylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine	80AX(B)2703
3,4-Diphenyl-5-(4-nitrophenyl)- Δ^2 -1,2,4-thiadiazoline	86JCR(S)156

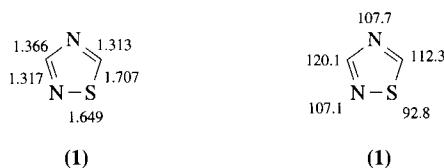


Figure 2 Bond lengths (Å) and angles (°) of 1,2,4-thiadiazole.

4.08.3.2 UV Spectra

1,2,4-Thiadiazole has an absorption maximum at 229 nm ($\log \epsilon$ 3.7). The introduction of amino groups into the heteroaromatic nucleus results in a bathochromic shift. Thus, $\lambda_{\max}$ due to the 1,2,4-thiadiazole ring is moved to 247 nm in 5-amino and to 256 nm in 3,5-diamino-1,2,4-thiadiazole <84CHEC-I(6)463>.

4.08.3.3 IR Spectra

The review by Kurzer <65AHC(5)119> contains a table of IR spectral absorptions of 1,2,4-thiadiazoles which covers spectra published before 1965. Spectral data published between 1965 and 1980 is covered in CHEC-I <84CHEC-I(6)463>.

The prominent IR peaks for 1,2,4-thiadiazoles were attributed as follows: to ring skeletal vibrations (1560–1590 cm^{-1} , 1490–1550 cm^{-1}), to ring breathing and CH in-plane deformations (1215–1270 cm^{-1} , 1080–1185 cm^{-1} , 1020–1050 cm^{-1}), and to CH out-of-plane deformations ($\approx 735 \text{ cm}^{-1}$ and 795–860 cm^{-1}) <82AHC(32)285>.

4.08.3.4 NMR Spectra

Proton NMR spectral data appear throughout the literature. In general the chemical shifts of the protons in 1,2,4-thiadiazoles are downfield from benzene, the C-3 proton being farther downfield than the C-5 proton. For example, the C-5 proton in 3-phenyl-1,2,4-thiadiazole resonates at $\delta 9.9$ whereas the C-3 proton in 5-phenyl-1,2,4-thiadiazole resonates at $\delta 8.66$ <84CHEC-I(6)463>.

The relationship between the structure of 1,2,4-thiadiazolidines and their ^1H NMR spectral solvent effects has been studied by measurement of the NMR chemical shift differences ($\Delta\nu$) of 39 derivatives in various solvents (C_6D_6 , CCl_4); for methyl or methylene groups attached to an sp^2 -hybridized nitrogen, $\Delta\nu$ correlates linearly with Hammett σ constants and for those attached to an sp^3 -hybridized nitrogen, with Taft σ° constants <82AHC(32)285>.

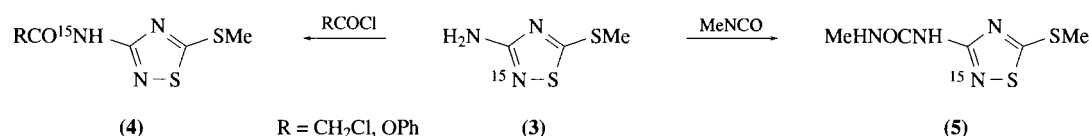
Carbon-13 NMR spectral data have appeared more widely in the literature over the past 12 years. The ^{13}C NMR chemical shifts for a variety of 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines derivatives are listed in Table 2.

Table 2 ^{13}C NMR Spectral data for 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines.

Compound	C-3 (δ)	C-5 (δ)	Ref.
2-Methyl-5-phenyl-1,2,4-thiadiazol-3(2H)-one	165.8	177.0	84JCS(P1)75
3-Phenyl-5-trichloromethyl-1,2,4-thiadiazole	173.9	190.5	86PS(26)151
3,5-Diphenyl-1,2,4-thiadiazole	188.1	173.8	83BCJ180
3-Azido-5-phenyl-1,2,4-thiadiazole	155.8	168.1	86CC800
3-Amino-5-phenyl-1,2,4-thiadiazole	171.0	185.7	86CC800
3-Ethoxycarbonyl-4-methyl-5-phenylimino-1,2,4-thiadiazoline	148.0	162.9	91JHC333
3-Ethoxycarbonyl-5-methylimino-4-phenyl-1,2,4-thiadiazoline	148.9	162.3	91JHC333
4-Methyl-5-phenylimino-3-(<i>p</i> -toluenesulfonyl)-1,2,4-thiadiazoline	154.9	161.8	91JHC333
4-Methyl-5-methylimino-3-(<i>p</i> -toluenesulfonyl)-1,2,4-thiadiazoline	155.5	161.9	91JHC333
3,5-Bis(ethoxycarbonylamino)-1,2,4-thiadiazole	158.2	176.8	89M997
4-Methyl-3-trichloromethyl-1,2,4-thiadiazolin-5-thione	154.4	200.9	91JOC3268
4-Methyl-3-(<i>p</i> -toluenesulfonyl)-1,2,4-thiadiazolin-5-thione	157.5	199.2	91JOC3268
4-Methyl-3-ethoxycarbonyl-1,2,4-thiadiazolin-5-thione	150.5	199.4	91JOC3268
3,4-Diphenyl-5-(<i>p</i> -nitrophenyl)- Δ^2 -1,2,4-thiadiazoline	155.6	74.5	86JCR(S)156

Solvent and concentration effects in nitrogen NMR studies can be very significant. The ^{14}N NMR chemical shifts for 1,2,4-thiadiazole (1) in ether solution (1 : 3 v/v) are +106 for N-2, and +70 for N-4. These values are shielded with respect to nitromethane. A similar degree of shielding is observed in the ^{14}N NMR spectra of 1,2,4-oxadiazole and in 1,2,5-thiadiazole <84OMR(22)215>.

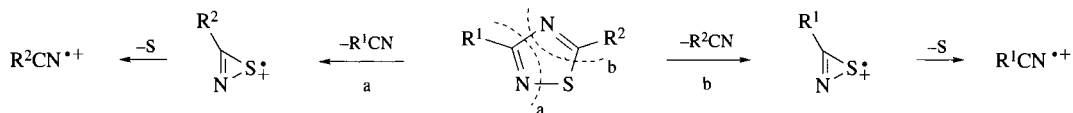
Nitrogen-15 NMR has been used to study the course of acylation and carbamidization reactions of 3-amino-5-methylthio-1,2,4-thiadiazole (3). Using a ^{15}N label in the 2-position of (3), its reaction with “hard” nucleophiles was found to proceed via initial reaction on the 2-position followed by a Dimroth rearrangement to give the acylated product (4) with the ^{15}N label in the exocyclic position. The reaction of (3) with “soft” nucleophiles, such as methyl isocyanate occurs directly on the exocyclic nitrogen to give the urea (5) (Scheme 1) <84CHEC-I(6)463>.



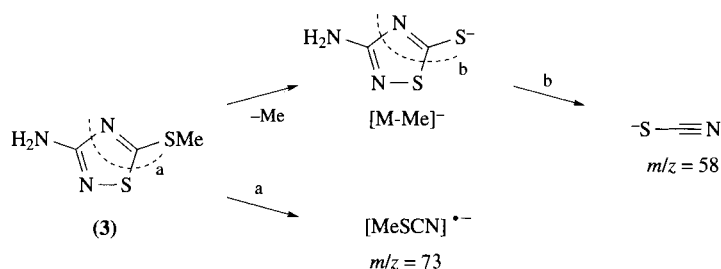
Scheme 1

4.08.3.5 Mass Spectra

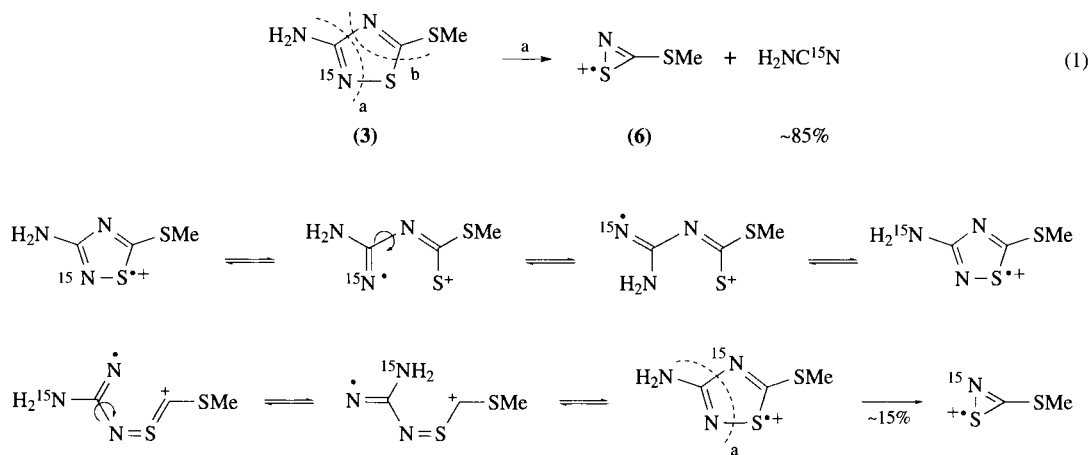
The mass spectra of 3,5-disubstituted 1,2,4-thiadiazoles follow two general fragmentation pathways (a and b) which are illustrated in Scheme 2 <84CHEC-I(6)463>.



A comparison between the positive and negative ion mass spectra of 3-amino-5-methylthio-1,2,4-thiadiazole (3) has been published <85JPR1017>. The positive ion spectrum follows the general pathway (Scheme 2) whereas the negative ion spectrum fragments to give the thiocyanate ion as the major fragment (Scheme 3).



The positive ion mass spectrum of 3-amino-5-methylthio-1,2,4-thiadiazole (3) has also been studied using ^{15}N isotopes. When a ^{15}N label was incorporated into the 2-position or the exocyclic nitrogen a 13–16% incorporation of the ^{15}N label was found in the mercaptothiazirinium ion (6) (Equation (1)). This incorporation is explained by a series of Dimroth rearrangements (Scheme 4) <86MI 408-01>.



4.08.4 THERMODYNAMIC ASPECTS

4.08.4.1 Intermolecular Forces

1,2,4-Thiadiazole (1) is a liquid at room temperature. The effects of substituents on melting and boiling points can be summarized as follows. Compounds with simple alkyl substituents in the 3-

and 5-positions are oils. Compounds with an aryl group in the 3- or 5-position are low melting solids and substitution of a second aryl group raises the melting point by approximately 60°C. Compounds containing an amino, hydroxy, or mercapto group are usually relatively high melting solids because of hydrogen bonding. Halo compounds tend to be oils or low melting solids.

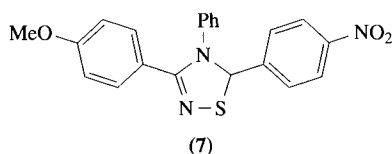
4.08.4.2 Stability and Stabilization

The heat of formation (ΔH_f) for 1,2,4-thiadiazole has been reported <90JPR885> but values for other thermodynamic functions (entropy, heat capacity, and free energy) are not available.

The thermal decomposition of some 3,5-disubstituted 1,2,4-thiadiazoles has been studied and some nonisothermal kinetic parameters have been reported <86MI 408-02>. Polarographic measurements of a series of methylated 5-amino-1,2,4-thiadiazoles show that thiadiazoles are not reducible in methanolic lithium chloride solution, while thiadiazolines are uniformly reduced at $E_{0.5} = -1.6 \pm 0.02$ V. This technique has been used to assign structures to compounds which may exist theoretically as either thiadiazoles or thiadiazolines <84CHEC-I(6)463>. The photoelectron spectrum for 1,2,4-thiadiazole has been published <84CHEC-I(6)463>.

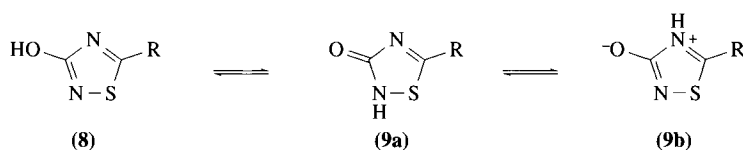
4.08.4.3 Conformation

X-ray crystallographic studies on 1,2,4-thiadiazoles (Table 1) show the 1,2,4-thiadiazole ring to be essentially planar. The x-ray structure of 4-phenyl-5-(*p*-nitrophenyl)-3-(*p*-methoxyphenyl)- Δ^2 -1,2,4-thiadiazoline (7) shows that the 1,2,4-thiadiazoline ring has a 30° fold around the S(1)–N(4) vector; atoms S-1, N-2, C-3 and N-4 are nearly co-planar <86JCR(S)156>.



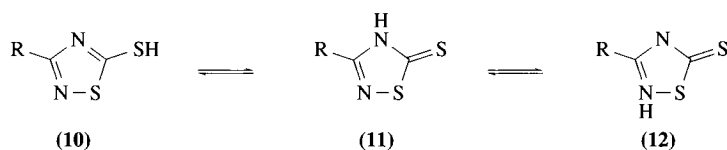
4.08.4.4 Tautomerism

3-Hydroxy-1,2,4-thiadiazoles can exist in three tautomeric forms (Scheme 5). Chemical evidence suggests that the OH form (8) predominates. However, UV data suggest that the lactam form (9) is the major tautomer in ethanol <84CHEC-I(6)463>.

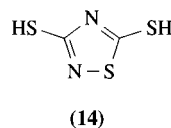
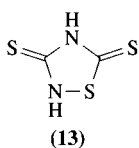


Scheme 5

3-Amino and 5-amino-1,2,4-thiadiazoles both exist predominantly in the amino forms. The IR spectrum of 5-mercapto-1,2,4-thiadiazole does not show a clear SH absorption as would be expected for structure (10), therefore the thione tautomers (11) and (12) have been suggested (Scheme 6). Similarly IR evidence suggests that perthiocyanic acid exists as the dithione (13) as opposed to (14) <84CHEC-I(6)463>.



Scheme 6



4.08.5 REACTIVITY OF FULLY CONJUGATED RINGS

4.08.5.1 General Survey

The parent compound is quite sensitive to acid and alkali, as well as to oxidizing and reducing agents. Studies of the nonfunctionalised ring system have employed homologs of 1,2,4-thiadiazole because substituents at the 3- and 5-positions stabilize the ring toward acid, alkali, oxidizing agents and reducing agents <65AHC(5)119>.

The 5-position in 1,2,4-thiadiazoles is most reactive in nucleophilic substitution reactions, for example, halogens may be displaced by a variety of nucleophiles <84CHEC-I(6)463>. However, halogens in the 3-position are inert towards most nucleophilic reagents.

Electrophilic reactions of 1,2,4-thiadiazoles are very limited. The parent base forms salts with mineral acids. It also forms a methiodide, and gives addition compounds with heavy-metal salts.

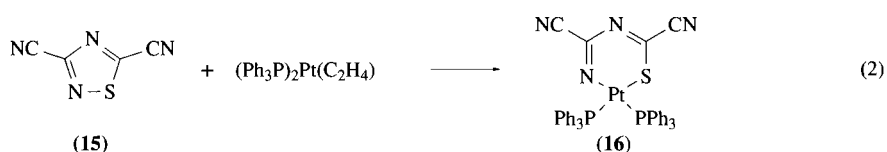
4.08.5.2 Thermal and Photochemical Reactions

1,2,4-Thiadiazoles are generally quite stable to heat due to the aromatic nature of the ring. Their thermal stability is influenced by the nature of the 3- and 5-substituents <65AHC(5)119>. Mass spectral decomposition patterns of substituted 1,2,4-thiadiazoles are discussed in Section 4.08.3.5.

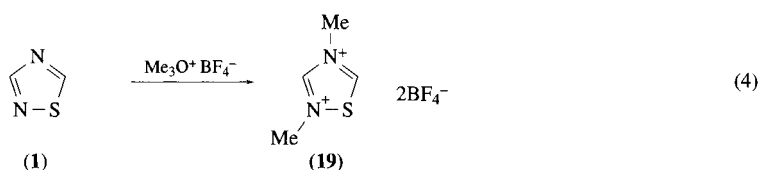
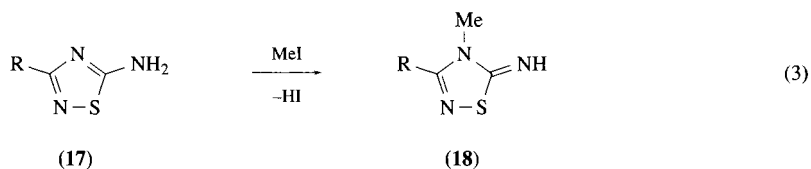
Photochemical behavior of 1,2,4-thiadiazoles has not been studied to date.

4.08.5.3 Electrophilic Attack at Nitrogen

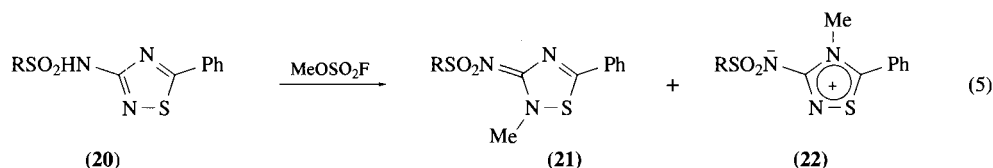
1,2,4-Thiadiazoles are weak bases. They form salts with mineral acids and addition compounds with heavy-metal salts. Ethenebis(triphenylphosphane)platinum(0) reacts with 1,2,4-thiadiazole-3,5-dicarbonitrile (**15**) to give a chelate complex. Insertion of platinum takes place at the S—N bond to give the six-membered metalloheterocycle (**16**) (Equation (2)) <84AG(E)971>.



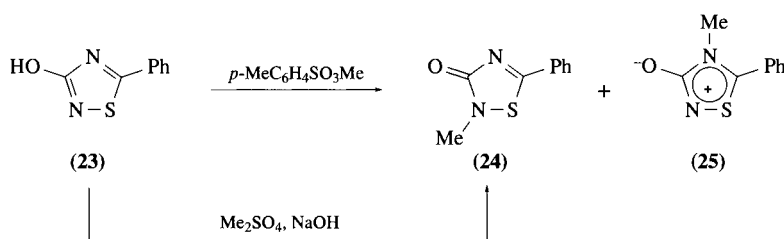
Methylation of 5-amino-1,2,4-thiadiazoles (**17**) (R = H, Ph) leads to N-4 derivatives (**18**) (Equation (3)) <84CHEC-I(6)463>. The diquaternary salt (**19**) of 1,2,4-thiadiazole (**1**) is obtained when trimethyloxonium tetrafluoroborate is used as the methylating agent (Equation (4)) <72JOC2259>.



Reaction of the sulfonamide (20) ($R = p\text{-Tol}$) with methylfluorosulfonate gives the N-2 derivative (21) ($R = p\text{-Tol}$) and the meso-ionic compound (22) ($R = p\text{-Tol}$) (Equation (5)) <84JCS(P1)75>.

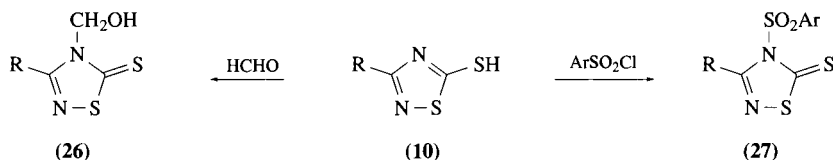


Methylation of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (23) with dimethyl sulfate and sodium hydroxide at room temperature gives the N-2 compound (24). When methylation is carried out using methyl toluene-4-sulfonate at 100°C compound (24) and the meso-ionic derivative (25) are produced (Scheme 7) <84JCS(P1)75>.



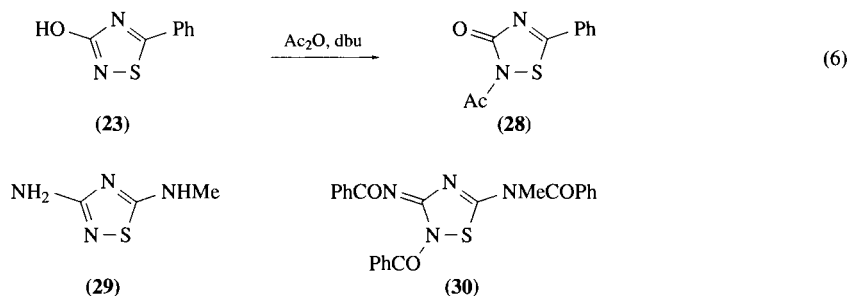
Scheme 7

Reaction of 3-phenyl-1,2,4-thiadiazole-5-thiol (10) ($R = \text{Ph}$) with formaldehyde and with aryl-sulfonyl chlorides leads to N-4 derivatives (26) and (27) (Scheme 8) <89MI 408-01>.



Scheme 8

The triacyl compound (30) is obtained when an excess of benzoyl chloride is used in the acylation of 3-amino-5-methylamino-1,2,4-thiadiazole (29). However, when acetic anhydride is used no ring nitrogen acylated product is obtained <84CHEC-I(6)463>. Acetylation of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (23) with acetic anhydride and dbu at room temperature gives a small amount of the N-2 compound (28) (Equation (6)) <85JHC1497>.



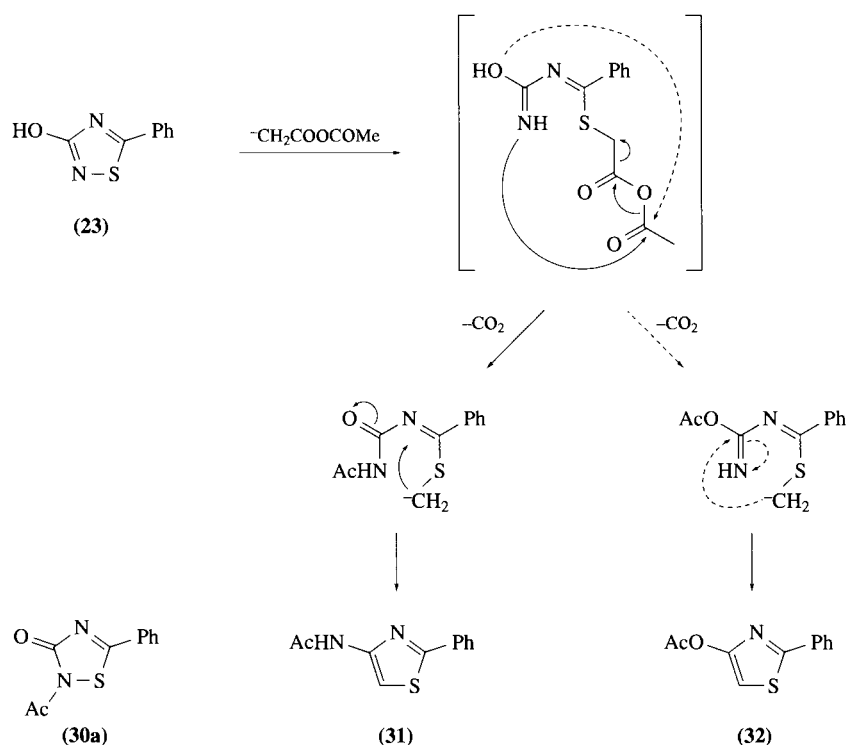
4.08.5.4 Electrophilic Attack at Carbon

Electrophilic reactions at the ring carbons of 1,2,4-thiadiazole are virtually unknown.

4.08.5.5 Electrophilic and Nucleophilic Attack at Sulfur

Although 1,2,4-thiadiazole 1,1-dioxides are known, they cannot be prepared by direct oxidation as ring cleavage occurs giving sulfate ion. They are only accessible by cyclization of precursors in which the sulfur is already oxidised.

Nucleophilic attack at sulfur is implicated in many reactions of 1,2,4-thiadiazoles <84CHEC-I(6)463> and in general “soft” nucleophiles attack at sulfur. For example, reaction of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**23**) with acetic anhydride in the presence of dbu at 130°C gives the thiazoles (**31**) and (**32**) <85JHC1497>. These products may be reasonably explained by the mechanism outlined in Scheme 9 in which the thiadiazole ring is opened by the acetic anhydride carbanion. There is some evidence that (**32**) may arise from attack of the carbanion on the *N*-acylated derivative (**30a**) (Scheme 9) <85JHC1497>.



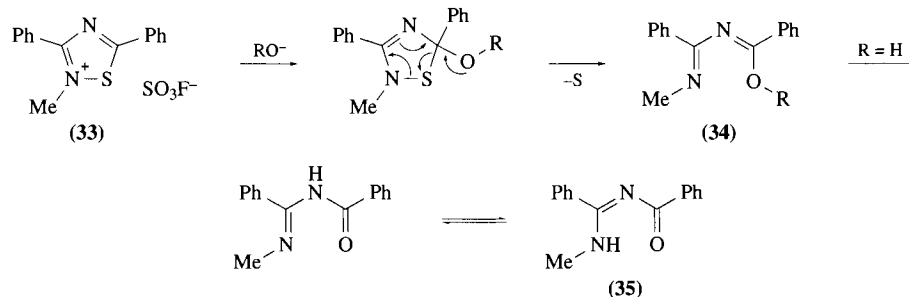
Scheme 9

4.08.5.6 Nucleophilic Attack at Carbon

Substituents in the 3- and 5-positions of 1,2,4-thiadiazoles exert a marked stabilizing effect on the heterocyclic ring towards alkalis and reducing agents. Thus, the parent compound is rapidly decomposed by cold aqueous alkali, whereas 3,5-diphenyl-1,2,4-thiadiazole reacts with alkalis only on prolonged boiling <65AHC(5)119>.

Nucleophilic attack at the C-5 carbon atom of 1,2,4-thiadiazoles has been proposed as a reaction mechanism for many of the ring transformations described throughout this chapter. Thus, 2-methyl-3,5-diphenyl-1,2,4-thiadiazolium fluorosulfate (**33**) is cleaved by alkoxide giving the benzimidate (**34**); in the case of hydroxide ions, reaction continues to the benzoylamidine stage (**35**) (Scheme 10) <82AHC(32)285>.

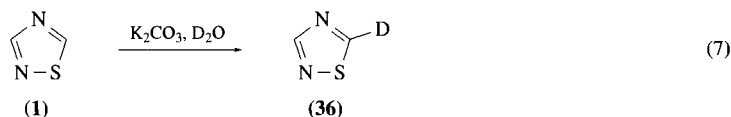
Comparable ring opening occurs with a variety of nitrogen and carbon nucleophiles giving linear products which may undergo recyclization to other heterocyclic systems <84CHEC-I(6)463>.



Scheme 10

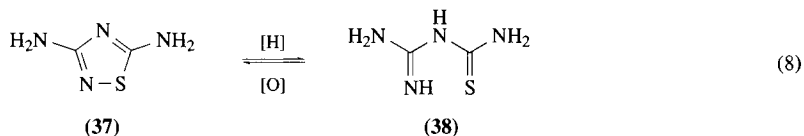
4.08.5.7 Nucleophilic Attack at Hydrogen

Treatment of 1,2,4-thiadiazole (1) with a weak base (K_2CO_3) in D_2O gives the monodeutero derivative (36) (Equation (7)). Under strongly alkaline conditions, the molecule is completely decomposed $\langle 76ZN(A)1681 \rangle$.

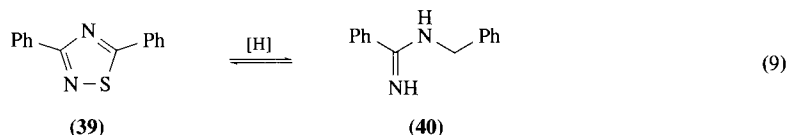


4.08.5.8 Reactions with Radicals and Electron-Deficient Species: Reactions at Surfaces

Reactions of 1,2,4-thiadiazoles with radicals and electron-deficient species are virtually unknown. Catalytic and dissolving metal reductions usually cleave the nucleus at its $N-S$ bond by a reaction that may be regarded as the reverse of its synthesis by the oxidative cyclization of amidinothiono structures (Section 4.08.9.4). For example, reduction of the diamino compound (37) gives the amidinothiourea (38) from which it may be prepared by oxidation (Equation (8)).



Reduction of 3,5-diphenyl-1,2,4-thiadiazole (39) results in loss of sulfur and formation of the benzamidine (40) (Equation (9)).



4.08.5.9 Reactions with Cyclic Transition States

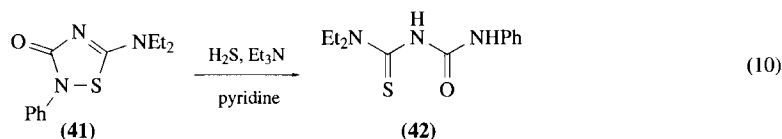
No proven 1,3-dipolar cycloaddition reactions of 1,2,4-thiadiazoles have been reported. For proposals related to these transition states see Section 4.08.6.1 and Scheme 13.

4.08.6 REACTIVITY OF NONCONJUGATED RINGS

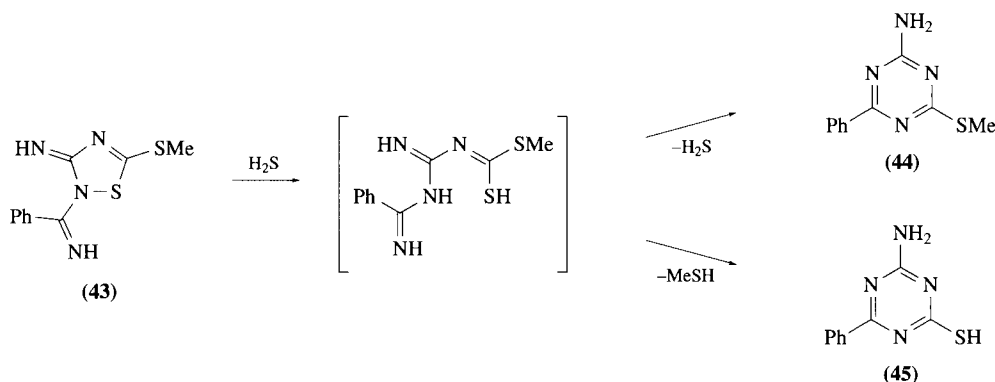
4.08.6.1 Isomers of Aromatic Compounds

1,2,4-Thiadiazolines are readily cleaved at the $N-S$ bond by reducing agents under very mild conditions. Thus the diethylamino derivative (41) is reduced with H_2S in pyridine/triethylamine to

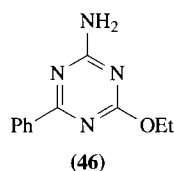
give the thiobiuret (**42**) (Equation (10)) <82S1068>. The lower stability of thiadiazolines compared to thiadiazoles is ascribed to the disappearance of the aromatic character of the ring.



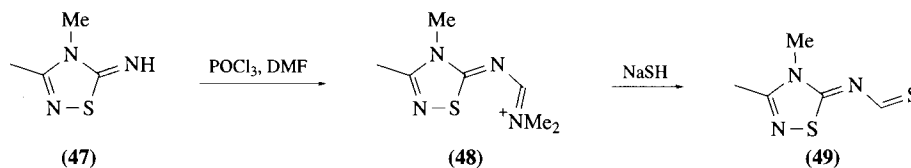
3-Imino-1,2,4-thiadiazolines provide examples of reductive ring cleavage in which the products are immediately recycled to new hetero ring systems. For example, the Δ^4 -1,2,4-thiadiazoline (**43**) is cleaved with H_2S to give the two *S*-triazines (**44**) and (**45**) (Scheme 11). Under similar conditions the 5-ethoxy analog of (**43**) gives the triazine (**46**) in 91% yield <82AHC(32)285>.



Scheme 11



Treatment of the imine (**47**) with phosphoryl chloride in dimethylformamide gives the Vilsmeier salt (**48**) which when reacted with sodium hydrogen sulfide gives the thio compound (**49**) (Scheme 12) <81AX(B)1449>.

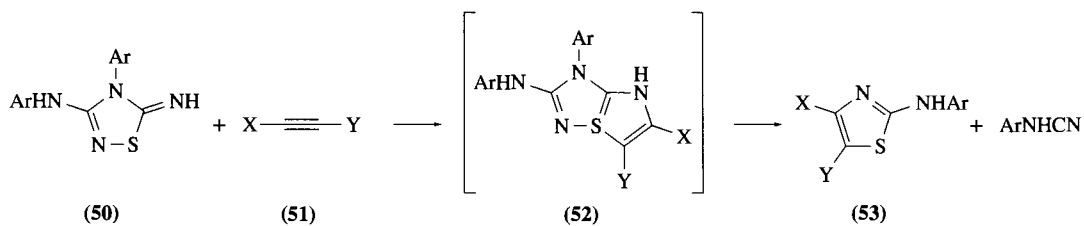


Scheme 12

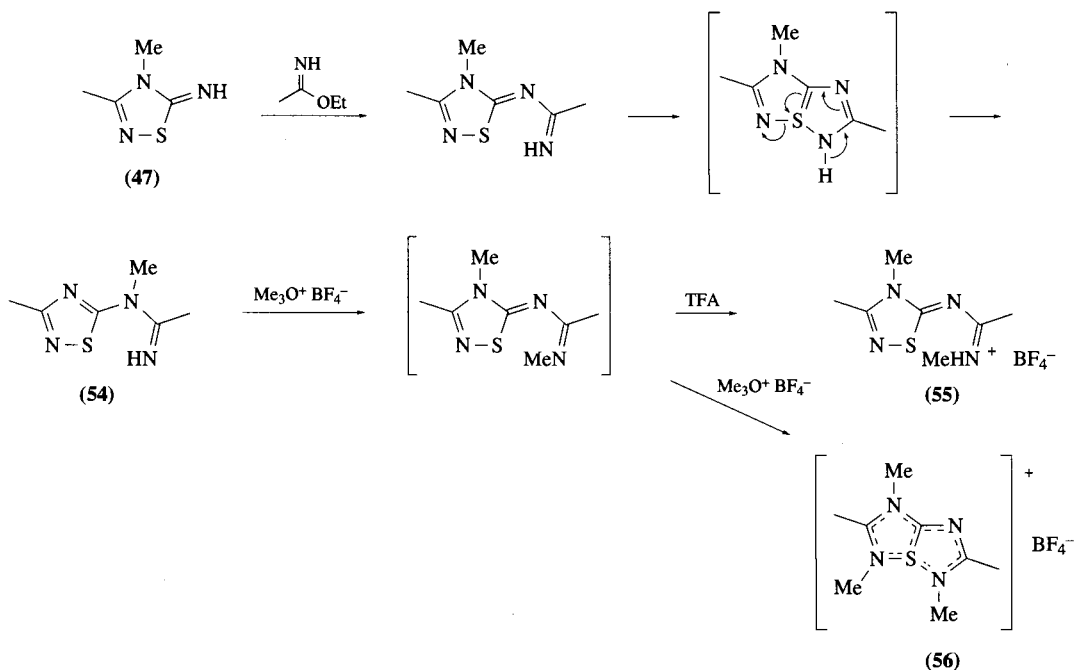
The thiadiazoline (**50**) ($\text{Ar} = p\text{-Tol}$) reacts with electron-deficient alkynes (**51**) to give arylimino-thiazoles (**53**). It has been suggested that the reaction proceeds via a 1,3-dipolar cycloadduct (**52**) (Scheme 13) <75TL459> or by a stepwise nucleophilic substitution reaction <84CHEC-I(6)463>.

In 1979 Akiba *et al.* reported the interaction of 3,4-disubstituted 5-imino- Δ^2 -1,2,4-thiadiazolines with imidates. This gives rearranged products which result from bond switching at hypervalent sulfur intermediates <79AG(E)166>. Thus, treatment of (**47**) with ethyl acetimidate gives the rearranged product (**54**) which on methylation with Meerweins reagent ($\text{Me}_3\text{O}^+\text{BF}_4^-$) and subsequent protonation leads to the salt (**55**). A second methylation step yields a salt which is formulated as (**56**). The structures of compounds (**54**), (**55**), and (**56**) were confirmed by x-ray analysis (Scheme 14) <81AX(B)180>.

When 5-imino- Δ^3 -1,2,4-thiadiazolines react with electrophilic reagents, rearrangement products are again isolated. For example, treatment of the thiadiazoline (**57**) with trichloroacetonitrile at

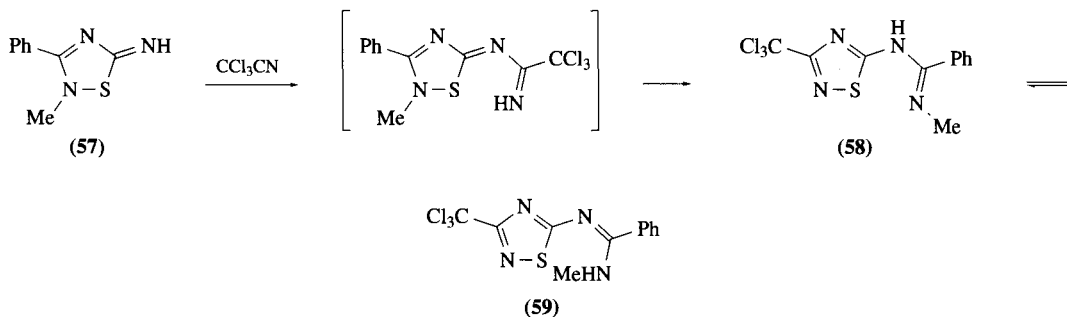


Scheme 13



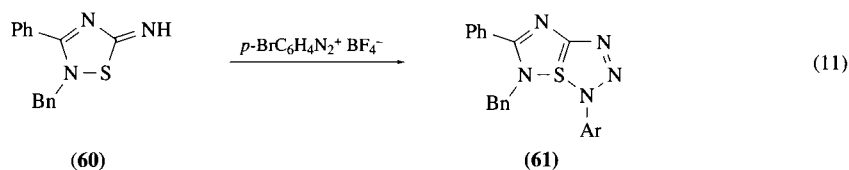
Scheme 14

room temperature gives a product which is shown by proton NMR spectroscopy to be a mixture of tautomers (58) and (59) (Scheme 15) <92JHC1317>.

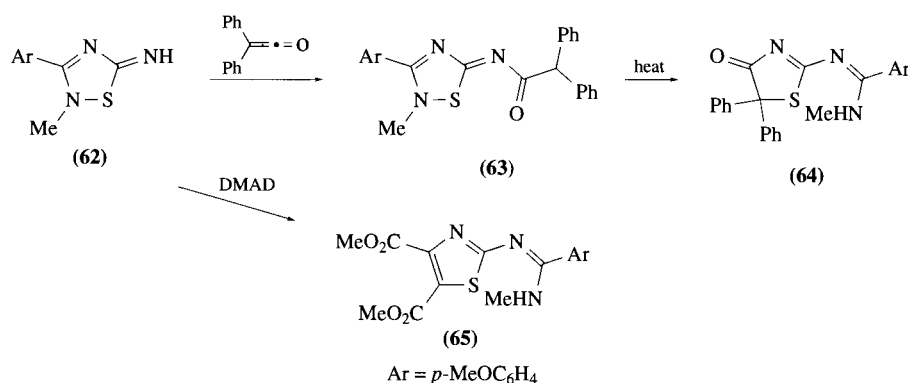


Scheme 15

Reaction of *p*-bromobenzenediazonium tetrafluoroborate with the thiadiazoline (60) in pyridine gives the 6a- λ^4 -thia-1,2,3,4,6-pentazapentalene (61) (Ar = 4-BrC₆H₄) (Equation (11)) whose structure was confirmed by x-ray analysis <93JHC349>.

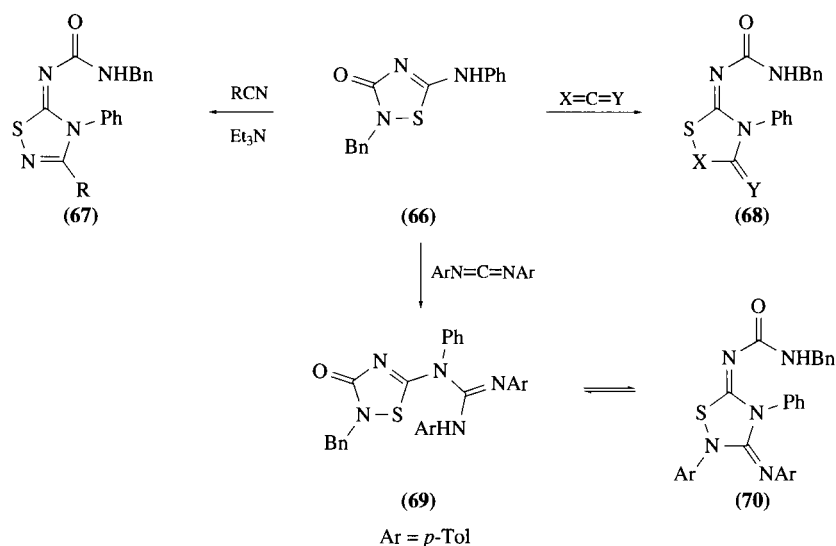


A series of carbonyl derivatives of 5-imino- Δ^3 -1,2,4-thiadiazolines have been prepared by acylation in the presence of triethylamine or pyridine <81JHC1309>. When diphenylketene is used as the acylating agent in reaction with (62) the product (63) is formed at room temperature; however, on heating in a polar solvent, rearrangement occurs to give the Δ^2 -thiazolin-4-one (64) whose structure has been verified by x-ray analysis. A similar ring transformation is observed when (62) is treated with dimethyl acetylenedicarboxylate, giving (65) (Scheme 16) <81JHC1309>.



Scheme 16

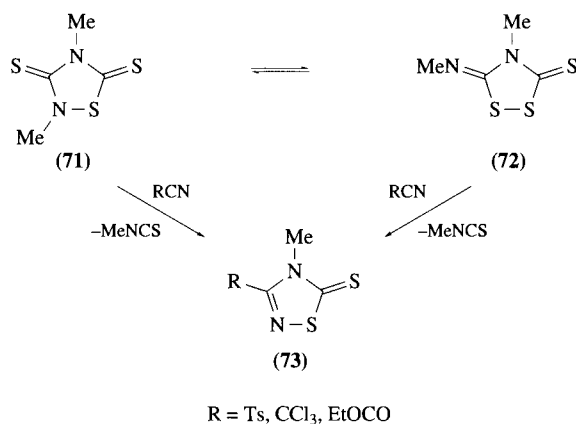
Bond switching rearrangement via hypervalent sulfur also occurs during the reaction of 5-anilino-2-benzyl-3-oxo- Δ^4 -1,2,4-thiadiazoline (66) with electrophilic nitriles, isothiocyanates, carbon disulfide, and ketenes giving compounds (67) and (68) (Scheme 17) <92JHC451>. However, reaction of (66) with *N,N'*-ditolylcarbodiimide gives the addition product (69) which rearranges only partially to (70) in several solvents (Scheme 17) <92JHC451>.



Scheme 17

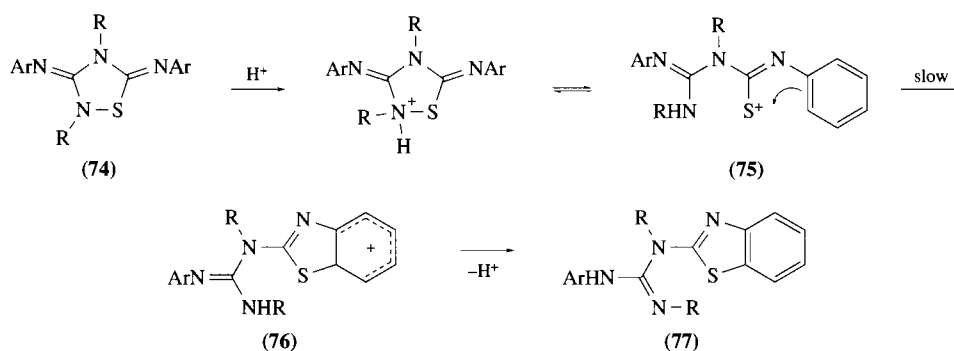
In 1991 L'abbé reported that the 1,2,4-thiadiazolidine (71) and the 1,2,4-dithiazolidine (72) are interconvertible in the presence of electrophilic nitriles and give the 1,2,4-thiadiazoline-5-ones (73) as products (Scheme 18) <91JOC3268>. It is suggested that the reaction goes by a consecutive

cycloaddition elimination mechanism via hypervalent sulfur intermediates in which the nitrile approaches in the plane of the heterocycle. For a discussion of the mechanism see the communication by L'abbé <91JOC3268>.



Scheme 18

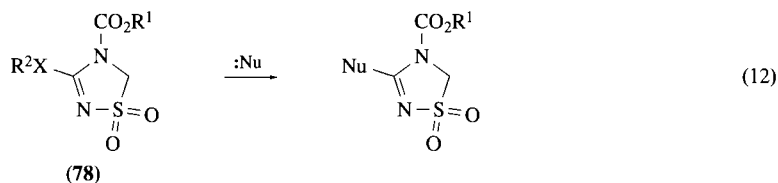
Substituted 3,5-diamino-1,2,4-thiadiazolidines (**74**) undergo isomerization in acid to give the corresponding 2-guanidinobenzothiazoles (**77**). The reaction proceeds by the mechanism shown in Scheme 19. The cation (**75**) is generated by protonation at N-2 of (**74**) and then N—S bond cleavage. Electrophilic attack by the sulfur at the phenyl ring in (**75**) gives (**76**) which on deprotonation leads to (**77**) (Scheme 19). When R is methyl, N-2 is strongly nucleophilic, and recyclization to (**74**) is favored; but when R is phenyl, N-2 is less nucleophilic, and the formation of (**77**) predominates <82AHC(32)285>.



Scheme 19

4.08.6.2 Dihydro Compounds

The 3-alkylthio or alkoxy group in 3,4-disubstituted Δ^2 -1,2,4-thiadiazoline 1,1-dioxide (**78**) (X = O and S) can be displaced by various nucleophiles (Equation (12)) <84CHEC-I(6)463>.



4.08.6.3 Tetrahydro Compounds

1,2,4-Thiadiazolidines cannot be prepared by reduction of the corresponding thiadiazoline or thiadiazole because reagents vigorous enough to reduce the double bond in these systems will cleave the ring (Section 4.08.5.8). No syntheses of 1,2,4-thiadiazolidines have been reported.

4.08.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4.08.7.1 General Survey of Substituents on Carbon

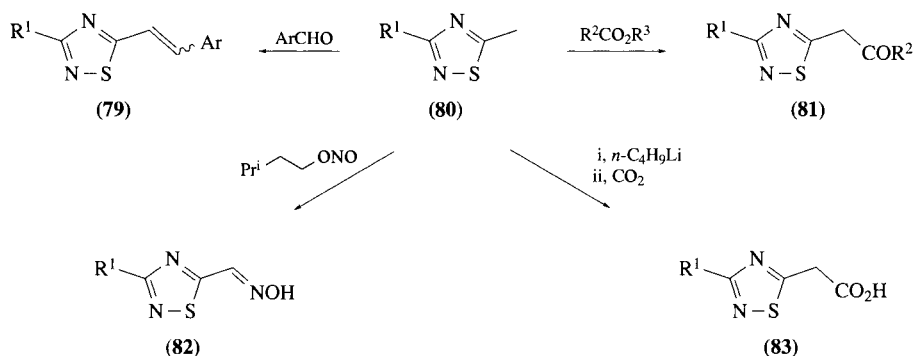
Substituents in the 3- and 5-positions of 1,2,4-thiadiazoles exert a marked stabilizing influence on the ring towards acids, alkalis, oxidizing agents, and reducing agents. For example, the parent compound is sensitive to acids and decomposed by cold aqueous alkali, but the 3,5-diphenyl analog resists the action of hot mineral acids, and prolonged boiling is required for attack by alkalis <65AHC(5)119>. In the 1,2,4-thiadiazole ring the electron density at the 5-position is markedly lower than at the 3-position and hence many of the properties of substituted derivatives relate to this. Thus, 5-halo derivatives approach 2-halothiazoles and 4-halopyrimidines in susceptibility to nucleophilic replacement of halogen, whereas 3-halo derivatives are relatively inert <84CHEC-I(6)463>. Hydroxy and thio 1,2,4-thiadiazoles are generally distinctly acidic, whereas amino-1,2,4-thiadiazoles are weak bases. The greater basicity of 5-amino-1,2,4-thiadiazole relative to the 3-amino isomer appears to be anomalous. The diazonium salts of 5-amino-1,2,4-thiadiazoles are considerably more stable and reactive than those of the 3-isomers and are among the most reactive of their kind among heterocycles of all types <65AHC(5)119>.

4.08.7.2 Benzenoid Rings

See fused heterocyclic rings in Section 4.08.7.10.

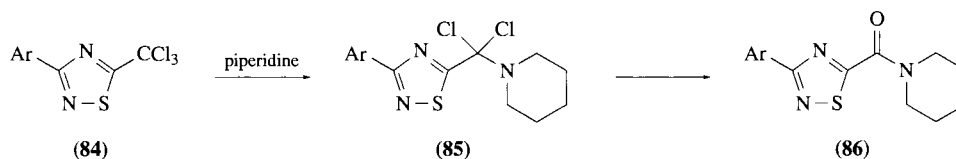
4.08.7.3 Alkyl Groups

Condensation of the 5-methyl group in (80) ($R^1 = \text{Me, Et, Ph, SMe}$) with aromatic aldehydes leads to 5-styrylthiadiazoles (79). The action of carboxylic acid esters gives ethoxalyl derivatives (81) and that of isoamyl nitrite produces the oxime (82) (Scheme 20) <82AHC(32)285>. These reactions are restricted exclusively to the 5-methyl group in (80) ($R = \text{Me}$), reflecting the greater reactivity of substituents in the 5-position compared to the 3-position in 1,2,4-thiadiazoles. This point is further illustrated when (80) ($R = \text{Me}$) is selectively converted into the carboxylic acid (83) on treatment with *n*-butyllithium and carbon dioxide (Scheme 20) <84CHEC-I(6)463>.



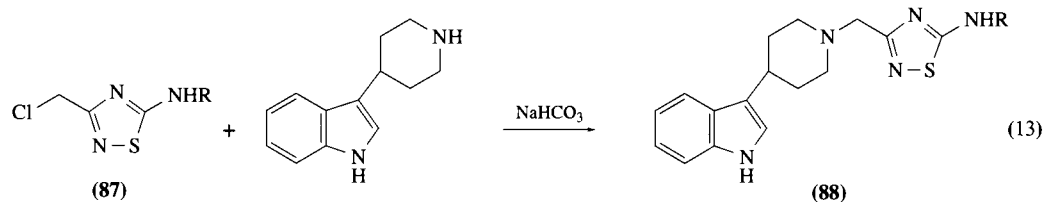
Scheme 20

Reaction of 5-trichloromethyl-1,2,4-thiadiazoles with secondary amines leads to amides. For example, treatment of (84) with piperidine gives (86) which presumably arises by nucleophilic displacement of chloride ion from the trichloromethyl group, followed by hydrolysis during work up of the resulting dichloro compound (85) (Scheme 21) <86PS(26)151>.



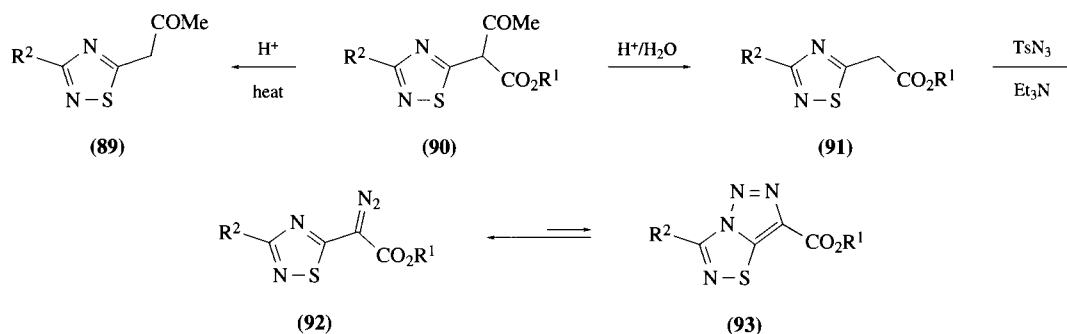
Scheme 21

The chlorine atom in the 3-chloromethyl derivatives (**87**) ($R = H$ and Pr^n) undergoes displacement with 3-(4-piperidyl)indoles in the presence of sodium bicarbonate giving (**88**) (Equation (13)) <88JAP(K)63301881>.



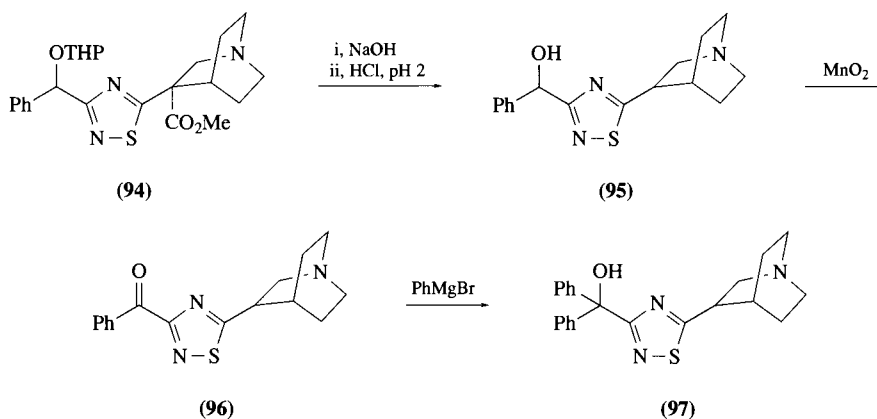
4.08.7.4 Other C-Linked Substituents

The β -ketoester (**90**) ($R^1 = Bu^1$) undergoes hydrolysis and decarboxylation on treatment with acid and subsequent heating, yielding the 5-acetyl derivative (**89**). In contrast, when (**90**) ($R^1 = Et$) is allowed to react with aqueous acid, the acetic acid (**91**) ($R^1 = H$) is isolated (Scheme 22) <82M793>. Treatment of the methyl ester (**91**) ($R^1 = R^2 = Me$) with triethylamine and tosyl azide leads to the diazoester which was shown by IR and NMR spectroscopy to exist in the open chain form (**92**) and not the cyclic form (**93**) (Scheme 22) <92JHC713>.



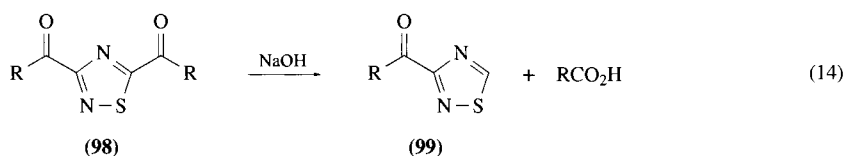
Scheme 22

Hydrolysis of the ester (**94**) with NaOH and adjustment of the resulting solution to pH 2 leads to rapid decarboxylation and deprotection to the alcohol (**95**). Subsequent oxidation with MnO_2 gives the ketone (**96**) which undergoes addition with PhMgBr to yield the tertiary alcohol (**97**) (Scheme 23) <90JMC2052>.

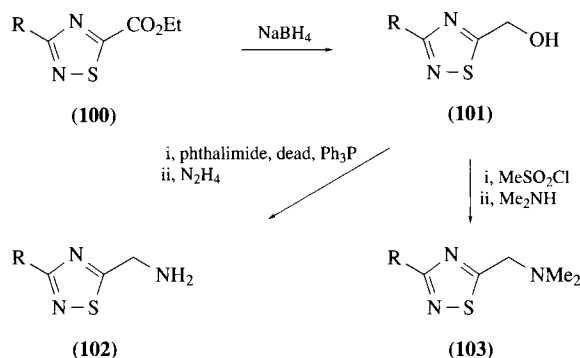


Scheme 23

3,5-Diaroyl and 3,5-diacyl-1,2,4-thiadiazoles (**98**) can be hydrolyzed with NaOH giving 3-mono-substituted ketones (**99**) (Equation (14)) <92JHC1433>.

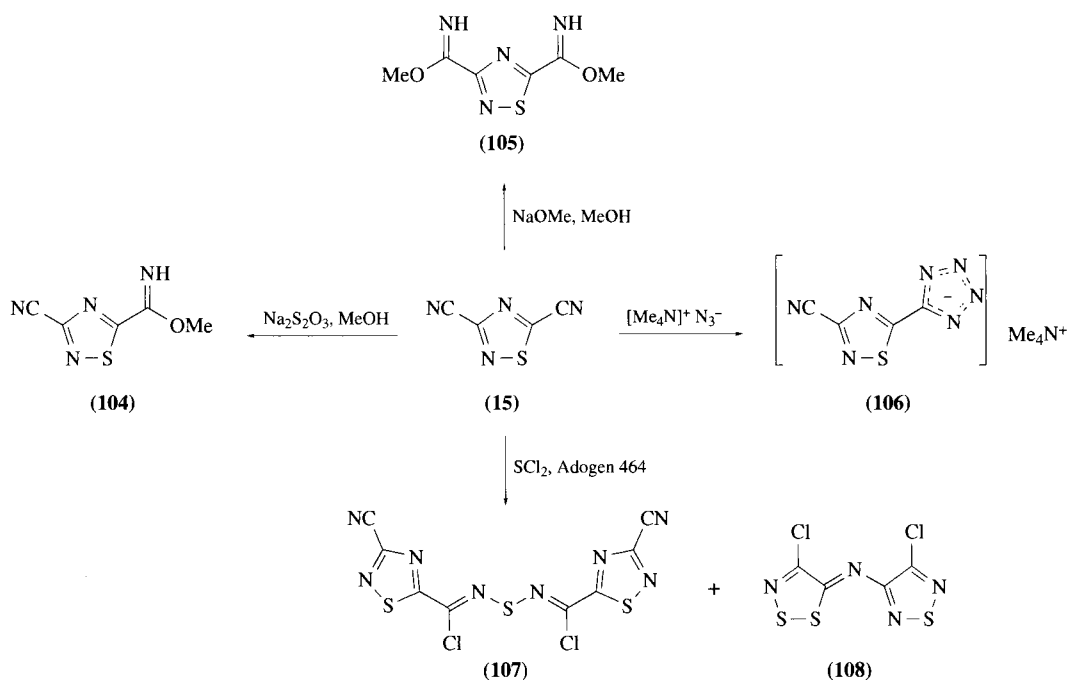


Reduction of the ester (**100**) with sodium borohydride gives the alcohol (**101**) which is converted to the primary amine (**102**) under Mitsunobu conditions, and the tertiary amine (**103**) via its mesylate (Scheme 24) <92JMC3691>.



Scheme 24

The nitrile substituents in 1,2,4-thiadiazole-3,5-dicarbonitrile (**15**) show different reactivities towards nucleophilic reagents, attack occurring first at the 5-cyano group. Thus, treatment of (**15**) with sodium thiosulfate in methanol leads to the imidic ester (**104**), whereas reaction with sodium methoxide in methanol yields (**105**) (Scheme 25) <84CB2681>. Reaction of the 3,5-dicarbonitrile (**15**) with tetramethylammonium azide gives the tetrazolide (**106**) (Scheme 25) whose structure was confirmed by x-ray analysis <90ZN(B)77>. The 3,5-dicarbonitrile (**15**) also reacts with SCl_2 in the presence of Adogen 464 giving (**107**) and (**108**) whose structures were determined by x-ray analyses of (**107**) and an adduct of (**108**) with AsF_5 (Scheme 25) <86ZN(B)162>.



Scheme 25

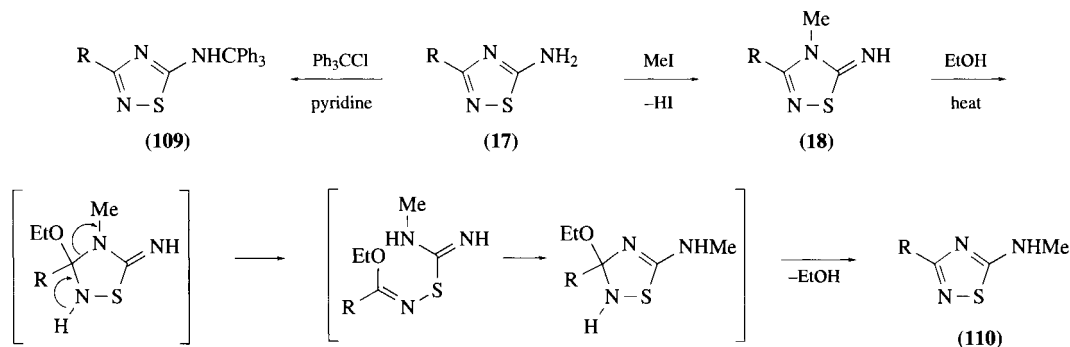
4.08.7.5 N-Linked Substituents

Amino-1,2,4-thiadiazoles are weak bases and form salts with picric, *p*-toluenesulfonic and mineral acids. 3-Amino-1,2,4-thiadiazoles are generally weaker bases than their 5-amino isomers (84CHEC-I(6)463).

In general, amino-1,2,4-thiadiazoles are resistant to the action of acids under mild conditions. Prolonged treatment with hot mineral acids, however, can result in decomposition with liberation of sulfur (65AHC(5)119). 5-Amino-1,2,4-thiadiazoles are decomposed by hot alkalis, with evolution of ammonia, the rate of degradation depending on the nature of the substituent in position 3. The corresponding 3-amino isomers are much more stable to alkali (84CHEC-I(6)463).

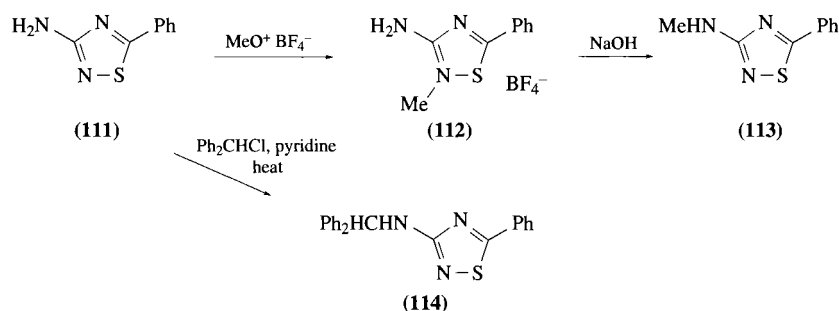
As a general rule, reducing agents cleave the N—S bond of amino-1,2,4-thiadiazoles, the ease of reduction depending largely on the nature of the substituents elsewhere in the molecule (65AHC(5)119). 5-Amino-1,2,4-thiadiazoles are readily cleaved with hydrogen sulfide and with potassium iodide in acid solution, whereas the 3-amino isomers are much more resistant to these reagents (84CHEC-I(6)463).

Alkylation of 5-amino-1,2,4-thiadiazoles (17) with methyl iodide leads to N-4 derivatives of type (18) which undergo a Dimroth rearrangement to (110) on warming in ethanol when R = H (Scheme 26). When R = methyl, phenyl, or benzyl the reaction is severely hindered (84CHEC-I(6)463). In contrast, benzhydryl and trityl chlorides (which are 'harder' electrophiles) alkylate (17) at the 5-amino function to give compounds of type (109) (Scheme 26).



Scheme 26

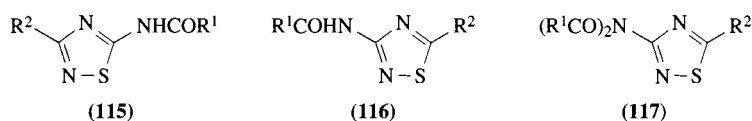
Methylation of 3-amino-5-phenyl-1,2,4-thiadiazole (111) with trimethyloxonium tetrafluoroborate produces the N-2 quaternary salt (112) which on basification undergoes a Dimroth rearrangement to give the 3-methylamino derivative (113) (Scheme 27) (82AHC(32)285). By analogy with 5-amino-1,2,4-thiadiazole (17) (R = H), the 3-amino-1,2,4-thiadiazole (111) is alkylated by benzhydryl and trityl chlorides to give (114) (Scheme 27).



Scheme 27

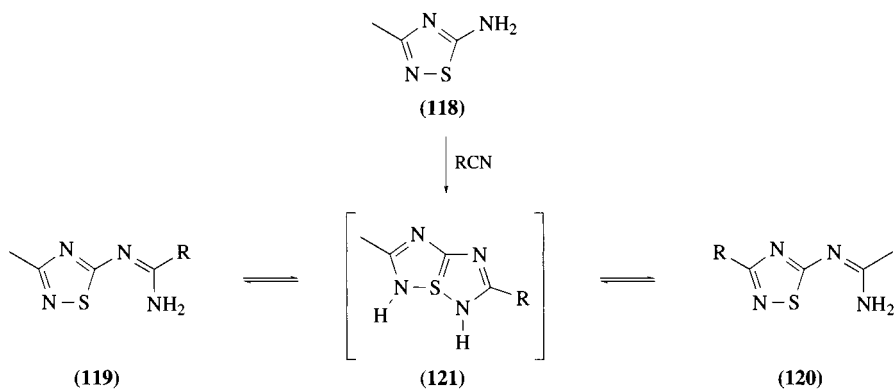
5-Amino-1,2,4-thiadiazoles yield monoacylated derivatives of type (115) under the usual conditions, whereas 3-amino-1,2,4-thiadiazoles give both monoacyl and diacyl derivatives ((116) and (117), respectively) (84CHEC-I(6)463). Treatment of 3-amino- and 5-amino-1,2,4-thiadiazoles with sulfonyl halides under basic conditions generally leads to low yields of sulfonamides. By

contrast, however, 3,5-diamino-1,2,4-thiadiazoles are selectively converted into amides and sulfonamides in good yield <84CHEC-I(6)463>.

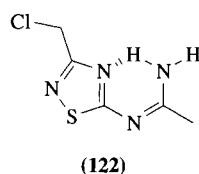


Both 3-amino and 5-amino-1,2,4-thiadiazoles form the expected derivatives with isocyanates, carbamates, and chloroformates; the products from the reaction with the 5-amino isomer have been claimed as herbicides and bactericides <84CHEC-I(6)463>.

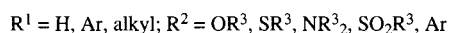
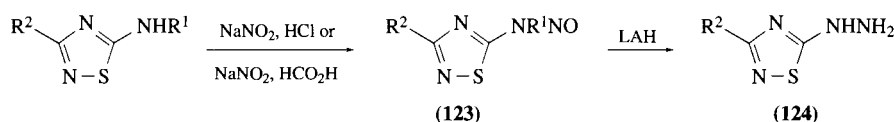
The condensation of 5-amino-3-methyl-1,2,4-thiadiazole (**118**) with aliphatic or aromatic nitriles yields 1:1 adducts, which are, according to their ¹H NMR spectra, equilibrium mixtures of (**119**) and (**120**) (Scheme 28) <82AHC(32)285>. These adducts are produced by a bond switch at the π -hypervalent sulfur in (**121**). X-ray analysis of the adduct formed from the reaction of (**118**) with chloroacetonitrile showed the adduct to exist as (**122**) in the crystals <81AX(B)185>. Further examples of this type of bond switch at π -hypervalent sulfur are observed in the reaction of 5-imino-1,2,4-thiadiazolines with various electrophilic reagents (Section 4.08.6.1).



Scheme 28



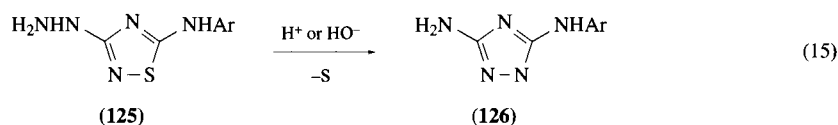
3-Amino-1,2,4-thiadiazoles fail to yield nitrosamines under the usual conditions but the more stable 5-nitrosamines (**123**) can be prepared easily (Scheme 29) <65AHC(5)119>. The nitrosamino group in 5-nitrosamino-1,2,4-thiadiazoles (**123**) is fairly reactive and may be converted into various functional groups with the appropriate reagents <84CHEC-I(6)463>.



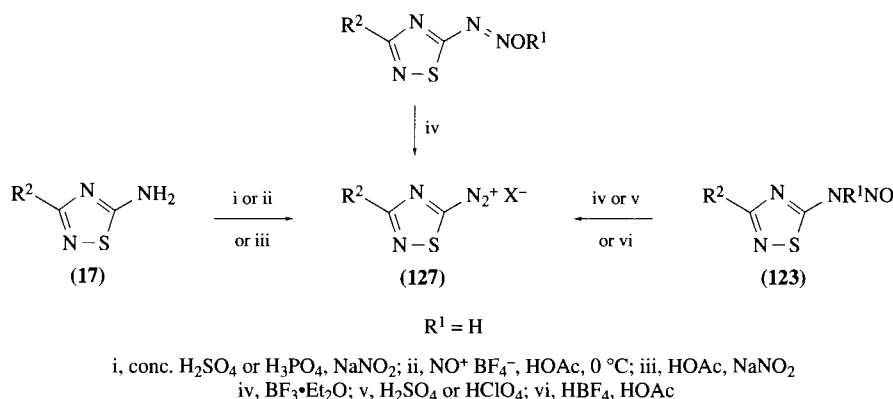
Scheme 29

5-Hydrazino-1,2,4-thiadiazoles (**124**), which can be prepared by reduction of the corresponding nitrosamine (**123**) (Scheme 29) with LAH, are stable in acid and base and readily form hydrazone derivatives on reaction with suitable carbonyl compounds <65AHC(5)119>. In contrast, 3-hydrazino-1,2,4-thiadiazoles (**125**), which are synthesized by ring closure methods, are very sensitive to acid

and base and undergo elimination of sulfur to give 5-arylamino-1,2,4-triazoles (**126**) (Equation (15)) <84CHEC-I(6)463>.

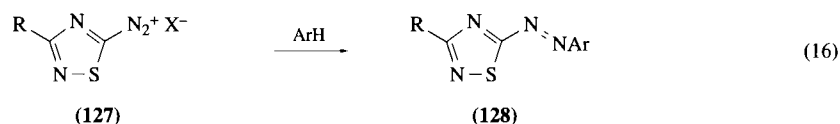


Diazonium salts of type (**127**) have been prepared by the methods indicated in Scheme 30 and can often be isolated as crystalline tetrafluoroborate or perchlorate salts <84CHEC-I(6)463>.

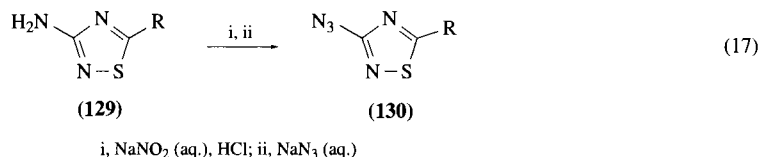


Scheme 30

Some of the more common reactions of 1,2,4-thiadiazole-5-diazonium salts (**127**) can be found in the review by Kurzer <65AHC(5)119>. These include the coupling of the diazonium salts with aromatic compounds to form monoazo dyes of type (**128**) (Equation (16)) for use in polymers. Diazonium salts incorporating the 1,2,4-thiadiazole nucleus are particularly reactive coupling reagents due to the electronegative nature of the ring and the high positive charge localized on the terminal nitrogen of the diazo group.



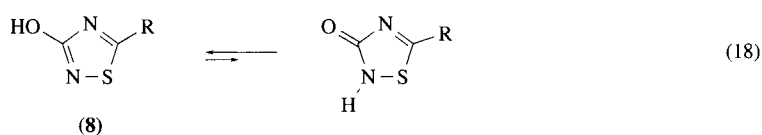
3-Amino-1,2,4-thiadiazoles (**129**) are diazotised at -10°C in phosphoric acid, and couple in the usual way with reactive aromatic compounds such as naphthol, giving moderate yields of diazo dyes <82AHC(32)285>. Diazotization of (**129**) ($\text{R} = \text{H}$ and Ph) may be accomplished using aqueous sodium nitrite and hydrochloric acid. Treatment of the resulting salt with sodium azide yields the 3-azido derivative (**130**) (Equation (17)) <86CC800>.



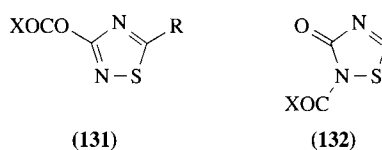
4.08.7.6 O-Linked Substituents

Hydroxy-1,2,4-thiadiazoles are generally distinctly acidic. 3-Ethyl-5-hydroxy-1,2,4-thiadiazole, for example, is more acidic than nitrophenol and 4-hydroxypyrimidine, but less so than 2,4-dinitrophenol. 3-Hydroxy-1,2,4-thiadiazoles fail to afford ketonic derivatives and give red to purple colors with iron(III) chloride, indicating their phenolic nature <65AHC(5)119>. Their IR spectra in

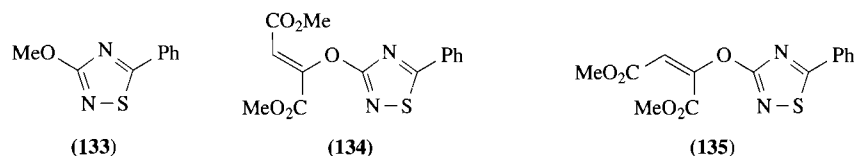
chloroform solution or nujol suggest that the hydroxy form (**8**) is mostly present (Equation (18)) <79JHC961>.



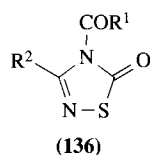
Reaction of 3-hydroxy-1,2,4-thiadiazoles with electrophilic reagents leads to attack at the hydroxy oxygen or attack at the N-2 position. In general 'hard' electrophiles (including acid chlorides of carboxylic, sulfonic, phosphoric, and sulfamic acids) attack at the hydroxy oxygen, giving predominantly 3-acyl derivatives (**131**), while 'soft' electrophiles (including isocyanate esters and acid anhydrides) attack at the N-2 position yielding derivatives of 1,2,4-thiadiazolin-3-ones (**132**) <82AHC(32)285>.



Methylation of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**23**) with dimethyl sulfate and sodium hydroxide at room temperature gives a mixture of (**24**) and (**133**). When methylation is carried out using methyl toluene-4-sulfonate at 100°C, no *O*-methylation is observed and compound (**24**) and the meso-ionic derivative (**25**) are produced, (Scheme 7) <84JCS(P1)75>. Reaction of (**23**) with dimethyl acetylenedicarboxylate yields the fumarate (**134**) and the maleate (**135**) derivatives which are formed by nucleophilic addition <84JCS(P1)75>.



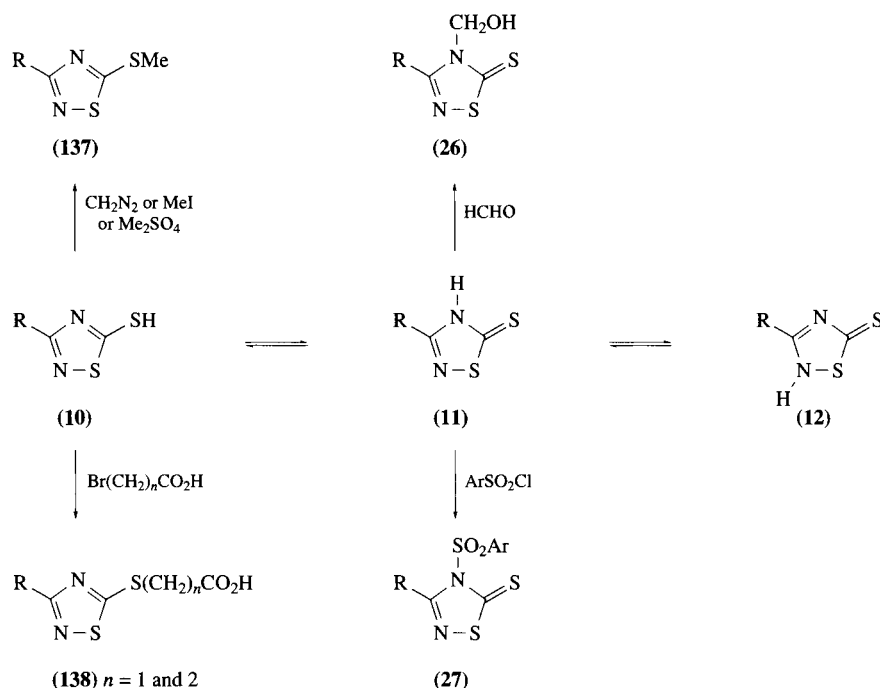
Acetylation of 3-alkyl-5-hydroxy-1,2,4-thiadiazoles with ethyl chloroformate or carboxylic acid chlorides leads to N-4 derivatives of type (**136**) <75GEP(O)2405324>.



4.08.7.7 S-Linked Substituents

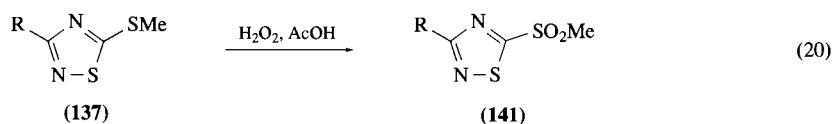
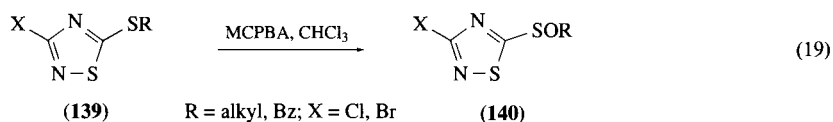
Mercapto-1,2,4-thiadiazoles are distinctly acidic. The pK_a of 5-thio-3-methyl-1,2,4-thiadiazole at 25°C is 5.18 <65AHC(5)119>. The position of equilibrium in the tautomers of 5-thio-1,2,4-thiadiazoles (**10**) ($R = H$) appears to be on the thione side (**11**) or (**12**). The solid state IR spectrum of (**10**) ($R = Ph$) shows no sign of SH absorption <92PS(66)321>. However, treatment of (**10**) ($R = Ph$, *p*-Tol) with diazomethane does not produce any *N*-methylated products, but only the 5-methyl derivatives (**137**) ($R = Ph$, *p*-Tol). Methylation of (**10**) ($R = Ph$) with methyl sulfate and with methyl iodide in sodium hydroxide gives only the *S*-methyl derivatives (**137**) (Scheme 31) <92PS(66)321>. In 1989 Yousef *et al.* reported that (**10**) ($R = Ph$) reacted with aromatic sulfenyl chlorides and with formaldehyde to give the *N*-substituted products (**26**) and (**27**) (Scheme 31). At the same time, alkylation

of (10) ($R = \text{Ph}$) with bromoacetic and 3-bromopropanoic acids gives 5-substituted carboxylic acids (138) ($n = 1$ and 2) <89MI 408-01>.

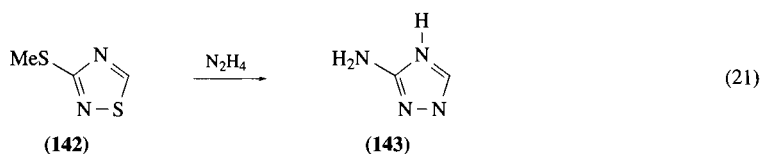


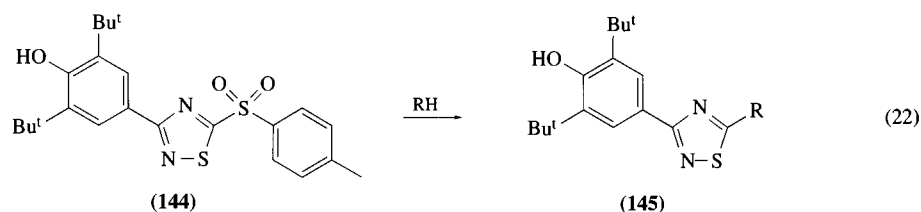
Scheme 31

1,2,4-Thiadiazole sulfides are readily oxidised to the corresponding sulfoxides and sulfones. For example, the sulfide (139) is converted into the sulfoxide (140) (Equation (19)) using *m*-chloroperbenzoic acid <84CHEC-I(6)463> and reaction of the 5-methylthio derivative (137) ($R = \text{Ph}$) with hydrogen peroxide in acetic acid gives the sulfone (141) ($R = \text{Ph}$) (Equation (20)) <89MI 408-01>.

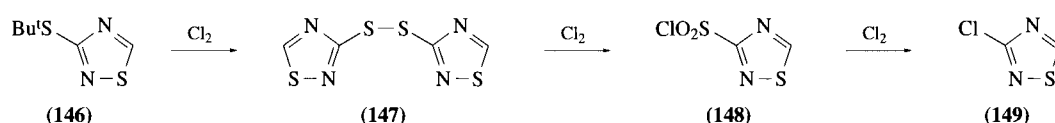


The 3-alkylthio groups in 1,2,4-thiadiazoles are difficult to replace. Thus, 3-alkylthio-1,2,4-thiadiazoles resist the action of aniline at 100°C, ammonia at 120°C, molten urea and ammonium acetate; however, hydrazine attacks 3-methylthio-1,2,4-thiadiazole (142) forming 3-amino-1,2,4-triazole (143) (Equation (21)) <65AHC(5)119>. In contrast to 3-alkylthiogroups, 5-sulfonyl groups in 1,2,4-thiadiazoles are readily displaced with various nucleophiles, for example reaction of (144) with various amines gives (145) (Equation (22)) <92JMC3691>.



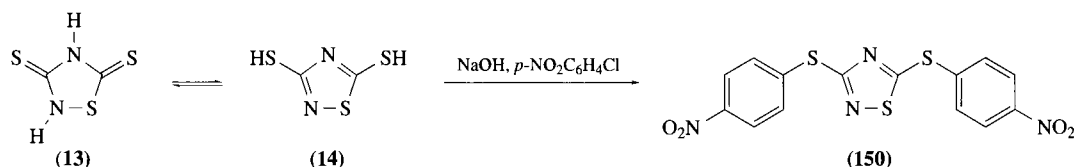


Reaction of chlorine with thio-1,2,4-thiadiazoles yields sulfonyl chlorides, sulfenyl chlorides, or chloro compounds, depending on the nature of the substrate and on the experimental conditions employed. Thus, treatment of (146) with one mole of chlorine yields the disulfide (147), whilst an excess of chlorine converts (147) into the sulfonyl chloride (148) and then further into the 3-chloro derivative (149) (Scheme 32) <82AHC(32)285>.



Scheme 32

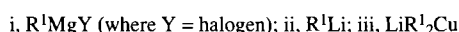
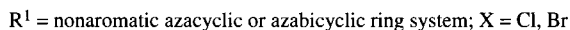
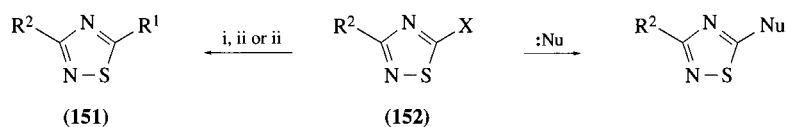
The IR spectrum of 1,2,4-thiadiazolidine-3,5-dione indicates that the dithione structure (13) predominates. However, the dithione can be readily dialkylated on sulfur and treatment with 1-chloro-4-nitrobenzene in aqueous sodium hydroxide yields (150) (Scheme 33) <89EUP330020>.



Scheme 33

4.08.7.8 Halogen Atoms

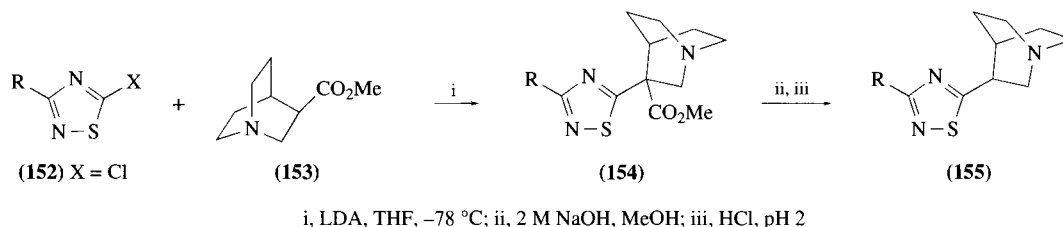
The reactivity of 5-halogen substituents in the 1,2,4-thiadiazole structure (152) is well known; nucleophilic substitution at this centre is a common route to other 1,2,4-thiadiazoles, including 5-hydroxy, alkoxy, thio, alkylthio, amino, sulfonamido, hydrazino, hydroxylamino, and azido derivatives (Scheme 34) <65AHC(5)119>. More recently in the late 1980s, the 5-halogen substituent in (152) has been replaced by Grignard, organolithium, and organocuprate reagents to give compounds of type (151) (Scheme 34) <89EUP307142>.



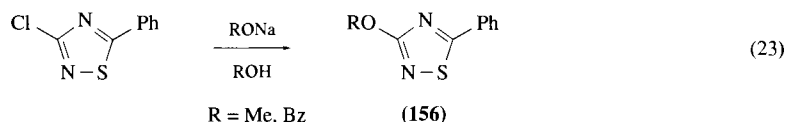
Scheme 34

Active methylene anions also displace the 5-halogen substituent; for example, the 5-chloro derivative (152) ($\text{X} = \text{Cl}$) reacts with the sodium salt of ethyl acetoacetate to give (90) ($\text{R}^1 = \text{Et}$) which is readily hydrolyzed and decarboxylated (Scheme 22) <82M793>. The 5-chloro substituent in (152) ($\text{X} = \text{Cl}$) is also readily displaced by the lithium enolate of 3-(methoxycarbonyl)quinuclidine (153) to give (154) which on hydrolysis with sodium hydroxide and then decarboxylation with hydrochloric

acid leads to (155) (Scheme 35) <90JMC2052>. The nucleophilic displacement reactions follow second order kinetics, the rate-determining step being the addition at C-5 of the nucleophile, followed by the rapid elimination of halogen <84CHEC-I(6)463>. Halogens in the 3-position of 1,2,4-thiadiazoles are inert towards most nucleophilic reagents. However, displacement of the 3-halogen atom can be achieved by reaction with sodium alkoxide in the appropriate alcohol to give compounds of type (156) (Equation (23)) <65AHC(5)119>.



Scheme 35



4.08.7.9 Metals and Metalloid-linked Substituents

Metallation of the 1,2,4-thiadiazole ring is not known to date, presumably because of its instability to base.

4.08.7.10 Fused Heterocyclic Rings

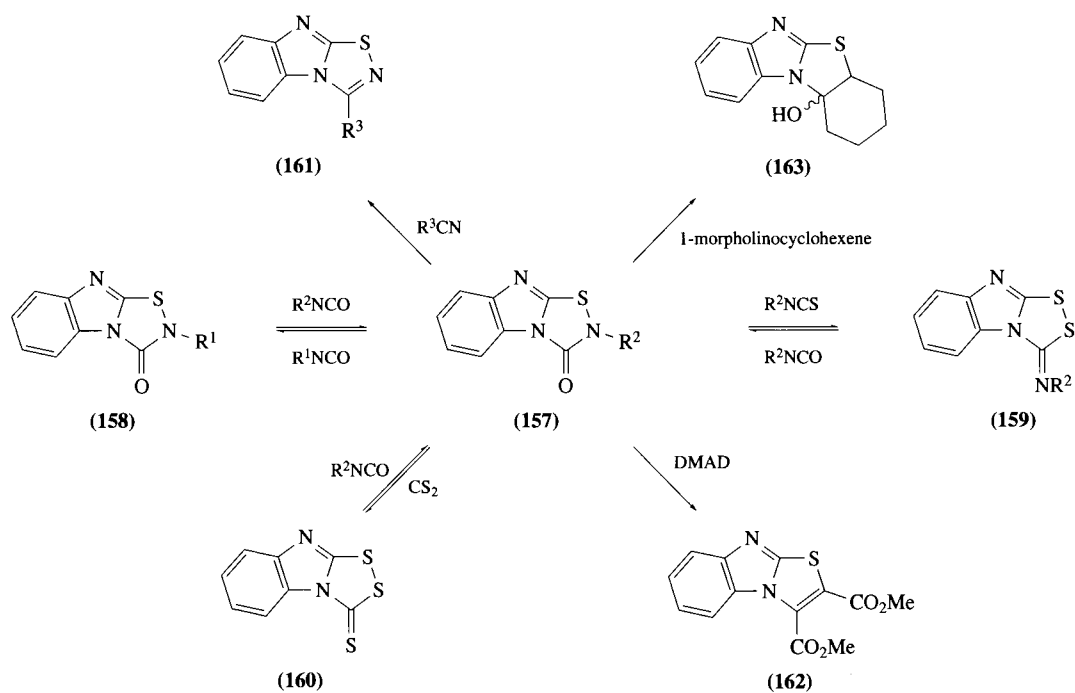
Reaction of benzimidazo[1,2-*d*][1,2,4]thiadiazol-3(2H)-ones (157) with isocyanates, isothiocyanates, carbon disulfide, aryl cyanates, acetylenedicarboxylates, and enamines results in exchange of the isocyanate component of (157), to give the corresponding condensed benzimidazole derivatives (158)–(163) (Scheme 36) <85JCS(P1)1007>. Unlike the reactions with isocyanates, isothiocyanates and carbon disulfide, the reactions with aryl cyanates, acetylenedicarboxylates and enamines are not reversible. Under more severe conditions, treatment of (164) with aryl isothiocyanates leads to (165) which results from the rearrangement illustrated in Scheme 37. The exchange reactions are assumed to proceed through a λ^4 -thia-azapentalene like intermediate (166) (Scheme 38) <85JCS(P1)1007>.

Thermolysis of the thiadiazole (164) leads to elimination of isocyanate and sulfur giving the triazine derivative (167). If the thermolysis is carried out in the presence of phenols 2-aryl-benzimidazoles (168) are produced <85JCS(P1)1007>. The S—N bond of (157) is readily cleaved with both N- and C-nucleophiles. Thus, treatment of (157) with an excess of amine gives the sulfenamide (169) (Scheme 39) and reaction of (157) with active methylene compounds leads to derivatives of type (170) (Scheme 39) which on heating furnish (171). Cyanide ion inserts into the S—N bond of (164), probably via the intermediate (172) which immediately recyclizes to give the thiadiazinone (173) (Scheme 40) <85JCS(P1)1007>.

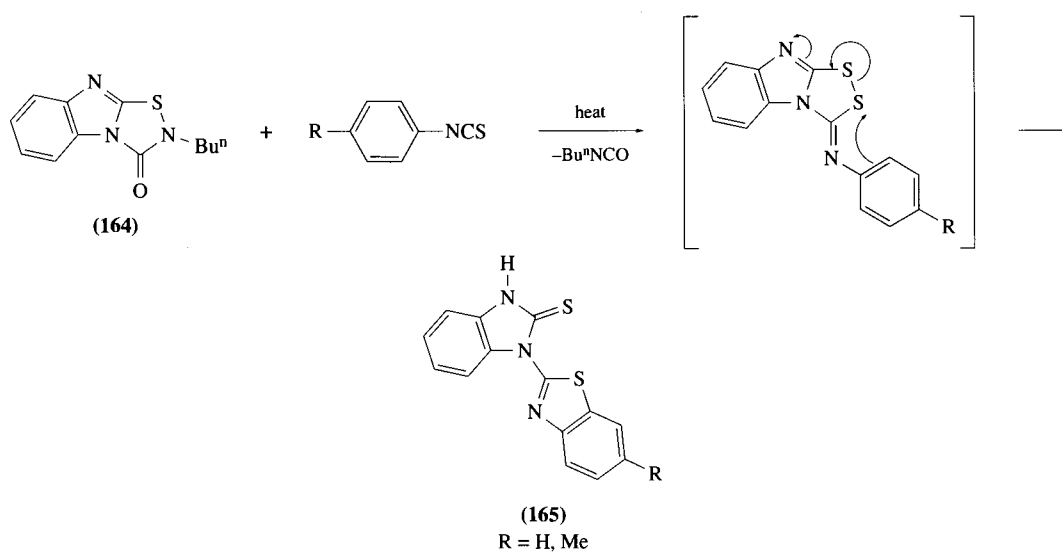
4.08.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

4.08.8.1 Substituents Attached to Ring Nitrogen Atoms

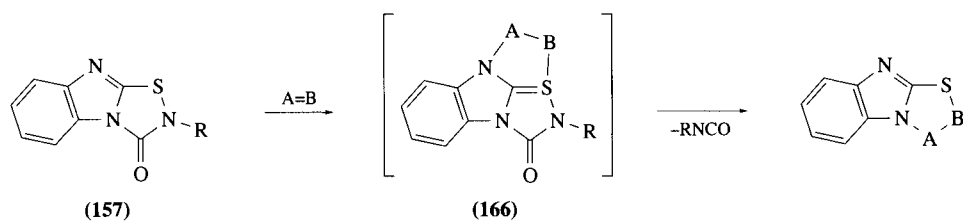
Only a small number of reactions of substituents attached to the ring nitrogens of 1,2,4-thiadiazoles have been reported. The initial N-4 derivative (175) obtained by reacting phenacyl bromide with 5-amino-1,2,4-thiadiazole (174) undergoes an internal cyclization to give the fused imidazolothiadiazole (176) (Scheme 41) <65AHC(5)119>. Also, the primary alcohol function in (26) (R = Ph) can be displaced with various amines to give compounds of type (177) (Equation (24)).



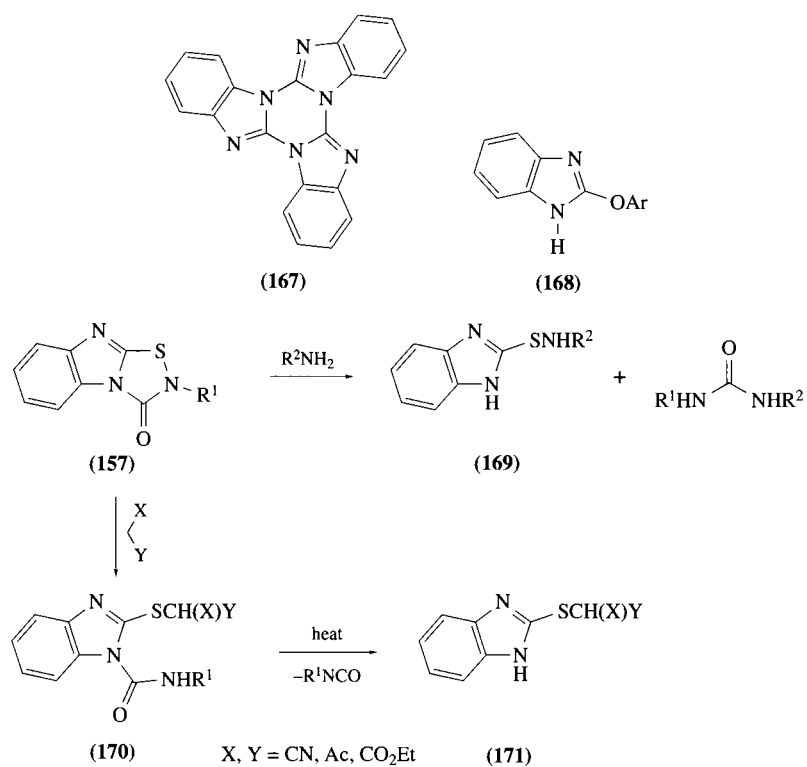
Scheme 36



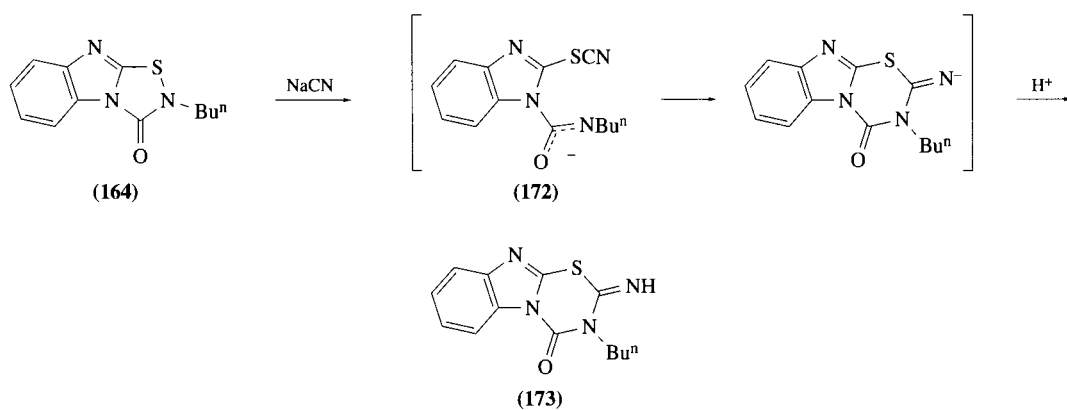
Scheme 37



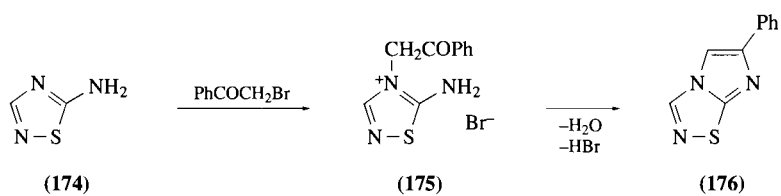
Scheme 38



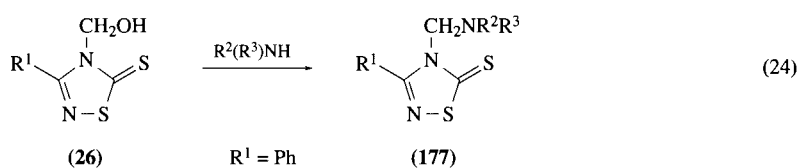
Scheme 39



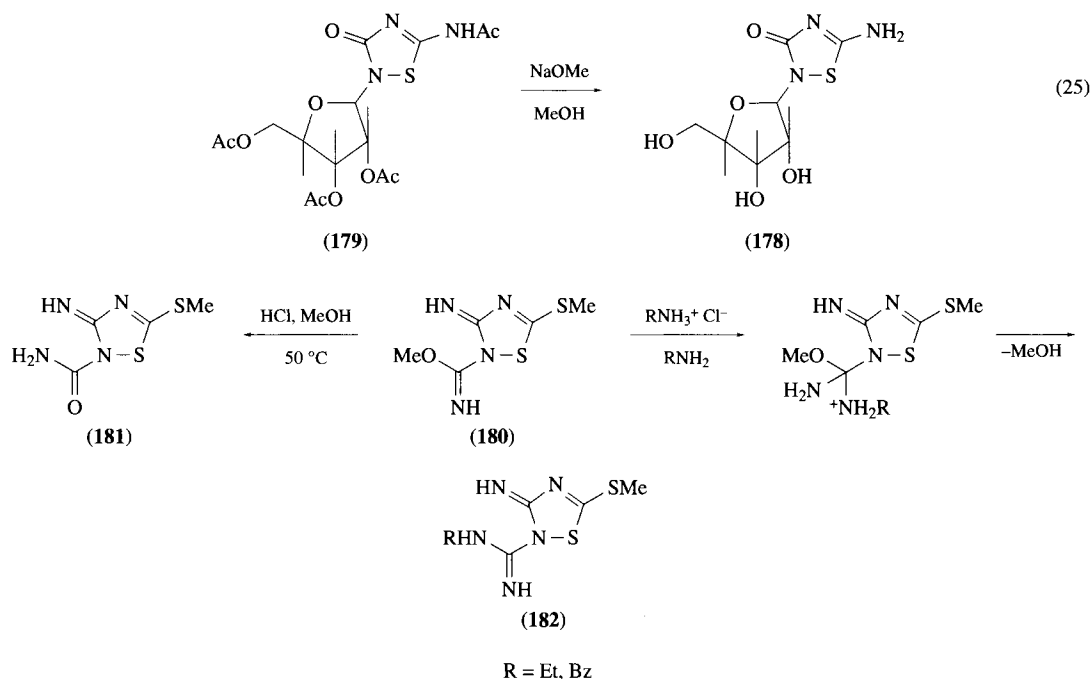
Scheme 40



Scheme 41



The final step in the synthesis of the thiadiazole nucleoside (**178**) is achieved by prolonged treatment of (**179**) with methanolic sodium methoxide (Equation (25)) <82AHC(32)285>. Reaction of the Δ^4 -1,2,4-thiadiazoline (**180**) with dry HCl in methanol leads to the 2-carbamoyl compound (**181**). When (**180**) is treated with a mixture of free amines and amine hydrochlorides in the ratio of 2 : 1 in refluxing ethanol, 2-amidino-3-imino-5-methylthio derivatives (**182**) are formed in good yield (Scheme 42) <84CHEC-I(6)463>.



Scheme 42

4.08.8.2 Substituents Attached to Ring Sulfur Atoms

Reactions of substituents attached to ring sulfur atoms in 1,2,4-thiadiazoles are virtually unknown.

4.08.9 RING SYNTHESIS FROM NONHETEROCYCLIC COMPOUNDS

4.08.9.1 Introduction

The synthesis of a wide range of 1,2,4-thiadiazole derivatives has long been possible by some well established routes <82AHC(32)285>. In general, 1,2,4-thiadiazoles are prepared by the appropriate intra- or intermolecular ring closing reactions. In accordance with established practice <65AHC(5)119>, the syntheses of 1,2,4-thiadiazoles are classified according to the nature of the fragments from which the heterocyclic ring is built. The potential ring closure routes are designated types A to G (Figure 3). Presumed intermediates in these reactions are not considered sufficient criteria for assignment of reaction type unless they have been isolated and their conversion to 1,2,4-thiadiazoles demonstrated.

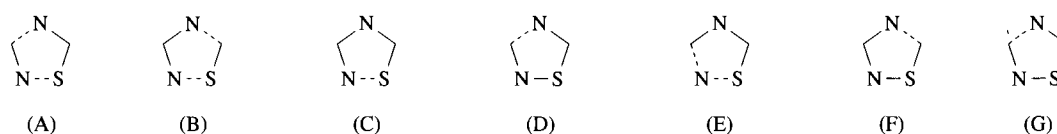
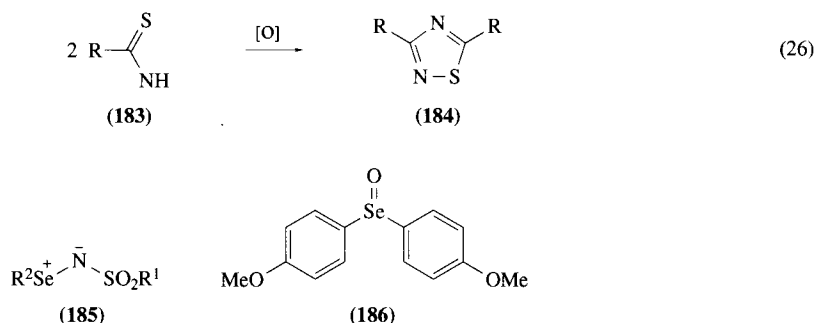


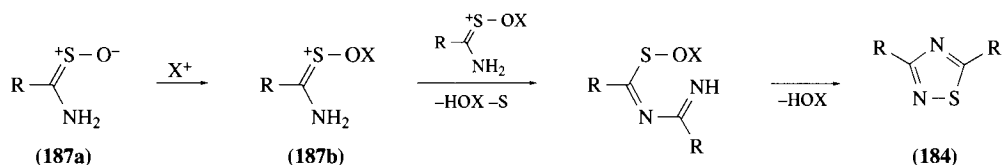
Figure 3 Potential ring closure routes in the synthesis of 1,2,4-thiadiazoles.

4.08.9.2 Type A Syntheses

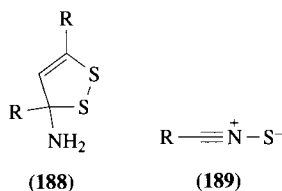
The oxidation of thioamides (**183**) with a wide variety of oxidizing agents is a well employed method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles (**184**) <82AHC(32)285>; however, this method is limited mainly to arylthioamides. The most common oxidizing agents tend to be halogens, hydrogen peroxide, and nitrous acid; yields from these reactions are variable and depend on the thioamide, oxidant, and conditions used (Equation (26)). Byproducts such as nitriles and isothiocyanates are usually formed. Selenium compounds (**185**) <88ZOR2489> and (**186**) <83JAP(K)5857372> have both been used as oxidizing agents to convert aryl thioamides into 1,2,4-thiadiazoles in high yields.



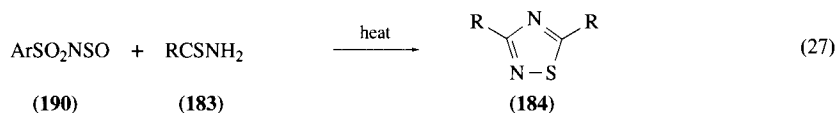
DMSO in the presence of an electrophilic reagent such as 1-methyl-2-chloropyridinium iodide, trimethylsilyl chloride, benzoyl chloride, acetic anhydride, or hydrochloric acid reacts with both aryl and benzyl thioamides at room temperature to give thiadiazoles (**184**) in high yield. Thioamides also react with NBS under similar conditions to give (**184**), again in high yield. Thioamide-S-oxides (**187a**) also afford (**184**) when treated with the above electrophilic reagents at room temperature <85BCJ995>. The latter results support a general mechanism for these oxidations which involves the initial formation of a sulfonium salt (**187b**, X = halogen, TMS, COR or 2-(*N*-methylpyridyl)) and then proceeds as shown in Scheme 43 <85BCJ995>. Earlier suggestions that the dithiazoline (**188**) <82AHC(32)285> and the nitrile sulfide (**189**) <84TL409> were involved were deemed not to be feasible.



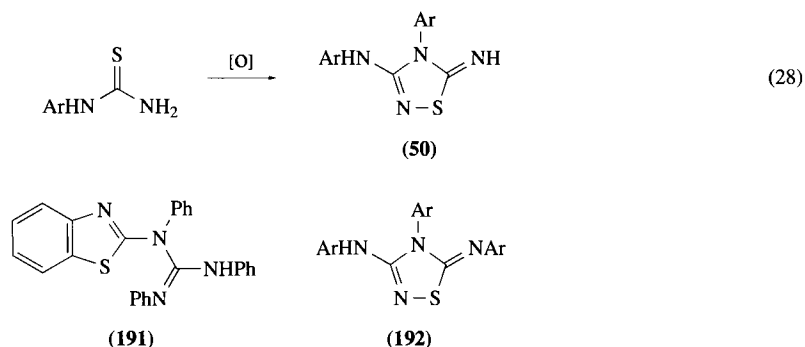
Scheme 43



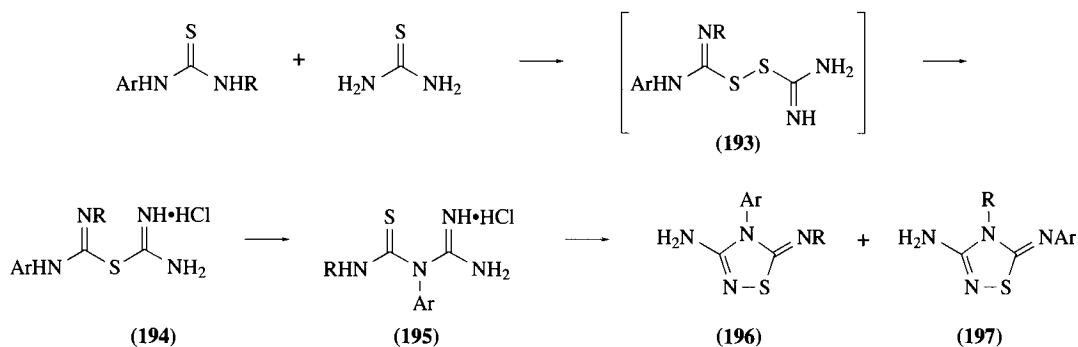
The thermolysis of thioamides (**183**) with *N*-sulfinylsulfonamides (**190**) gives moderate yields of 1,2,4-thiadiazoles (Equation (27)), a competing and sometimes dominant side reaction is the formation of nitriles <84CHEC-1(6)463>. No new examples of this type of reaction have been found in the 12 years since 1984.



3,5-Diamino-1,2,4-thiadiazoles (**50**) ("Hectors bases") are the oxidation products from *N*-arylthioureas (Equation (28)). A large number of examples of this type of reaction are known, typical oxidants giving good yields being acidic hydrogen peroxide, nitrous acid, and iron(III) chloride. When 1,3-substituted thioureas are oxidized, the product isolated depends on the oxidant employed. Treatment of 1,3-bisarylthiourea with hydrogen peroxide gives 2-guanidinobenzothiazoles (**191**), while benzoyl peroxide in dichloromethane affords 1,2,4-thiadiazolidines (**192**), probably by a free radical mechanism.



Oxidation of mixtures of thiourea and *N*-aryl-*N'*-alkylthioureas with hydrogen peroxide yields only 3-amino-4-aryl-5-alkylamino-1,2,4-thiadiazolines (**196**) <80IJC(B)667>. The mechanism of this reaction, in common with most oxidation reactions of thioureas, involves initially the formation of a disulfide (**193**) which is cleaved to cyanamide or carbodiimide, thiourea and sulfur; this is followed by recombination of the former two to give a bisformamidine sulfide (**194**) which isomerizes by migration of an amidino group to an amidinothiourea (**195**). In general, it is found that during the formation of the amidinothiourea, an amidino group migrates to an aryl substituted nitrogen in preference to an unsubstituted or alkyl substituted nitrogen which are more likely to be protonated under the reaction conditions (Scheme 44). When the aryl group is sterically crowded, as in 2,6-xylyl, the product resulting from the amidino group migration to the alkyl substituted nitrogen is also observed (**197**) <91IJC(B)600>.

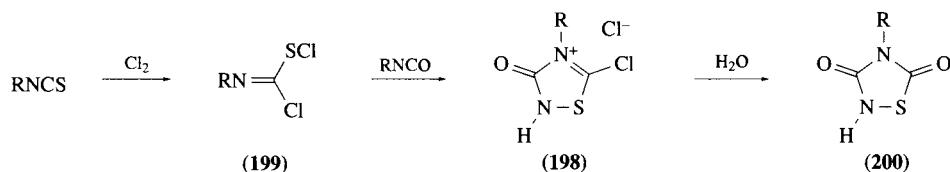


Scheme 44

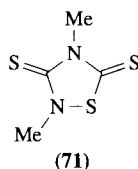
Aqueous solutions of methyl isothiocyanate are slowly oxidized in air to give 2,4-dimethyl-1,2,4-thiadiazoline-3,5-thione (**71**) <82AHC(32)285>. When mixtures of alkylisothiocyanates and alkylisocyanates are chlorinated, 3-oxathiadiazolium salts (**198**) are formed via an intermediate iminochloromethylsulfenyl chloride (**199**). Hydrolysis of these salts yields 2,4-dialkyl-1,2,4-thiadiazolidin-3,5-diones (**200**) (Scheme 45) <80USP4183816>.

4.08.9.3 Type B Syntheses

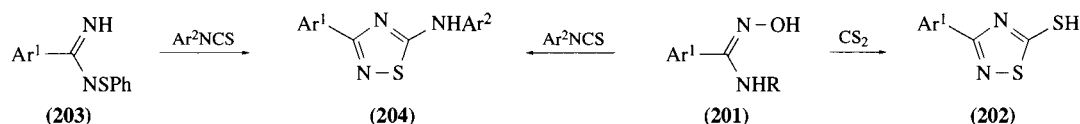
Amidoximes (**201**) ($\text{R} = \text{H}$) yield 5-thio-1,2,4-thiadiazoles (**202**) when treated with carbon disulfide; no reaction is observed when R is methyl <91CAT225>. The corresponding 5-amino derivatives



Scheme 45

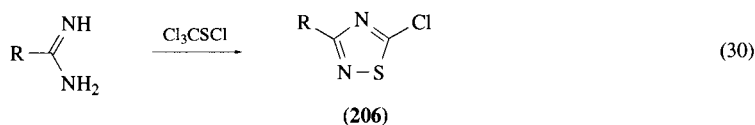
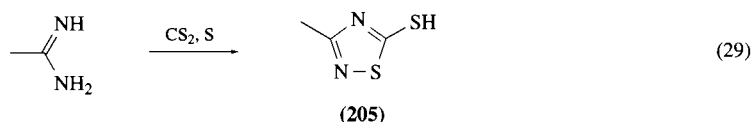


(204) are obtained from the reaction of (201) (R = H) or *N*-sulfenylamidines (203) with aryl-isothiocyanates (Scheme 46) <82AHC(32)285>.

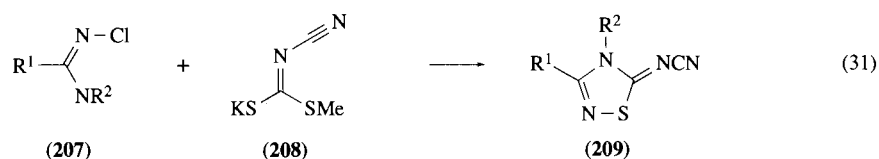


Scheme 46

Amidines are converted into 1,2,4-thiadiazoles by reaction with isothiocyanates, iminosulfonyl chlorides, di- and trichloromethyl sulfonyl chlorides, and carbon disulfide in the presence of sulfur <82AHC(32)285>; for example, 5-mercapto-3-methyl-1,2,4-thiadiazole (205) is obtained by the treatment of acetamidine with carbon disulfide and sulfur under basic conditions (Equation (29)) <85JAP85255783>. A useful method for the synthesis of 5-chloro-1,2,4-thiadiazole (206) (R = 6-methyl-2-pyridyl) involves the reaction of amidines with trichloromethylsulfonyl chloride (Equation (30)) <91JAP9183590>.

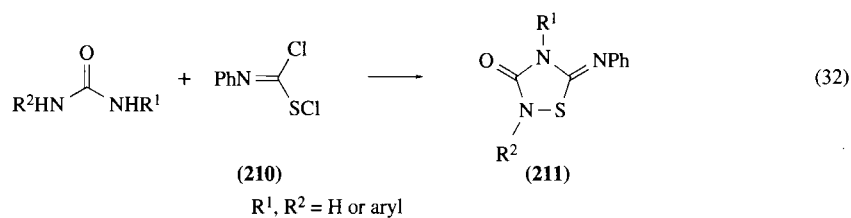


The *N*-haloamidine (207) reacts with the potassium salt of *S*-methyl cyanocarbonimidodithioate (208) to give 3,4-disubstituted 5-cyanimino-4,5-dihydro-1,2,4-thiadiazoles (209) (R¹ = aryl; R² = aryl, alkyl) (Equation (31)) <91EGP295368>.

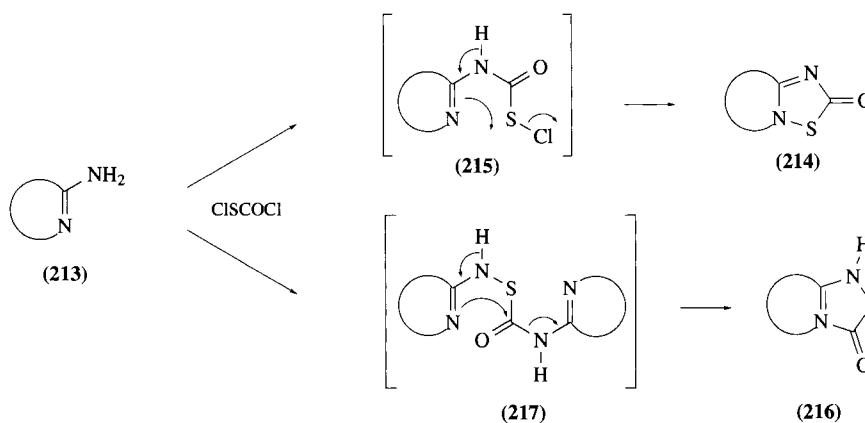


Ureas, thioureas, guanidines, carbodiimides, and cyanimides react with chlorocarbonylsulfonyl chloride to produce 1,2,4-thiadiazol-5-one derivatives <84CHEC-I(6)463>. Ureas also react with iminosulfonyl chlorides (210) to give 5-phenylimino-1,2,4-thiadiazol-3-ones (211) (Equation (32))

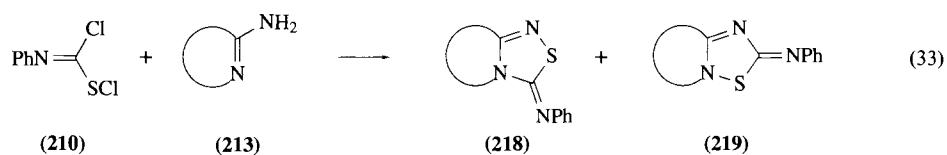
<80JIC1123>. Xanthogenic acid *O*-esters and salts (**212**) react with formamidine in the presence of sulfur to give 5-thio-1,2,4-thiadiazole (**10**) ($R = H$) <89JAP(K)01308270>.



Cyclic amidines (**213**) react with chlorocarbonylsulfonyl chloride to give bicyclic 1,2,4-thiadiazoles. The product isolated from this reaction depends on the mode of addition. When (**213**) is added to chlorocarbonylsulfonyl chloride, 3-oxo derivatives (**214**) are isolated via the postulated intermediate (**215**). Addition of chlorocarbonylsulfonyl chloride to (**213**) leads to 5-oxo derivatives (**216**), via the proposed bis(intermediate) (**217**) (Scheme 47) <84CHEC-I(6)463>. Cyclic amidines (**213**) have also been treated with 1-chloro-1-phenyliminomethanesulfonyl chloride (**210**) to afford 3*H*-1,2,4-thiadiazoles (**218**). The other possible product from this reaction, the 2*H*-isomer (**219**) has been shown to be unstable, rearranging to a benzothiazole. Heterocycles (**213**) which have been used in this transformation include 2-aminopyridine, 3-aminopyridazine, 2-aminobenzothiazole, 2-aminopyrimidine and 2-aminothiazole (Equation (33)) <86S1027>.

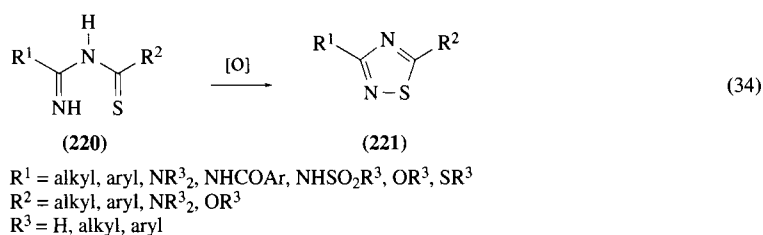


Scheme 47

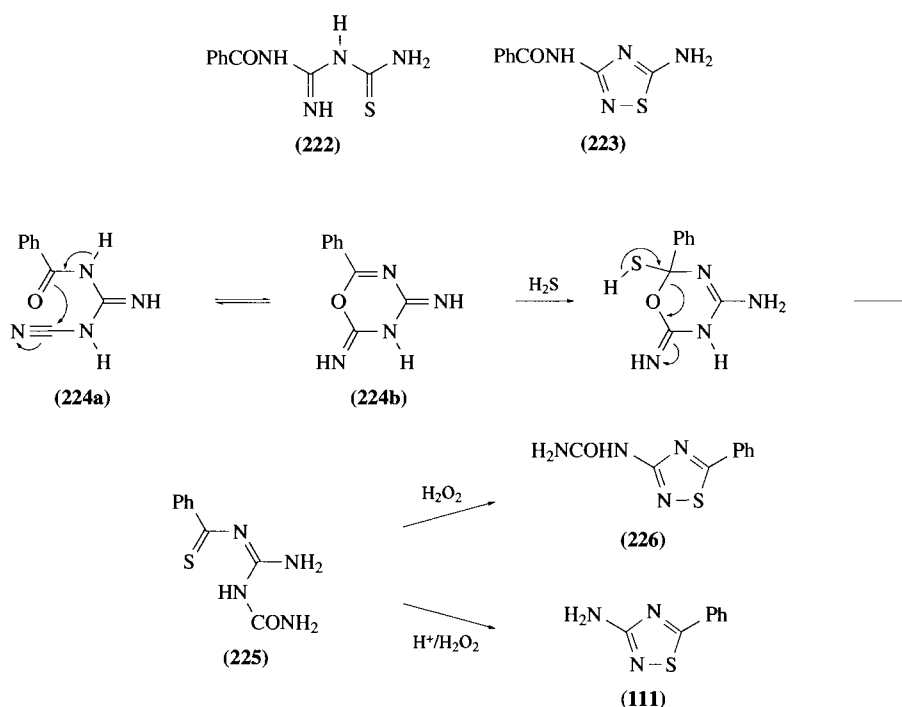


4.08.9.4 Type C Syntheses

The oxidation of thioacylamidines (**220**) ($R^1 = \text{alkyl, aryl}$) and thioacylguanidines (**220**) ($R^2 = \text{NR}^3_2$) affords a wide range of 3,5-disubstituted 1,2,4-thiadiazoles (**221**). A wide variety of oxidizing agents have been used for this conversion (Equation (34)) <82AHC(32)285>.

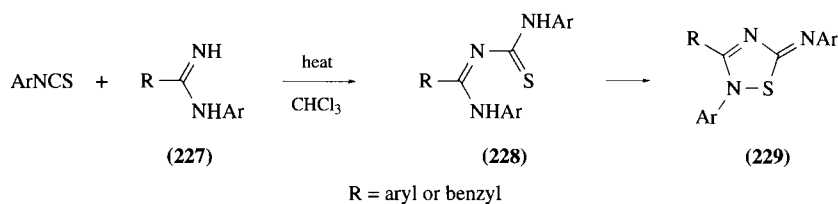


Treatment of the guanidine (**224**) with hydrogen sulfide in ethanolic solution was reported <52JOC1162> to give the thioamide (**222**). The structure of this thioamide was revised in 1984 to (**225**) <84JCS(P1)75>. Consequently, an earlier report <56JCS4524> which claimed that the product obtained by the treatment of the thioamide (**222**) with hydrogen peroxide under neutral conditions was the 1,2,4-thiadiazole (**223**) is now incorrect. The guanidine (**224a**) exists in equilibrium with (**224b**) which reacts with hydrogen sulfide to give (**225**) which is then oxidized under neutral conditions to give the 3-ureido-1,2,4-thiadiazole (**226**) (Scheme 48). 3-Amino-5-phenyl-1,2,4-thiadiazole (**111**) is obtained when (**225**) is treated with acidic hydrogen peroxide.



Scheme 48

Imidoylthioureas can be oxidatively ring closed to form 5-imino-1,2,4-thiadiazolines. Phenyl isothiocyanate reacts with various aryl or benzyl amidines (**227**) to give imidoylthioureas (**228**) which on treatment with *N*-chlorosuccinimide afford 5-imino-1,2,4-thiadiazolines (**229**) (Scheme 49) <85S83>.

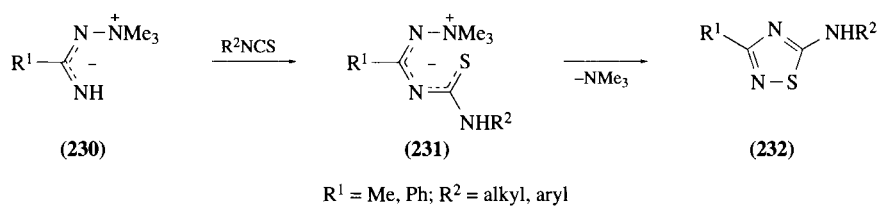


Scheme 49

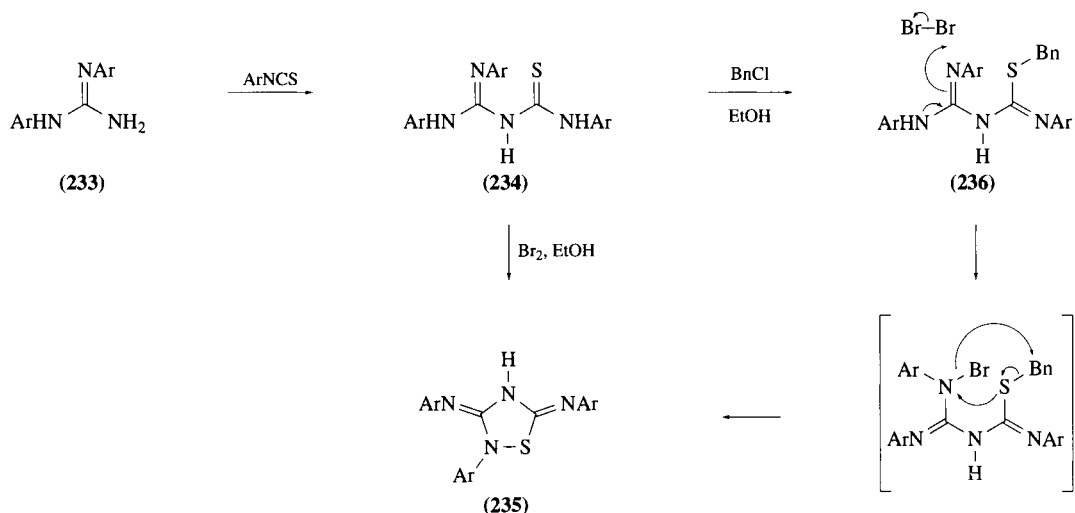
In a variation of this approach the reaction of amidrazone ylides (**230**) with both alkyl and aryl isothiocyanates yields thiocarbonyl substituted amidrazone ylides (**231**) which can be thermally cyclized to 5-amino-1,2,4-thiadiazoles (**232**) with the elimination of trimethylamine (Scheme 50) <81JHC201>.

The reaction of arylisothiocyanates with guanidines (**233**) affords amidinothioureas (**234**), which can be converted into 3,5-diarylimino-1,2,4-thiadiazolines (**235**) directly on treatment with bromine in ethanol. Alternatively, (**234**) can be alkylated with benzyl chloride to give the *S*-benzyl derivative (**236**) which on treatment with bromine in chloroform gives (**235**) (Scheme 51) <87JIC675>.

An alternative synthesis of amidinothioureas involves the reaction of α -chloroformamidines (**237**)

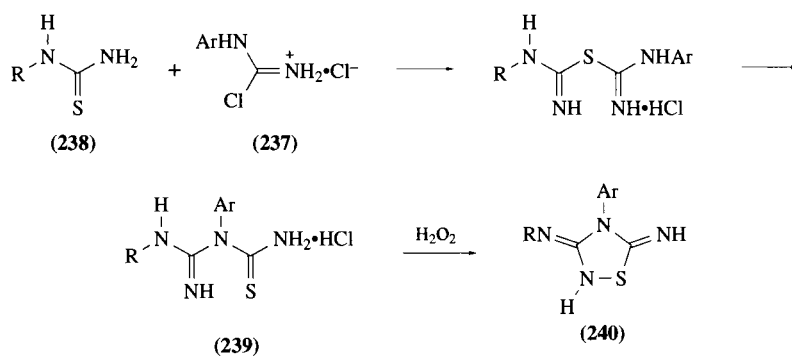


Scheme 50



Scheme 51

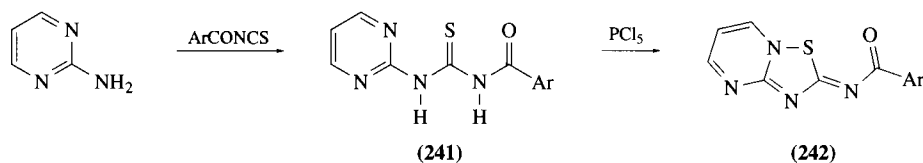
with substituted thioureas (238) to give bis(formamidine) salts (239). Oxidation of (239) with hydrogen peroxide affords 3,5-diimino-1,2,4-thiadiazolidines (240) (Scheme 52) <81JJC(B)825>.



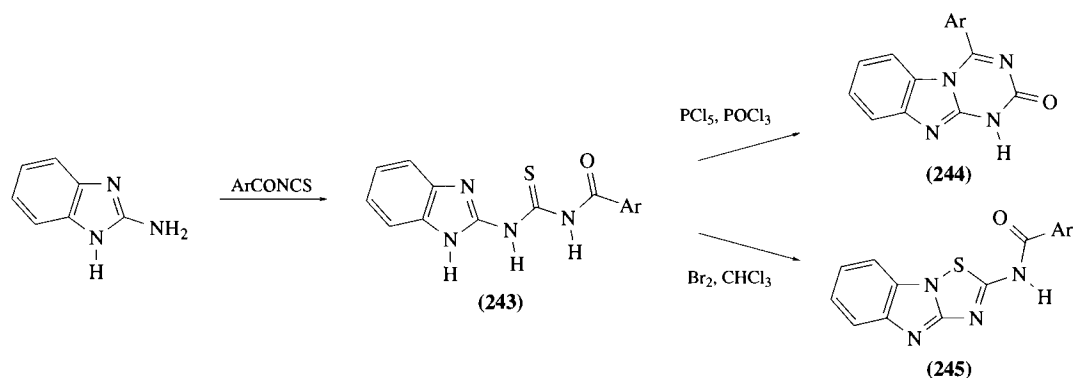
Scheme 52

2-Aminopyrimidine and 2-aminobenzimidazole both react with aroylthiocyanates to give amidinothioureas. The amidinothiourea (241) derived from 2-aminopyrimidine is oxidatively cyclized with PCl₅ to give the pyrimido[3,2-*b*]-1,2,4-thiadiazoline (242) (Scheme 53) <89SC2621>. The reaction of the amidinothiourea (243) derived from 2-aminobenzimidazole with PCl₅ in POCl₃ did not lead to a 1,2,4-thiadiazoline; the triazinone (244) was the only product isolated. However, oxidation of (243) with Br₂ in CHCl₃ affords the benzimidazolo-[1,2-*b*]-1,2,4-thiadiazoline (245) (Scheme 54) <89SC965>.

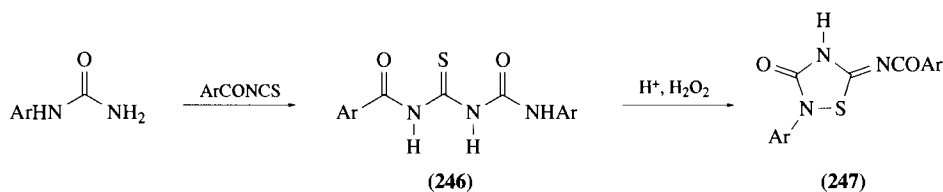
The addition of arylthioureas to benzoylthiocyanate affords good yields of 5-aryl-1-benzoyl-2-thiobiurets (246). Treatment of (246) with acidic hydrogen peroxide gives 5-benzoylamino-3-oxo-1,2,4-thiadiazolines (247) in high yields (Scheme 55) <81S232>.



Scheme 53

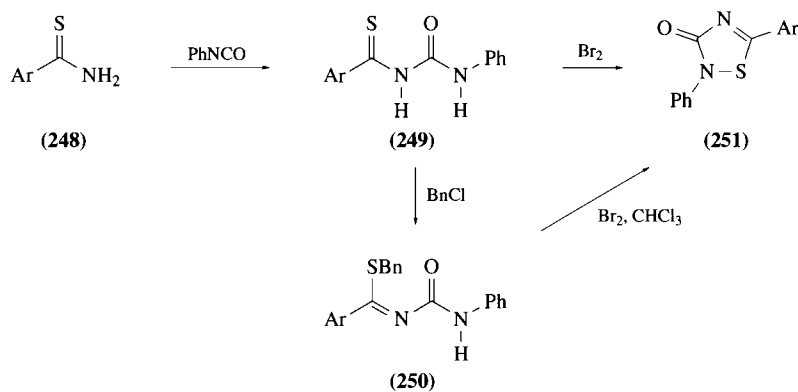


Scheme 54



Scheme 55

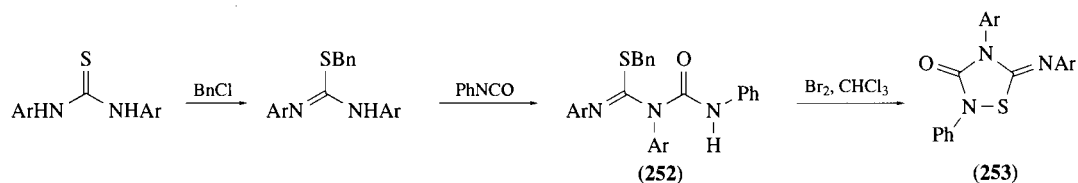
The reaction of arylthioamides (**248**) with phenylisocyanate affords the arenethiocarboxamide (**249**), which can be benzylated to give (**250**) and then converted into 5-aryl-3-oxo-2-phenyl-1,2,4-thiadiazoline (**251**) on treatment with bromine in chloroform. Alternatively, (**249**) can be transformed into (**251**) by direct oxidation with bromine (Scheme 56) <85IJC(B)977>.



Scheme 56

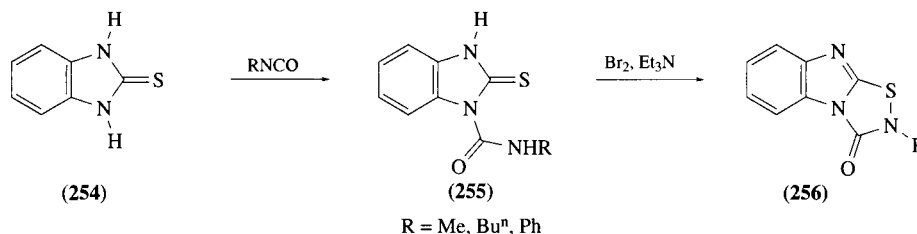
This method has been extended to include 1,3-diarylthioureas which are benzylated and then treated with phenylisocyanate to give *S*-benzylisothiobiurets (**252**). Oxidative debenzilation with

bromine in chloroform leads to 5-arylamino-3-oxo-1,2,4-thiadiazolidines (**253**) (Scheme 57) <86JCB202>.



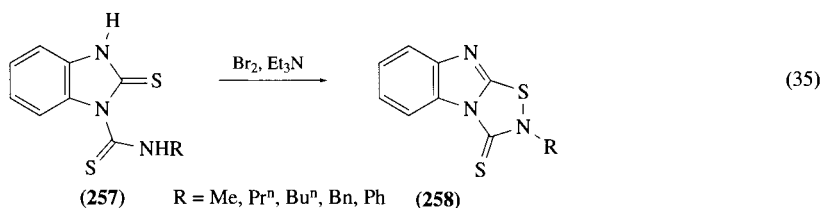
Scheme 57

Reaction of alkyl or aryl isocyanates with benzimidazolinethione (**254**) affords the *N*-carbamyl derivative (**255**). Treatment of (**255**) with bromine in triethylamine gives the benzimidazolo[1,2-*d*]-1,2,4-thiadiazoline (**256**) (Scheme 58). A related thioanalogue (**258**) was obtained by a similar process from the *N*-thiocarbonyl derivative (**257**) (Equation (35)) <83T2311>.



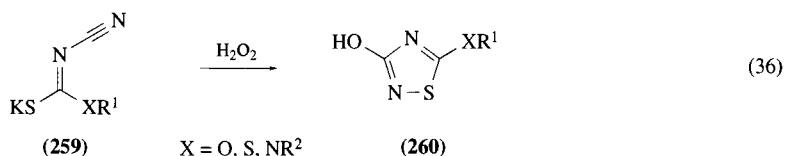
R = Me, Buⁿ, Ph

Scheme 58



R = Me, Prⁿ, Buⁿ, Bn, Ph

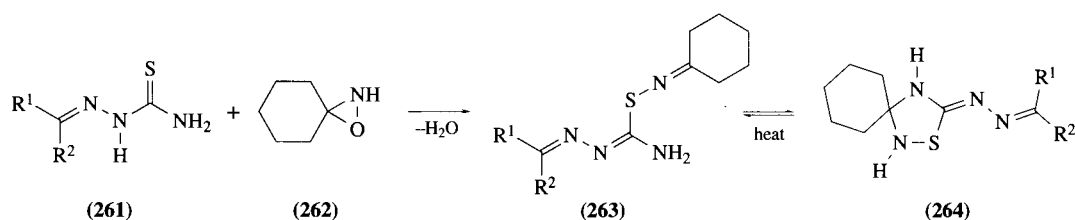
Cyanodithioimidocarbonate salts and alkylated derivatives (**259**) are useful reagents for the preparation of 1,5-substituted 1,2,4-thiadiazoles (**260**) <84CHEC-I(6)463>. A small number of examples of this approach have been reported in the 12 years from 1984 to 1996 (Equation (36)) <85JPR823, 87JPR355>.



X = O, S, NR²

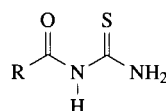
4.08.9.5 Type D Syntheses

An example of a type D synthesis involves the reaction of thiosemicarbazones of aldehydes, ketones and esters (**261**) with 3,3-pentamethyleneoxaziridine (**262**). Thioximes (**263**) which are initially formed by nucleophilic ring opening of the oxaziridine ring by sulfur can then be thermally cyclized to 5-imino-3,3-pentamethylene-1,2,4-thiadiazolidines (**264**) (Scheme 59). *N*-Acylthioureas (**265**) (R = Me, Ph) also undergo this transformation but whereas the reaction is fairly general for thiosemicarbazones (**261**), only acetyl and benzoyl thioureas give 1,2,4-thiadiazolidines <87JPR1008>.



R¹, R² = Me, H; Me, Me; -(CH₂)₅-; Ph, H; Ph, OEt

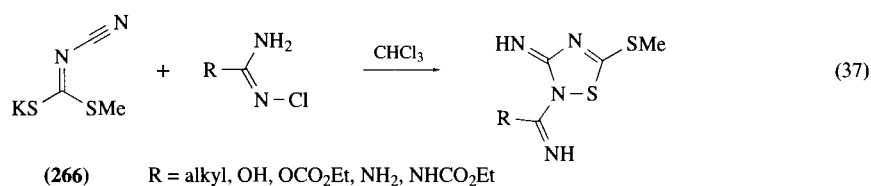
Scheme 59



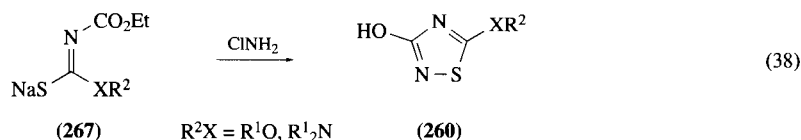
(265) R = Ph, Me

4.08.9.6 Type E Syntheses

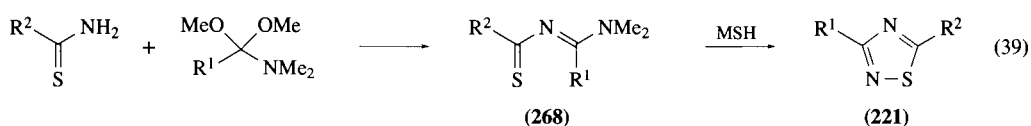
N-Chloro derivatives of amidines, isoureas and guanidines react with potassium *S*-methylcyanodithioiminocarbonate (266) to yield 2,5-substituted 3-amino-1,2,4-thiadiazoles (Equation (37)) <84CHEC-I(6)463>.



Chloroamine reacts with both (266) and ethoxycarbonylthioiminocarbonates (267) to give 3-amino and 3-hydroxy-1,2,4-thiadiazoles (260) (Equation (38)) <84CHEC-I(6)463>.



Thioamides or thioureas condense with *N,N*-dimethylacetyl dimethyl acetal to give imino compounds (268) which react with amino transfer reagents like hydroxylamine-*O*-sulfonic acid and mesitylsulfonyloxyamine (MSH) to give 3,5-substituted 1,2,4-thiadiazoles (221) in excellent yields (Equation (39)) <84CHEC-I(6)463>.



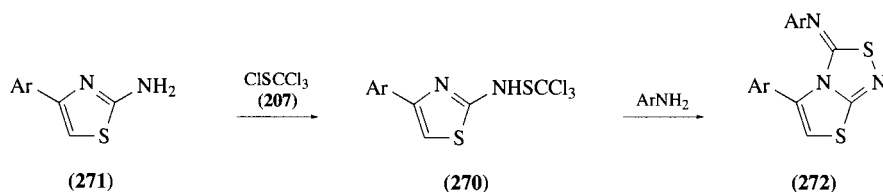
A more recent example, from the early 1990s, of a type E synthesis involves the reaction of the thioamide (269) with 3,3-pentamethyleneoxaziridine (262) to give the 3,5-substituted 1,2,4-thiadiazoles (Equation (40)) <91EGP293114>.



R = alkyl, aryl, heteroaryl

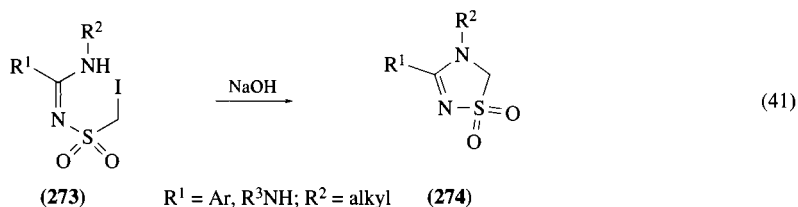
4.08.9.7 Type F Syntheses

The condensation reaction of cyclic amidines with trichloromethylsulfenyl chloride yields sulfenamides, which afford 5-arylimino-1,2,4-thiadiazolines on treatment with aromatic amines <84CHEC-I(6)463>. An example of this type of reaction starting from 2-amino-4-arylthiazoles (**271**) affords 3*H*-thiazolo[2,3-*c*]-1,2,4-thiadiazoles (**272**), via the sulfenamide (**270**) (Scheme 60) <88IJC(B)501>.



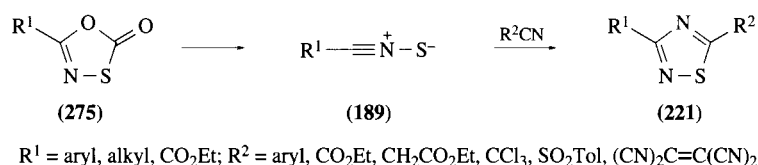
Scheme 60

1,2,4-Thiadiazole *S,S*-dioxides (**274**) have been prepared by the cyclization of *N*-halomethylsulfonyl amidines and guanidines (**273**) (Equation (41)) <84CHEC-I(6)463>.



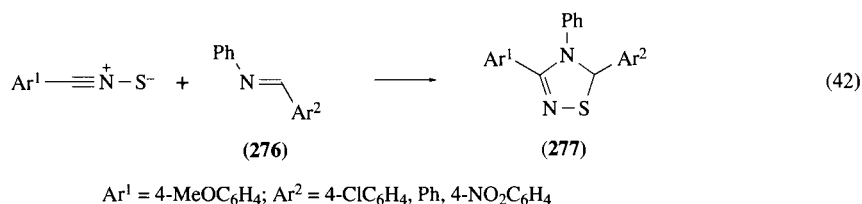
4.08.9.8 Type G Syntheses

The 1,3-dipolar cycloaddition reaction between nitrile sulfides (**189**), produced by the thermal decomposition of oxathiazolones (**275**) and nitriles, is a general method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles (**221**) of unambiguous structure (Scheme 61) <84CHEC-I(6)463>. More recently, in the mid-1980s, trichloroacetonitrile <86PS(26)151> and tosyl cyanide <93JHC357> have been used as acceptor molecules to give the 5-trichloromethyl and 5-tosyl derivatives in high and moderate yields, respectively. Displacement of the tosyl group by a range of nucleophiles leads to a wide variety of 5-substituted analogues.



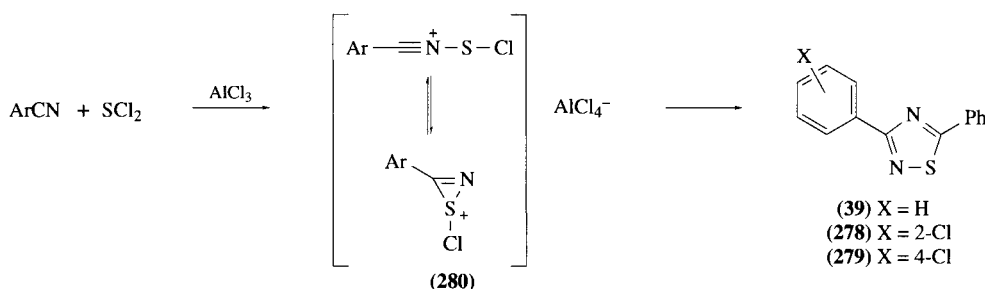
Scheme 61

In contrast, the reaction of Schiff's bases (**276**) with aryl nitrile sulfides yields 1,2,4-thiadiazolines (**277**) in very low yields (2–5%) (Equation (42)) <86JCR(S)156>.



4.08.9.9 Miscellaneous Synthetic Methods

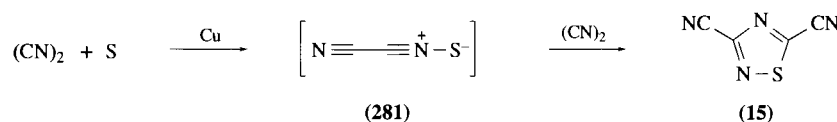
The reaction of sulfur dichloride with benzonitrile in the presence of a Lewis acid catalyst yields 3,5-diphenyl-1,2,4-thiadiazole (**39**), along with the 3-*o*-chlorophenyl (**278**) and 3-*p*-chlorophenyl (**279**) analogues in a total yield of 80%. The proposed mechanism proceeds via a complex between benzonitrile, Lewis acid; for example, aluminum trichloride, and sulfur dichloride to give an intermediate (**280**) which then adds a second molecule of nitrile (Scheme 62) <83BCJ180>.



Scheme 62

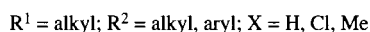
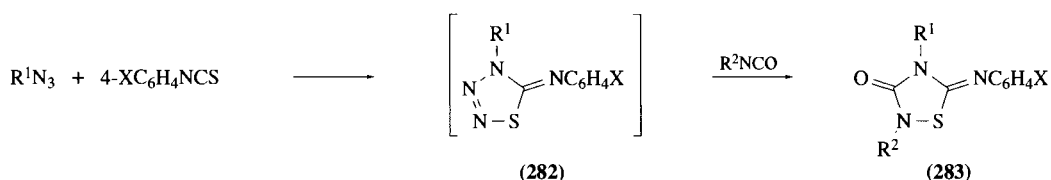
Thiadiazole (**39**) (X = H) can also be obtained in 75% yield when benzonitrile, sulfur, and a catalytic amount of tri-*n*-octylamine are heated to 250°C. A benzonitrile sulfide intermediate may also be involved in this reaction <84CHEC-I(6)463>.

3,5-Dicyano-1,2,4-thiadiazole (**15**) is formed in 70% yield by the cyclocondensation of cyanogen with sulfur using a copper catalyst at 100–150°C. The authors propose a mechanism involving the cyanonitrile sulfide intermediate (**281**) which then undergoes a 1,3-dipolar cycloaddition reaction with a second molecule of dicyanonitrile (Scheme 63) <84GEP(O)3309515>.



Scheme 63

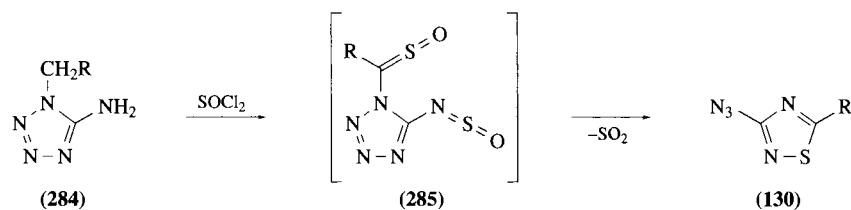
A mixture of alkyl azides, substituted phenyl isothiocyanate and aryl or alkyl isocyanate are reported to yield 5-arylamino-1,2,4-thiadiazolin-3-ones (**283**) via a proposed 1,2,3,4-thiatriazoline (**282**) (Scheme 64) <84CHEC-I(6)463>.



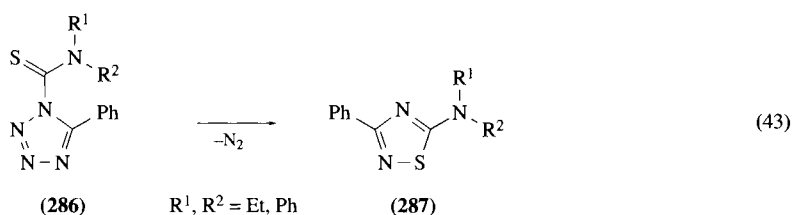
Scheme 64

The first synthesis of an azido substituted 1,2,4-thiadiazole has been reported <86CC800>. When 1-alkyl-5-aminotetrazoles (**284**) are heated with an excess of thionyl chloride, 3-azido-1,2,4-thiadiazoles (**130**) are formed via the proposed intermediate (**285**) (Scheme 65).

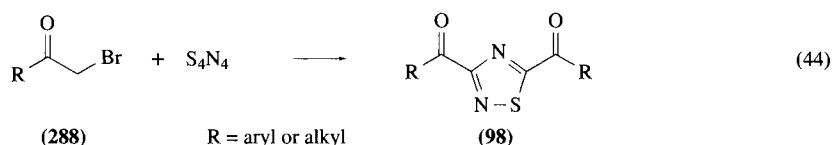
A similar transformation occurs during the thermolysis of 1-thiacarbamyl-5-phenyl tetrazole (**286**) to give 5-amino-3-phenyl-1,2,4-thiadiazole (**287**) (Equation (43)) <92JPR283>.



Scheme 65



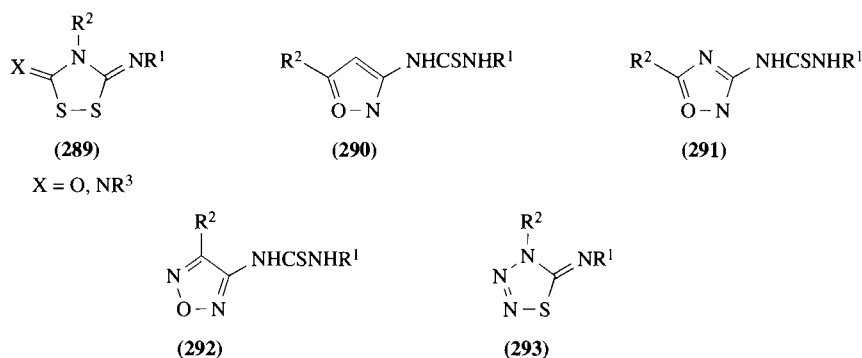
Reaction of tetrasulfur tetranitride with aryl and alkyl bromomethyl ketones (288) in refluxing chlorobenzene gives 3,5-diaroyl and 3,5-diacyl-1,2,4-thiadiazoles (98) in yields of 17–60% (Equation (44)) <92JHC1433>.



4.08.10 RING SYNTHESIS BY TRANSFORMATION OF OTHER HETEROCYCLES

4.08.10.1 Introduction

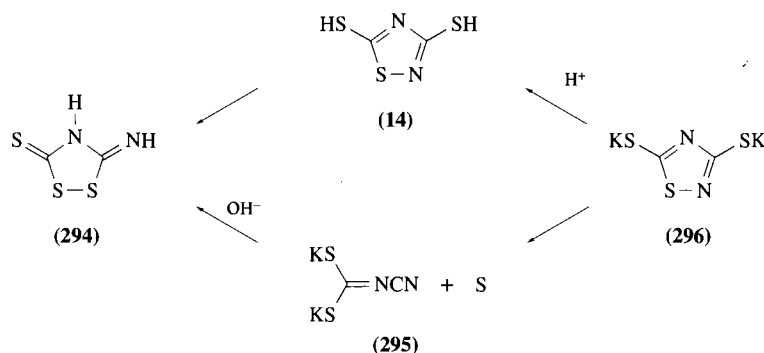
A number of ring systems have been converted into 1,2,4-thiadiazole derivatives. The most common include: 5-imino-1,2,4-dithiazolidines (289), isoxazoles (290), oxadiazoles (291), and (292), and 5-imino-1,2,3,4-thiatriazolines (293). In general a ring opening reaction is followed by rotation and ring closure, or the heterocyclic ring may act as a masked 1,3-dipole which reacts with a suitable dipolarophile.



4.08.10.2 Dithiazolidine Rearrangements

The interconversion between dithiazoles and thiadiazoles and the relationship between isoperthiocyanic acid (294) and perthiocyanic acid (14) have been elucidated <82AHC(32)285>. A mixture

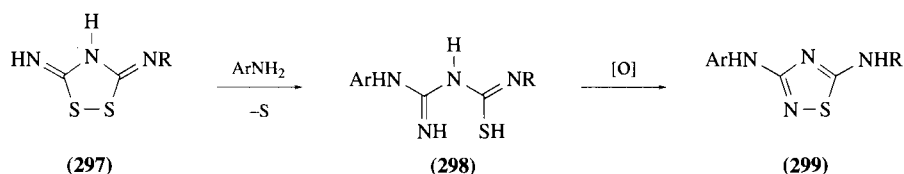
of hydrochloric acid and ammonium thiocyanate react to give 3-imino-5-thiono-1,2,4-dithiazolidine (isoperthiocyanic acid, **(294)**) which isomerizes under the influence of alkali, via the intermediate cyanodithioimidocarbonate (**(295)**) to the percyanate anion (**(296)**). Acidification of (**(296)**) liberates the unstable 3,5-dithio-1,2,4-thiadiazole (perthiocyanic acid, **(14)**) which reverts back spontaneously to the starting material (**(294)**) (Scheme 66).



Scheme 66

The dipotassium salt of 3,5-dithio-1,2,4-thiadiazole (**(296)**) can be easily prepared by refluxing a solution of dipotassium cyanodithioimidocarbonate (**(295)**) with sulfur in methanol <82AHC(32)285>.

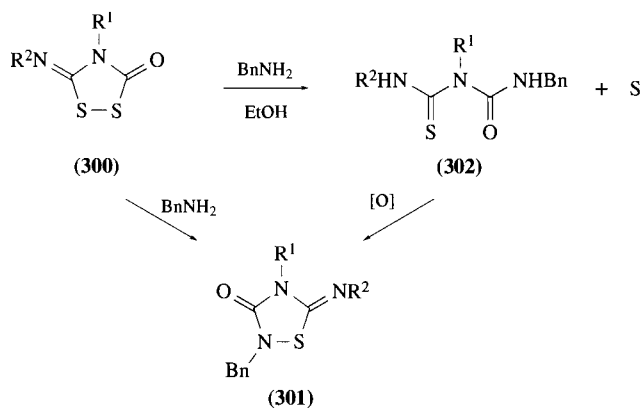
The treatment of thiurets (diimino-1,2,4-dithiazolidines, **(297)**) with aromatic amines results in ring opening to form thiocarbamylguanidines (**(298)**) and sulfur; cyclization to 3,5-diamino-1,2,4-thiadiazole derivatives (**(299)**) can occur spontaneously or upon oxidation (Scheme 67) <84CHEC-I(6)463>.



Scheme 67

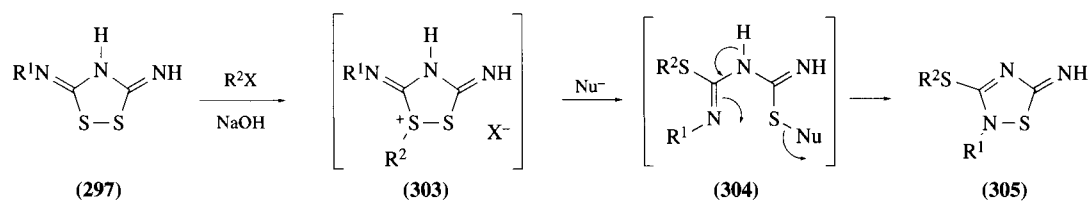
A similar transformation occurs when 5-imino-3-oxo-1,2,4-dithiazolidine (**(300)**) is treated with neat benzylamine to give 2-benzyl-3-oxo-5-imino-1,2,4-thiadiazolidine (**(301)**). When the reaction is carried out in ethanolic solution the thiobiuret (**(302)**) is formed which can then be oxidized to (**(301)**) (Scheme 68) <82JIC71>.

The alkylation of thiurets (**(297)**) in basic media affords 3-thio-5-imino-1,2,4-thiadiazolidines (**(305)**)



Scheme 68

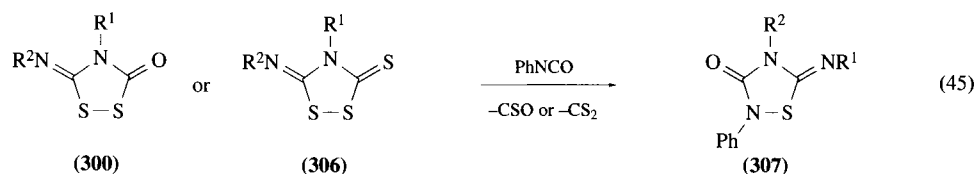
possibly via intermediates such as (303), and (304) (Scheme 69). Treatment of (305) with acid results in isomerization back to (297) <84CHEC-I(6)463>.



Scheme 69

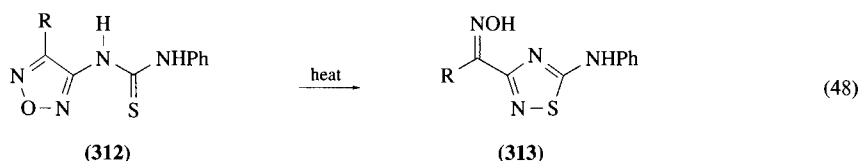
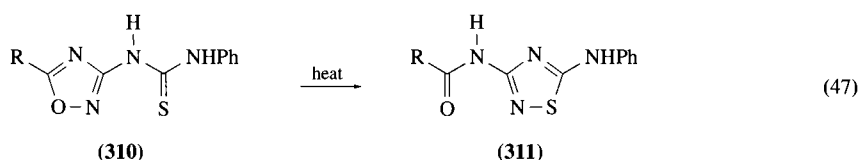
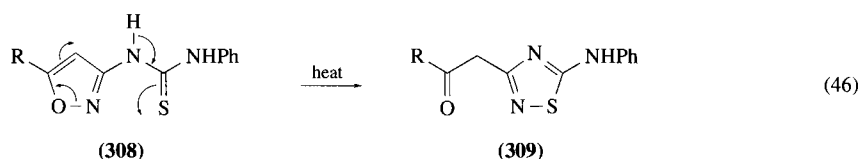
Isothiocyanate sulfide (72) undergoes a Dimroth rearrangement upon heating to afford *N,N'*-dimethyldithiono-1,2,4-thiadiazole (71). This reaction can be reversed by treating (71) with acid followed by neutralization <84CHEC-I(6)463>. Compound (72) also possesses two functions (S—C=N and S—C=S) that are capable of reacting as masked 1,3-dipoles. Reaction of (72) or (71) with a range of nitriles affords 1,2,4-thiadiazolines (73) and methyl isothiocyanate in good yields (Scheme 18) <91JOC3268>.

A related cycloaddition/elimination reaction occurs when 5-imino-1,2,4-dithiazolidin-3-ones (300) or -3-thiones (306) are treated with phenylisocyanate to afford 2-phenyl-5-imino-1,2,4-thiadiazolidin-3-ones (307) (Equation (45)) <92JPR685>.



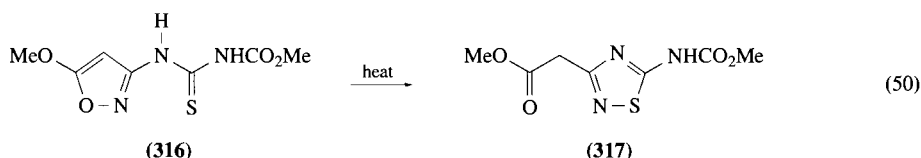
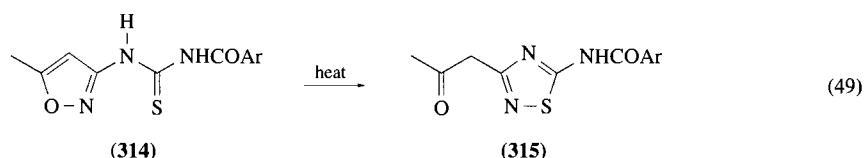
4.08.10.3 Oxazole and Oxadiazole Rearrangements

5-Alkyl-3-aminoisoxazoles, 5-alkyl-3-amino-1,2,4-oxadiazoles, and 5-alkyl-3-amino-1,2,5-oxadiazoles, when heated with phenyl isothiocyanate produce the corresponding thioureas (308) (Equation (46)), (310) (Equation (47)) and (312) (Equation (48)) which subsequently rearrange by a common mechanism to yield 1,2,4-thiadiazoles (309), (311), and (313), respectively <84CHEC-I(6)463>.



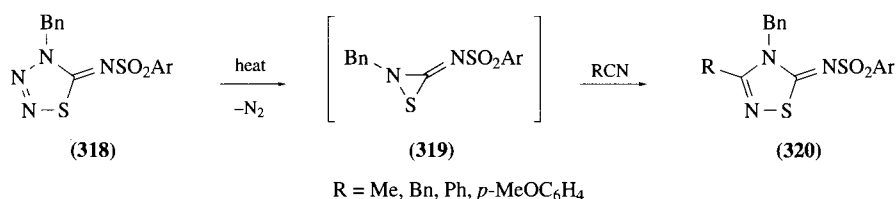
3-Amino-5-methylisoxazole reacts with aroylisothiocyanates to yield the thiourea (314) which can be thermally cyclized to (315) in high yield by a similar mechanism (Equation (49)) <88SUL101>.

3-Amino-5-methoxyisoxazole also reacts with methoxycarbonylthiocyanate at 20°C to give the 1,2,4-thiadiazole (**317**) in high yield via the thiourea (**316**) (Equation (50)) <93TL6423>.

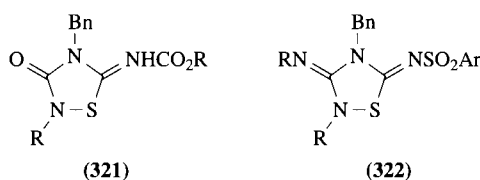


4.08.10.4 Thiatriazoline Rearrangements

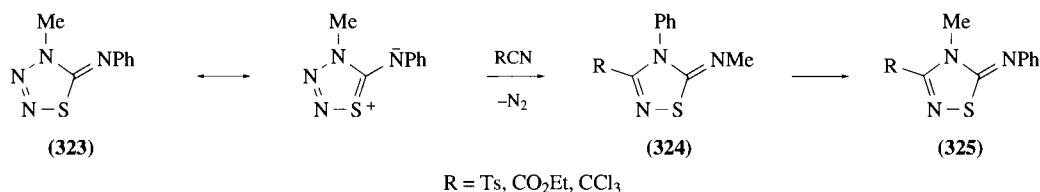
The thermolysis of 4-benzyl-5-sulfonyliminothiatriazolines (**318**) in the presence of a variety of nitriles yields 5-imino-1,2,4-thiadiazolines (**320**). These reactions have been interpreted as proceeding via a thiaziridinimine intermediate (**319**) (Scheme 70) <76JOC3403>. 1,2,4-Thiadiazoles are also obtained when the thermolysis is carried out in the presence of isocyanates to give (**321**) and carbodiimides to give (**322**) <84CHEC-I(6)463>.



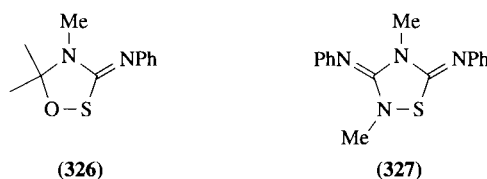
Scheme 70



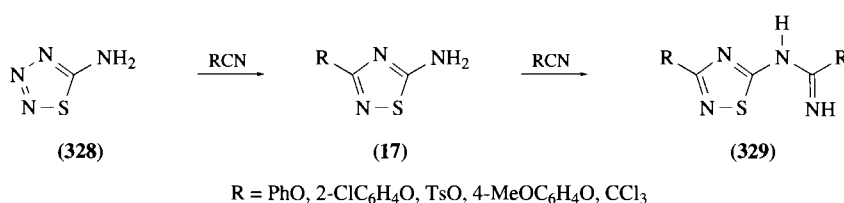
In contrast, the 5-phenyliminothiatriazoline (**323**) reacts as a masked 1,3-dipole with a variety of electrophilic nitriles. Tosyl cyanide and ethyl cyanofornate both react with (**323**) in refluxing chloroform to give initially (**324**) which then isomerizes to (**325**) as the reaction proceeds (Scheme 71) <91JHC333>. When the solvent is changed to acetone the reaction with the nitriles proceeds faster due to the formation of the adduct (**326**) which is capable of undergoing cycloaddition/elimination reactions at 20°C. Trichloroacetonitrile does not react with (**323**) in chloroform solution; in acetone, 2,4-dimethyl-3,5-diphenylimino-1,2,4-thiadiazolidine (**327**), a decomposition product of (**323**), and a small amount of (**324**) (R = CCl₃) are formed <91JHC333>.



Scheme 71

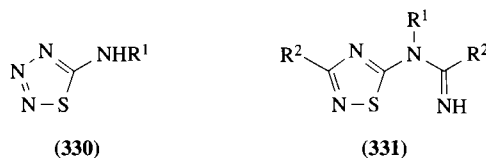


5-Aminothiatriazole (**328**) reacts with a number of aryl cyanates at 0°C to afford 3-substituted 5-amino-1,2,4-thiadiazoles (**17**) in moderate yields. 5-Aminothiatriazole (**328**) also reacts with trichloroacetonitrile to give (**17**) (R = CCl₃) in 92% yield. When these reactions are carried out at 30°C, the thiadiazoles (**17**) react with a second mole of aryl cyanate to give the amidino compounds (**329**) (Scheme 72) <85JOC1295>.

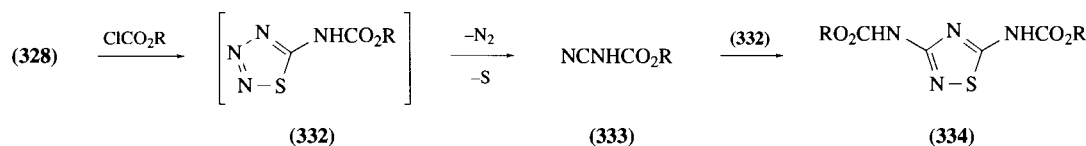


Scheme 72

5-Alkyl or aryl aminothiatriazoles (**330**) in contrast react with cyanates even at -70°C to give 5-amidino substituted 1,2,4-thiadiazoles (**331**); weaker electrophiles, such as isothiocyanates, thio-cyanates, and cyanamide do not react with aminothiatriazoles <85JOC1295>.



5-Aminothiatriazole (**328**) also reacts with chloroformates to afford 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazoles (**334**) in moderate yields. The proposed mechanism involves the unstable carbamic ester (**332**) which upon loss of nitrogen and sulfur gives alkoxycarbonyl cyanamide (**333**), which then reacts with (**332**) to give (**334**) (Scheme 73) <89M997>.

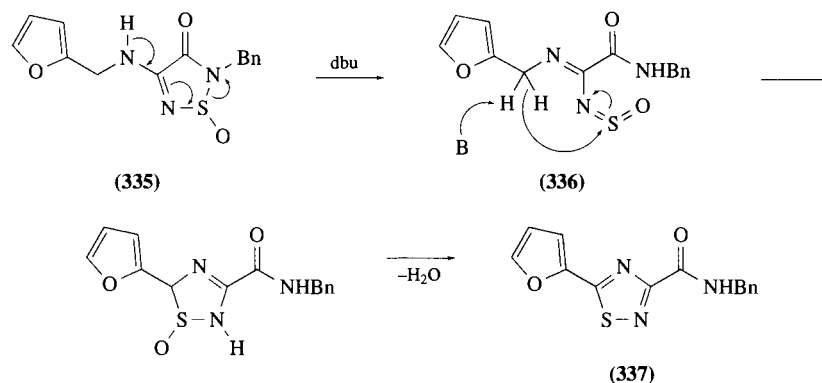


Scheme 73

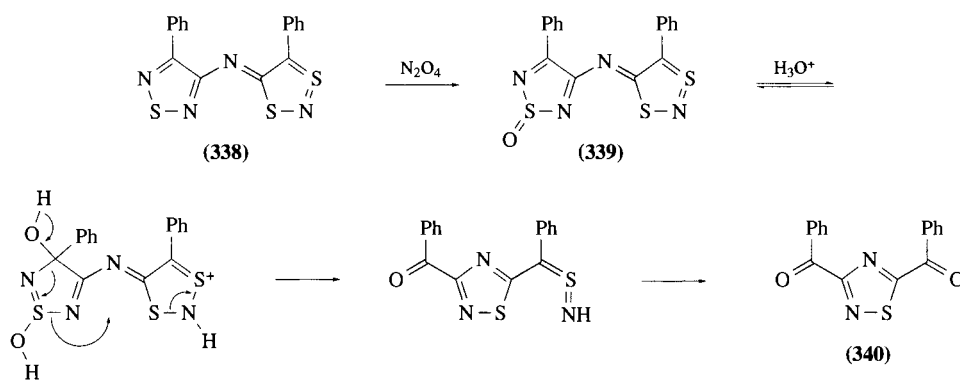
4.08.10.5 Miscellaneous Ring Transformations

The 1,2,5-thiadiazole-1-oxide (**335**) when treated with a strong base in refluxing xylene gave the 1,2,4-thiadiazole (**337**) in low yield. The reaction is thought to proceed by carbanion addition to a sulfinylamine intermediate (**336**) (Scheme 74) <86H(24)1193>.

The reaction of tetrasulfur tetranitride with phenylacetylene affords the imine (**338**), which can be oxidized to the monoxide (**339**). The monoxide (**339**) then undergoes facile hydrolysis to 3,5-dibenzoyl-1,2,4-thiadiazole (**340**) probably by the mechanism shown in Scheme 75 <89CC1134>.



Scheme 74



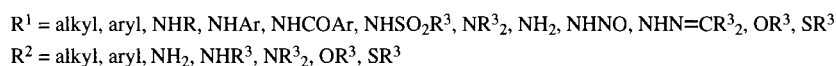
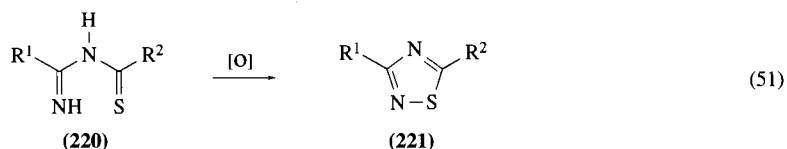
Scheme 75

4.08.11 PRACTICAL METHODS FOR SYNTHESIS OF DERIVATIVES

4.08.11.1 General Survey

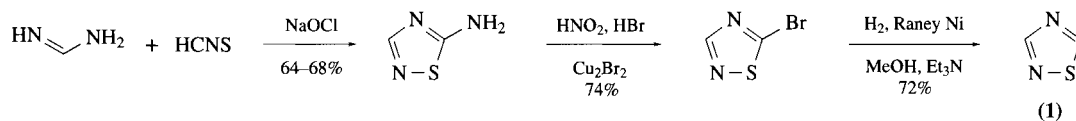
The transformation of 1,2,4-thiadiazoles bearing a reactive substituent such as amino or halogen group in the 5-position is the most useful method for the synthesis of 5-substituted 1,2,4-thiadiazole derivatives. The latter compounds can be reacted with nucleophiles to afford a wide range of derivatives.

The oxidation of thioacyl amidines and related compounds (220) is a versatile ring forming reaction which can furnish a range of 3- and 5-substituted 1,2,4-thiadiazoles (221) (Equation (51); see also Equation (34)). Other ring forming reactions which can give specific types of derivatives are discussed in the following sections.



4.08.11.2 Parent Compound

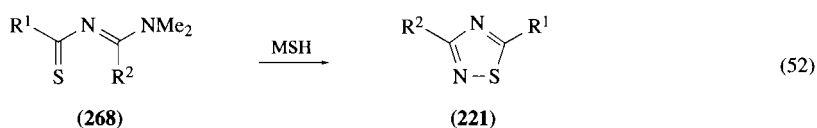
The only synthesis of 1,2,4-thiadiazole (1) was reported by Goerdler *et al.* in 1955 and is illustrated in Scheme 76 <84CHEC-I(6)463>. Owing to the sensitivity of (1) to ring-opening reactions, it is not a suitable starting material for the preparation of other derivatives.



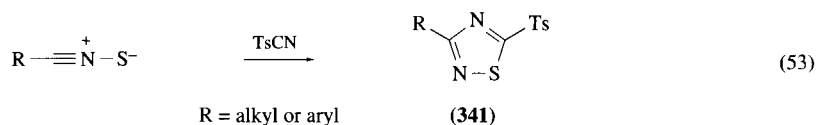
Scheme 76

4.08.11.3 C-Linked Derivatives

The coupling of thioamides with a variety of oxidizing agents is a widely utilized method for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles. The yields reported for this method are quite variable (Equation (26)) <84CHEC-I(6)463>. Thioamides also condense with *N,N*-dimethylacetyl dimethyl acetal to give imino compounds (**268**) which react with amino transfer reagents such as mesityl-sulfonyloxyamine (MSH) to yield 3,5-diaryl and 3,5-dialkyl 1,2,4-thiadiazoles (**221**) in excellent yields (Equation (52); see also Equation (39)) <84CHEC-I(6)463>.

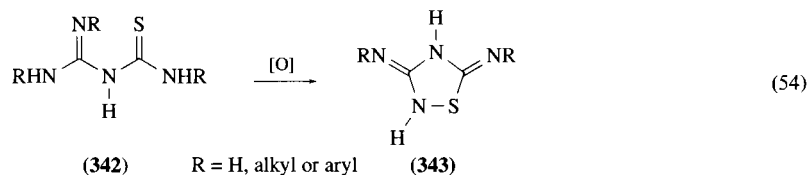


The 1,3-dipolar cycloaddition reaction of nitrile sulfides with nitriles yields 3,5-disubstituted 1,2,4-thiadiazoles of unequivocal structure. This method has received considerable attention in recent years. Electron deficient nitriles such as tosyl cyanide afford high yields of 5-tosyl derivatives (**341**) (Equation (53); see also Scheme 61) <93JHC357>.



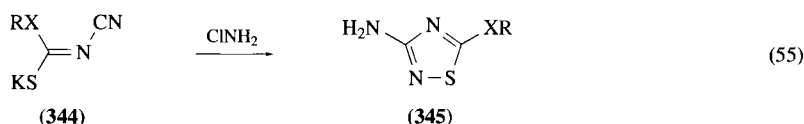
4.08.11.4 N-Linked Derivatives

Amidinothiureas (**342**) are oxidized by a range of oxidizing agents to give 3,5-diimino derivatives (**343**) (Equation (54); see also Schemes 51 and 52) <81IJC(B)825, 87JIC675>.



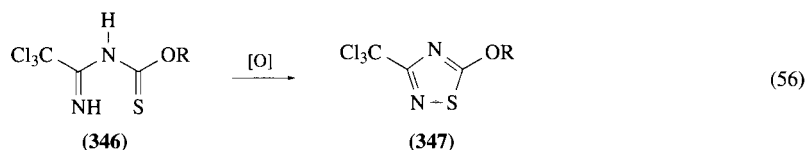
The oxidation of *N*-arylthiureas produces “Hectors bases” which readily isomerize to give 3,5-diamino-1,2,4-thiadiazoles (Equation (28)). Imidoylthiureas (**228**) when treated with *N*-chlorosuccinimide afford 5-imino-1,2,4-thiadiazolines (**229**) (Scheme 49) <85S83>.

A variety of 3-amino and 3,5-diamino-1,2,4-thiadiazoles (**345**) have been obtained by the treatment of iminocarbonates (**344**) with chloramine at low temperatures (Equation (55); see also Equation (38)) <84CHEC-I(6)463>.

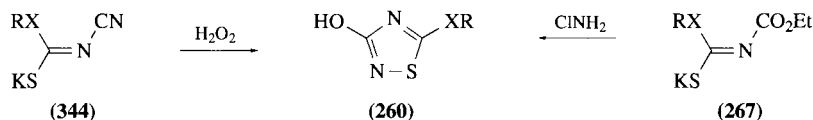


4.08.11.5 O-Linked Derivatives

The oxidation of *N*-alkoxythiocarbonylamidines (**346**) is a good method for the preparation of 5-alkoxy-1,2,4-thiadiazoles (**347**) (Equation (56)), <84CHEC-I(6)463>.



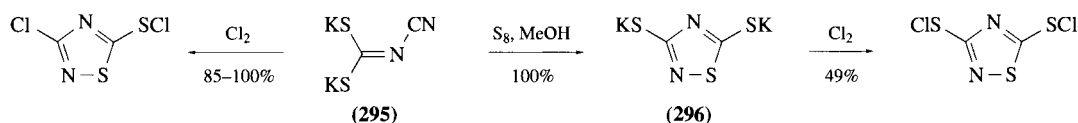
3-Hydroxy and 3-hydroxy-5-alkoxy derivatives (**260**) result from the oxidation of imino-dicarbonates of type (**344**) (X = O, S, N) with hydrogen peroxide (Scheme 77; see also Equation (36)) <84CHEC-I(6)463>. Products of type (**260**) are also obtained from the reaction of imino-dicarbonates (**267**) with chloramine (see also Equation (38)).



Scheme 77

4.08.11.6 S-Linked Derivatives

The most convenient method of preparing thio derivatives of 1,2,4-thiadiazoles is via dipotassium cyanodithioiminocarbonate (**295**), as illustrated in Scheme 78 <84CHEC-I(6)463>.

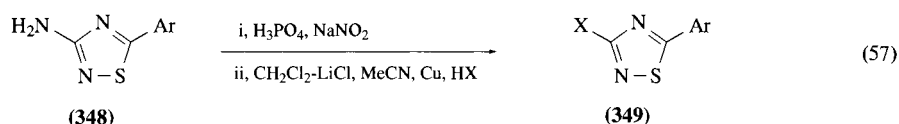


Scheme 78

Amidines and amidoximes react with carbon disulfide and a mixture of carbon disulfide and sulfur to afford 5-mercapto-1,2,4-thiadiazole derivatives (Scheme 46 and Equation (29)). The latter compounds are also obtained when xanthogenic acid *O*-esters react with ureas in the presence of sulfur <89JAP(K)01308270>.

4.08.11.7 Halogen-linked Derivatives

A useful method for the synthesis of 5-chloro-1,2,4-thiadiazoles (**206**) is the reaction of amidines with trichloromethylsulfenyl chloride (see Equation (30)). 3-Halo derivatives (**349**) (X = Cl, Br, I) (Equation (57)) have been obtained in moderate yields from the corresponding amines (**348**) via the Sandmeyer–Gatterman reaction <84CHEC-I(6)463>. 3-Chloro-1,2,4-thiadiazolin-5-ones (**350**) and (**351**) can be prepared by reacting chlorocarbonylsulfenyl chloride with carbodiimides or cyanamides respectively (Scheme 79) <84CHEC-I(6)463>.



4.08.12 IMPORTANT COMPOUNDS AND APPLICATIONS

4.08.12.1 Introduction

1,2,4-Thiadiazoles have a wide variety of uses, in particular as biologically active compounds in agriculture and in medicine, as dyestuffs, lubricant additives, and vulcanization agents. Reviews of

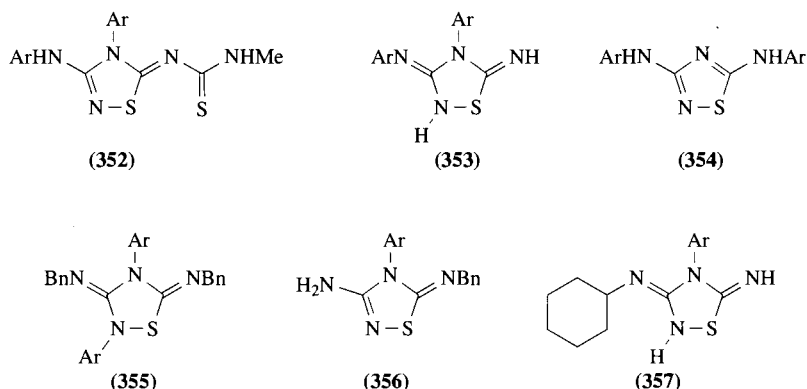


Scheme 79

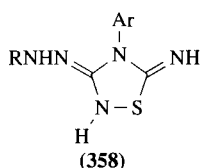
the relevant literature prior to 1982 are available <82AHC(32)285, 84CHEC-I(6)463>. During the 12 years from 1982 to 1994, 1,2,4-thiadiazole derivatives have been reported in particular to have numerous biological applications.

4.08.12.2 Biologically Active Compounds

Since 1982 a variety of 1,2,4-thiadiazole derivatives have been reported to possess analgesic, anticonvulsant, anti-inflammatory, and local anaesthetic properties. The majority of these compounds appear to be 3,5-diamino substituted. Thus, products such as (74), (352), (353), (354), and (50) are claimed to exhibit analgesic and anticonvulsant activity <87MI 408-01, 89MI 408-02, 91MI 408-01, 92MI 408-01, 92MI 408-02> while compounds such as (74) (R = Buⁿ), (355), and (356) show anti-inflammatory activity <91MI 408-03, 91MI 408-02>, and (357) local anaesthetic activity <85MI 408-01>.



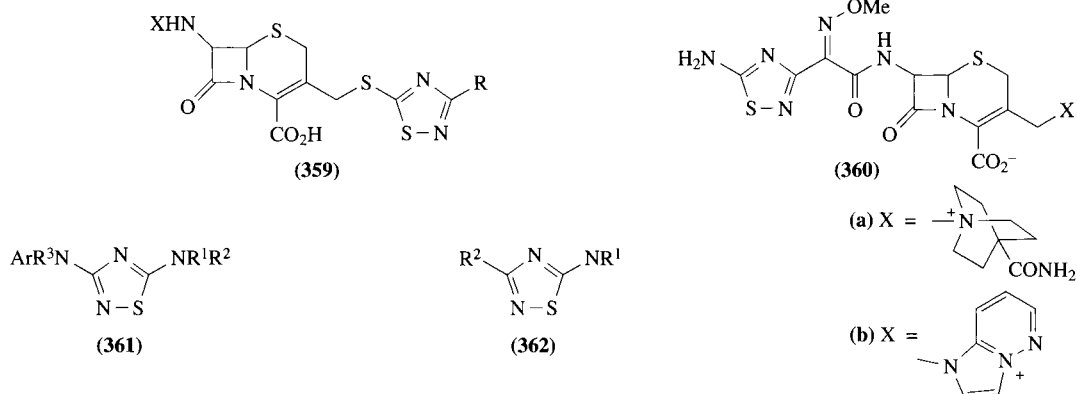
Several amino derivatives have been shown to have antibacterial activity, for example, thiazolidines of type (358) and 3*H*-thiazolo[2,3-*c*]-1,2,4-thiadiazoles (272) <87MI 408-02, 88IJC(B)501>.



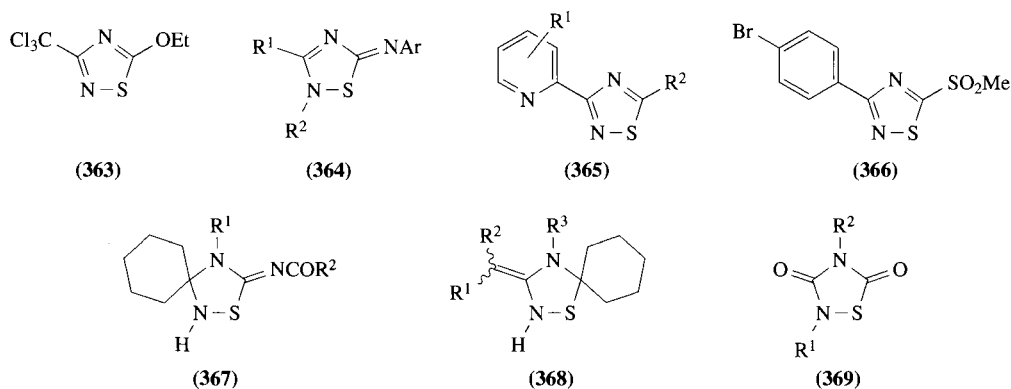
Cephalosporins incorporating the 1,2,4-thiadiazole ring have been prepared and shown to have good antibiotic properties. Thus, compounds of type (359) have been the subject of numerous patent specifications <82AHC(32)285>. More recently, in the early 1990s, cephalosporins such as (360a) and (360b) have been reported as clinically useful antibiotics having excellent antimicrobial activities <92JAN103, 92JAN709>.

3,5-Diamino-1,2,4-thiadiazoles of type (361) have been patented for use in the treatment of hypertension <82EUP44266>, while 5-amino-1,2,4-thiadiazoles such as (362) are claimed to be useful for treating autoimmune diseases and in the prevention of graft rejection. Compounds of type (362) also have antirheumatic properties and are, in particular, useful in the treatment of rheumatoid arthritis and immune diseases such as systemic lupus <91EUP455356>.

The excellent pesticidal and fungicidal properties of 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole (363) are well known <82AHC(32)285>. It is a commercial product and is marketed under a variety of names of which Terrazole is the most common. Since 1984, a variety of 1,2,4-thiadiazole derivatives have been found to possess fungicidal activity. Thus, compounds such as (364), (365), and (366) and

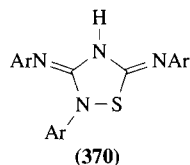


the spirocyclic compounds (367) and (368) are claimed to have fungicidal properties <83BEP897119, 89EGP270910, 91EGP289527, 91JAP9183590, 92MI 408-03, 93GEP413138>. The two compounds (357) and (272) which were reported to have local anaesthetic and bactericidal activity also possess antifungal activity <85MI 408-01, 88IJC(B)501>. The 1,2,4-thiadiazolidine-3,5-diones (369) have been reported to be useful as agricultural biocides <85EGP231070>.



4.08.12.3 Other Applications

Divalent metal salts of 1,2,4-thiadiazole are claimed to be effective antiwear extreme pressure additives for lubricating greases <84EUP104667>. More recently, in the early 1990s, 2-phenyl-3-phenylimino-5-arylimino-1,2,4-thiadiazolidines (370) have been reported to be useful for this purpose <91MI 408-04>. The two spirocyclic compounds (367) and (368) which were reported to have fungicidal activity are also claimed to be useful vulcanization agents <85MI 408-01, 88IJC(B)501>.



4.09

1,2,5-Thiadiazoles

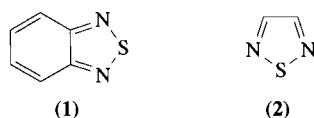
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4.09.1 INTRODUCTION

Since 1889 when Hinsburg discovered 2,1,3-benzothiadiazole (**1**), 1,2,5-thiadiazoles have consistently attracted the attention of both physical and organic chemists. Historically, research focused first on the synthesis and substitution of benzo derivatives (**1**) (1890–1958). Once the parent 1,2,5-thiadiazole (**2**) was reported, synthetic thiadiazole chemistry advanced and efforts turned to understanding the aromaticity, chemical bonding, and substituent effects of the ring system (1958–1972). With the discovery of the potent β -adrenergic blocker timolol, a new chapter of ‘applied’ thiadiazole research began and has continued unabated. Since 1972, other functionalized thiadiazoles with unique pharmacological properties and potential commercial applications have received increasing attention.



The period from 1889 until the early 1960s of 1,2,5-thiadiazole chemistry has been reviewed at key intervals <B-61MI 409-01, 68AHC(9)107, 70RCR923>. The two decades (1960–1980) which show a virtual explosion in the area have been comprehensively reviewed <84CHEC-I(6)513>. In this chapter, the literature from 1981 to 1994 is surveyed with emphasis on novel findings, useful extensions, and confirmation of previous hypotheses.

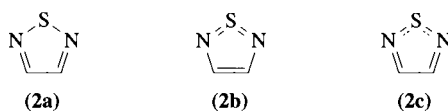
4.09.2 THEORETICAL METHODS

Little has been added to the firm body of evidence that 1,2,5-thiadiazole (**2**) is a planar, cyclic molecule of C_{2v} symmetry. The previous edition of this series <84CHEC-I(6)513> details the molecular geometry, molecular calculations, and electronic structures of the ring systems. A few recent efforts, however, are noteworthy.

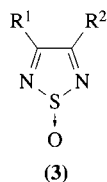
4.09.2.1 Molecular Calculations

In attempting to approximate (CNDO/2) the nature of the 1,2,5-thiadiazole ring (**2a** vs. **2b**), a nontraditional view has been proposed <83IJC(B)802> with two $C=N$ bonds and one three-center two-electron π -bond delocalized over the N—S—N system. This would account for the electron-rich N—S—N nature of the molecule. Classical structures (**2a**, **2b**) are viewed as unlikely versus a hybrid structure (**2c**).

Oxidation of the thiadiazole sulfur to its mono-oxide (**3**) causes a loss in aromatic character which

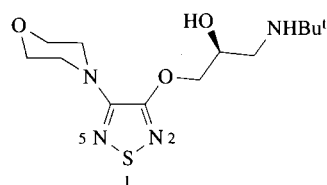


can be seen by x-ray and by a measurable inversion barrier of the pyramidal sulfur at 120°C. Calculation of this barrier (31.9 kcal mol⁻¹) agrees with the observed value (33 kcal mol⁻¹) <82JA1375>.

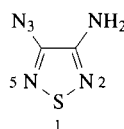


4.09.2.2 Molecular Geometry

Four x-ray structures have been reported which confirm the spectroscopic conclusions made about 1,2,5-thiadiazole. The planar, symmetric, and aromatic nature of the 1,2,5-thiadiazole ring can be seen in the crystal structure of s-timolol hemihydrate (**4**) <90AX(C)2431>. These structural elements are virtually unaffected by the nature of the 3,4-substituents (**5**) <90AX(C)1749>.

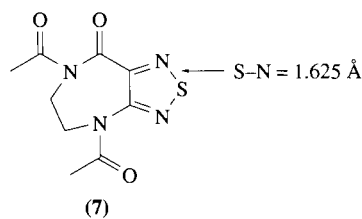
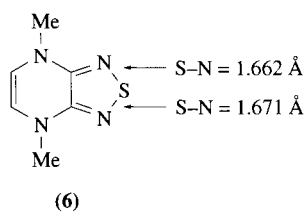


(4) S-N₂ = 1.654 Å
S-N₅ = 1.644 Å



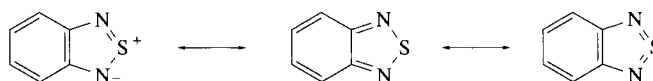
(5) S-N₂ = 1.641 Å
S-N₅ = 1.638 Å

Fusion with a pyrazine ring gives an interesting 12 π -electron system (**6**) which is completely planar except for the C—H bonds of methyl substituents <90AG(E)643>. Even fusion with a 1,4-diazepine has only minimal effects on the 1,2,5-thiadiazole ring (**7**) <93MI 409-01>.



4.09.2.3 Electronic Structures

While it may be intellectually unsatisfying, the electronic structure of 1,2,5-thiadiazole cannot be depicted in a single drawing. The physical and chemical data as they relate to the position and nature of the double bonds can best be represented by a series of canonical forms (Scheme 1) <84CHEC-1(6)513>.



Scheme 1

4.09.3 EXPERIMENTAL STRUCTURAL METHODS

4.09.3.1 NMR Spectroscopy

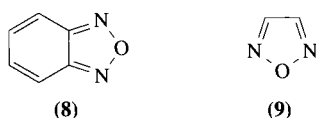
A detailed comparative analysis of the ^1H , ^{13}C , and ^{15}N NMR spectra of 1,2,5-thiadiazoles and the shifts relative to analogous heterocycles has been carried out $\langle 84\text{CHEC-I}(6)513 \rangle$.

NMR spectroscopy of molecules partially oriented in nematic solvents has been used to study internal potential and preferred conformations of medium-sized molecules. The NMR spectra of 3-phenyl-1,2,5-oxadiazole, -thiadiazole, and -selenadiazole in the nematic phase have been analyzed $\langle 77\text{JCS}(P2)561 \rangle$. A twisted conformation of the bond between the two rings was found. The angle of twist for the selenium, sulfur, and oxygen derivatives varies over a range of only a few degrees. The sulfur derivative has the lowest twist angle, suggesting that the conjugation between the phenyl and heterocyclic rings is the strongest of this series. NMR studies of (1) in nematic phases show that the preferred molecular orientation is with the C_2 -axis along the direction of the magnetic field. This resembles the way most aromatic molecules are oriented under such conditions $\langle 72\text{MCLC}367 \rangle$.

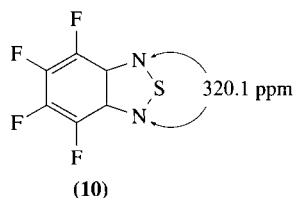
The ^1H NMR spectra of the benzenoid ring system in 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, and benzo-2,1,3-oxadiazole have been fully analyzed as $\text{AA}'\text{BB}'$ spin systems and their chemical shifts and coupling constants compared $\langle 67\text{KGS}297, 69\text{CPB}1821, 69\text{SA}(A)1027 \rangle$. The chemical shifts and coupling constants exhibit interesting features related to the nature of the Group VIA heteroatoms. The chemical shift $V_{\delta\text{AB}}$ decreases with more delocalized π -electron distribution, suggesting a d -orbital model for sulfur. Substituent effects on coupling constants in 2,1,3-benzoselenadiazole have been documented $\langle 72\text{JCS}(P2)1682 \rangle$. Calculated and measured spectra of 2,1,3-benzothiadiazole and 2,1,3-benzoselenadiazole are in good agreement $\langle 69\text{KGS}62 \rangle$. The *ortho* coupling constant $J_{\text{A'B'}}$ in 5-substituted 2,1,3-benzoselenadiazole is larger than the corresponding coupling ($J_{\text{AB}} = J_{\text{A'B'}}$) in 1,2,5-selenadiazole and this is particularly marked in the 5-methoxy derivative. Likewise, the *meta* coupling constant $J_{\text{AB'}}$ is increased and the *para* coupling $J_{\text{AA'}}$ is reduced by substitution. This increase in the *meta* coupling constant in the order $\text{H} < \text{Me} < \text{Cl} < \text{MeO} < \text{Me}_2\text{N}$ has also been found in a number of substituted quinolines $\langle 65\text{JCS}6004 \rangle$.

The ^{13}C NMR chemical shifts and one-bond coupling constants $J(^{13}\text{C}-\text{H})$ have been obtained for 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, and 2,1,3-benzooxadiazole in carbon disulfide $\langle 74\text{OMR}(6)430 \rangle$.

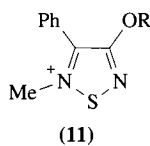
Since that time, however, a comprehensive ^{15}N study of azoles has been completed $\langle 84\text{OMR}(22)215 \rangle$. Significant increases in the nitrogen shielding were observed for the parent benzothiadiazole (1) (+49 ppm) and the parent 1,2,5-thiadiazole (2) (+34 ppm). In contrast, the corresponding oxadiazoles were highly deshielded; benzooxadiazole (8) (−36 ppm) and 1,2,5-oxadiazole (9) (−34 ppm).



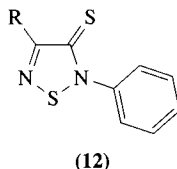
Perfluorination of the benzothiadiazole ring results in a dramatic change in the electronic nature of the system. ^{15}N NMR of the 4,5,6,7-tetrafluoro analogue (10) shows strong shielding of the nitrogens (320.1 ppm) versus the parent benzothiadiazole (1) (332.9 ppm) $\langle 83\text{JFC}(22)231 \rangle$.



Substitution of the ring nitrogens perturbs the system. Alkylation shows a clear positive charge on N-3 (11) $\langle 94\text{JST}(323)177 \rangle$. Protonation of timolo (4) occurs on the side chain $\text{N}-\text{H}$ with minimal effect on the thiadiazole ring $\langle 84\text{ACS}(B)67 \rangle$.



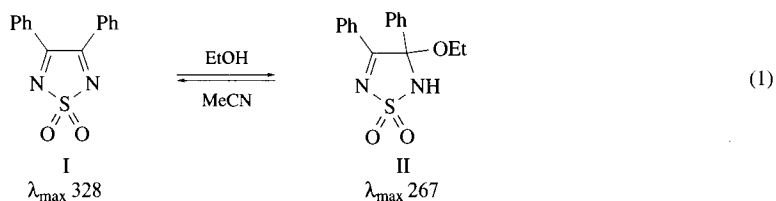
The ^{13}C NMR of a 3-thiono derivative (12) has also been reported <93ZOR491>.



4.09.3.2 UV Spectroscopy

The similarity of the UV absorption spectra of 1,2,5-thiadiazoles and the corresponding pyrazine analogues reveals their isoelectronic relationship <68AHC(9)107>. The pyrazine molecules have much better developed $n\text{--}\pi^*$ bands at longer wavelength. When one considers that the π -electron density in the five-membered ring is formally 1.2 electrons per atom, while it is 1.0 for a six-membered ring, the reduced tendency of the former to promote a nonbonding electron into the π -system is understandable <63PMH(2)61>. The substitution of a —CH=CH— group by a sulfur atom has little effect on the energy of the electronic transitions. The band assignments are readily inferred from shifts to shorter wavelengths in solvents of increasing polarity and the disappearance of the band in strong acid solution. The shorter wavelength band, due to the $\pi\text{--}\pi^*$ excitation, is relatively insensitive to changes in solvent polarity. No evidence of an $n\text{--}\pi^*$ transition could be found in the spectrum of 1,2,5-thiadiazole. From these observations, it can be inferred that the nitrogen lone-pairs are involved in the molecular orbital of the ring and that significant changes in symmetry of the molecular orbital take place on excitation. While 1,2,5-thiadiazole shows a marked displacement in UV absorption maxima compared to the aliphatic 1,4-diazene, indicating that sulfur is able to conjugate with the chromophore, there is virtually no difference in the absorption maxima of 1,3,4-thiadiazole compared to the aliphatic 1,2-diazene <67DIS(B)4330>.

In 1993, UV spectroscopy has been used to clarify the strong interactions of 1,2,5-thiadiazole dioxides with protic solvents. Based on shifts in the maximum from 328 nm to 267 nm, as well as a doubling in the extinction coefficient, it is likely that the adduct II (Equation (1)) is formed in alcoholic media <93JPO341>.



4.09.3.3 Mass Spectrometry

The major fragmentation pathways in the mass spectra of 1,2,5-thiadiazole, 1,2,5-selenadiazole, and 1,2,5-oxadiazole are well established <75ACS(B)483>. Direct loss of the heteroatom X from the molecular ions was not observed in any case. Application of the metastable defocusing technique revealed that elimination of X (O, S, and Se) takes place from RCNX^+ or the rearranged ion RNCX^+ , with formation of a fragment with m/e 103 (PhCN^+ or PhNC^+). Since this process appears to be the predominant pathway for the formation of these ions, the abundance of the m/e 103 fragment in the three spectra ($\text{R} = \text{Ph}$; $\text{X} = \text{O}, \text{S}$ and Se) indicates that the order of elimination of X is $\text{Se} > \text{S} > \text{O}$. The mass spectra of the parent compounds indicate the loss of HCN from the parent ions. Further fragmentation of RCNX^+ , however, is clearly affected by the nature of the

substituent. Elimination of selenium takes place from $\text{PhCNSe}^\dagger$, while $\text{HCNSe}^\dagger$ leads to abundant $\text{Se}^\dagger$ with elimination of HCN. Similar effects are found in the spectra of the thiadiazoles, but the sulfur ion is less abundant. This mode of fragmentation is negligible in the case of 1,2,5-oxadiazole.

The mass spectra of the benzo derivatives 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, and 2,1,3-benzooxadiazole indicate that stability of NO versus NS and NSe strongly influences fragmentation $\langle 780\text{MS}(13)379 \rangle$. Thus, while $\text{M}^+ - \text{NO}$ is the major fragmentation pathway in 2,1,3-benzooxadiazole, the corresponding loss of NX (S = S or Se) is much less important in 2,1,3-benzothiadiazole and not observed in the selenium analogue 2,1,3-benzoselenadiazole. The m/e 76 ion in the spectrum of 2,1,3-benzoselenadiazole has previously been suggested to be the benzyne ion $\langle 65\text{CC624} \rangle$. Metastable defocusing studies and exact mass measurements, however, have established its elemental composition as $\text{C}_5\text{H}_3\text{N}$. Similarly, the composition of the m/e 77 and 78 fragments was found to be $\text{C}_5\text{H}_3\text{N}$ and $\text{C}_5\text{H}_4\text{N}$, respectively. Intense parent ions are dominating features of the mass spectra of a number of substituted 2,1,3-benzothiadiazoles. The fragmentation of the heterocyclic ring (loss of H, HCN, and NS) is far less important than fragmentation of the substituents $\langle 75\text{ACS}(B)622 \rangle$.

4.09.3.4 IR and Raman Spectroscopy

The IR spectra of 2,1,3-benzothiadiazole and its derivatives show a well-defined aromatic system, evidenced by the correlation of the C—C and C—H stretching frequencies of 2,1,3-benzothiadiazole and its 4- and 5-substituted derivatives (Me, Cl, and Br) with the corresponding frequencies for benzene derivatives $\langle 69\text{CHE180}, 69\text{KGS235} \rangle$.

The IR and Raman spectra of 1,2,5-thiadiazole have been discussed extensively $\langle 67\text{G379}, 68\text{AHC}(9)107 \rangle$. The assignments of the fundamental vibrations of 3-chloro- and 3,4-dichloro-1,2,5-thiadiazole derivatives have been obtained and are, as expected, consistent with a planar molecule $\langle 66\text{SA1417}, 72\text{CJC627}, 73\text{CJC680} \rangle$. Good correlations were obtained for three ring stretching vibrations, the ring in-plane bending, and the ring out-of-plane bending modes. The polarized and depolarized raman spectra of 1,2,5-thiadiazole have been measured as a function of temperature $\langle 76\text{JCP}(64)4475 \rangle$. Due to the small depolarization ratios of totally symmetric vibrations, the contribution of the polarizability anisotropy to the polarized spectra is small and the widths of polarized spectra are determined mainly by non-reorientational isotopic relaxation processes.

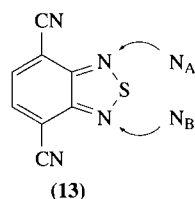
While the vibrational spectra of thiadiazoles have been well characterized $\langle 67\text{G379}, 68\text{AHC}(9)107 \rangle$ the “selenation” method was used to verify the assignments of a number of organic sulfur compounds, including the parent benzothiadiazole (**1**) $\langle 90\text{JST}(218)169 \rangle$.

4.09.3.5 ESR Spectroscopy

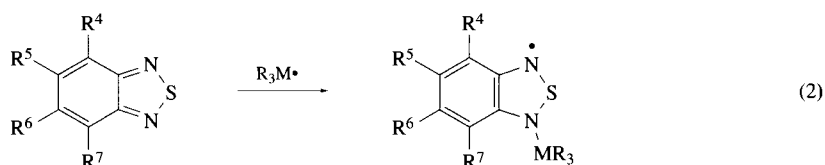
The electron spin resonance (ESR) spectra of the radical anions of 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, and 2,1,3-benzooxadiazole, generated by potassium metal reduction $\langle 67\text{JCS}(A)771 \rangle$ or by electrochemical reduction $\langle 67\text{KGS811} \rangle$, have been interpreted using molecular orbital theory. A p -orbital model gives a satisfactory description of the bonding of sulfur. Solvent effects on the nitrogen hyperfine splitting constants of the anion radicals of 2,1,3-benzothiadiazole and 2,1,3-benzoselenadiazole are discussed in terms of a mesoionic structure. The ESR spectrum of benzoselenadiazole anion radical has a pattern similar to that of 2-methyl-1,2,3-benzotriazole, indicating that replacement of selenium with an N -methyl group has little effect on the spin distribution $\langle 70\text{BCJ268} \rangle$. The unrestricted Hartree–Fock method has been employed in the study of spin density distributions in the radical anion of 2,1,3-benzothiadiazole. The results are in agreement with experimental ESR data after annihilation of the quarter spin resonance $\langle 69\text{JJC97} \rangle$.

The photo-reduction of 2,1,3-benzothiadiazole-4,7-dicarbonitrile (**13**) by EDTA in the presence of micelles gave a stable radical anion which could be observed by ESR $\langle 84\text{CC1324} \rangle$. The observed 17 line ESR signal was attributed to an overlapping quintet of quintets from a radical with $a_{(\text{NA})} = 0.255$ mT and $a_{(\text{NB})} = 0.075$ mT. The radical appears to be protected within the micelle when electron transfer is inhibited.

When the substituents at positions 4, 5, 6, and 7 of a 2,1,3-benzothiadiazole are not symmetric,



the position of a generated radical will be dependent on those substituents. ESR has been used to determine the position and ratio of nitrogen bearing radicals (Equation (2)) <91JOM(401)13>.



4.09.4 THERMODYNAMIC ASPECTS

4.09.4.1 Basicity

The ionization constants of isomeric thiadiazoles and related heterocycles, obtained by spectrophotometric methods, are given in Table 1. Diprotonation of these very weakly basic ring systems seems unlikely. In ring systems where a sulfur atom replaces an isoelectronic vinyl group α to a nitrogen atom, the pK_a is decreased by ca. 6 log units (for (2) ($pK_a -4.9$) and pyrazine ($pK_a 0.6$) $\Delta pK_a = -5.5$). When the same replacement is made β to an azine nitrogen atom, the observed decrease is ca. 2.6 log units (for thiazole ($pK_a 2.53$) and pyridine ($pK_a 5.23$) $\Delta pK_a = -2.70$). The difference in magnitudes of pK_a values can be explained by the inductive effect of the ring sulfur atom which more effectively withdraws electrons from the nitrogen lone-pair when located in the α -position. The extremely low basicity of the 1,2,5-isomer indicated that the π -orbital in the ring is of high electron density and that the lone-pair electron density on the nitrogen atoms is correspondingly low <67DIS(B)4330>.

Table 1 Ionization constants of isomeric thiadiazoles and related heterocycles.

Compound	pK_{a1}	pK_{a2}
1,2,5-Thiadiazole	-4.90	
1,2,3-Thiadiazole	-2.00	
1,2,4-Thiadiazole	-1.29	
1,3,4-Thiadiazole	-0.90	
Pyrazine	0.70	-5.8
Thiazole	2.33	
Isothiazole	-0.51	

The electronegative influence of the thiadiazole system greatly increases the acidity of substituents (Table 2). The effect is further enhanced in the 1-monoxide and 1,1-dioxide analogues. The ionization constants of 4- and 5-hydroxy-2,1,3-benzothiadiazoles were determined in water <70AC(R)801>.

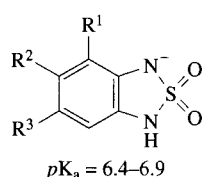
Cyclic sulfamides (14) exhibit enhanced acidity versus their acyclic counterparts by about 4 pK_a units. The sulfur d-orbitals and/or the added ring strain may be responsible <84JCS(P2)1851>.

4.09.4.2 Aromaticity

While it is clear that 1,2,5-thiadiazoles are clearly aromatic in nature, efforts have been made to quantify the degree of aromaticity. Three detailed comparative studies of relative aromaticity in five membered heterocyclic rings have been carried out by Bird <85T1409>, Katritzky <90JPR885>, and

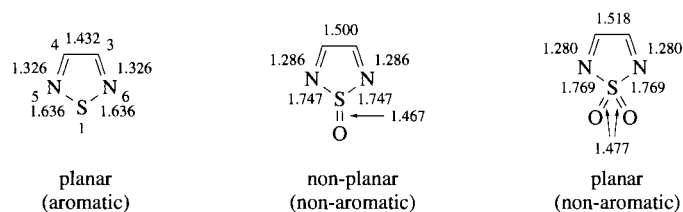
Table 2 Ionization constants of 1,2,5-thiadiazoles.

R^1	R^2	pK_{a1}	pK_{a2}	Ref.
CO ₂ H	H	2.47		68AHC(9)107
CO ₂ H	CO ₂ H	1.59	4.14	
OH	H	5.10		68AHC(9)107
OH	Me	5.10		68AHC(9)107
OH	OEt	4.40		68AHC(9)107
OH	Cl	3.65		68AHC(9)107
OH	CN	2.97		68AHC(9)107
OHb	OH	4.68	7.50	69OPP255
OH	OH ^a	2.62	6.58	69OPP255
OH	OH ^b	2.20	5.50	75JOC2743
NH ₃ ⁺	H	2.90		68AHC(9)107

^amono S oxide. ^bdi S oxide.

(14)

Rozas <92JPO74>. The degree of aromaticity is generally derived from measured bond lengths and planarity. Correlation is good in simple or symmetrical cases but begins to break down in highly functionalized systems. Oxidation of 1,2,5-thiadiazole (2) to its mono- and dioxides results in loss of aromaticity (Figure 1) <92JPO74>.

**Figure 1** Bond distance for 1,2,5-thiadiazole (3) and its oxides <92JPO74>.

The mesionic nature of substituted 1,2,5-thiadiazoles has provided examples of remarkably stable (heat, light, cycloaddition) charge-separated species. Stabilization is rationalized via delocalization of electron density from the electron-donating dithiazole ring into the electron-withdrawing thia-diazole ring (Figure 2) <89JCS(P1)2485>:

**Figure 2** Mesionic bicyclic imine.

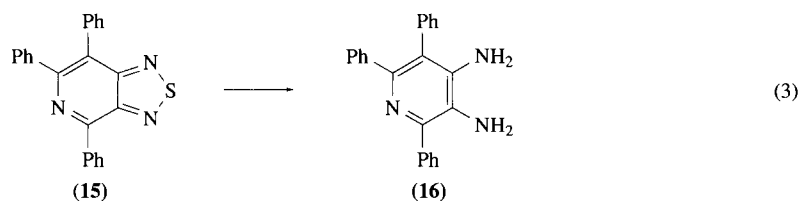
4.09.5 REACTIVITY OF FULLY CONJUGATED RINGS

4.09.5.1 General Survey of Reactivity

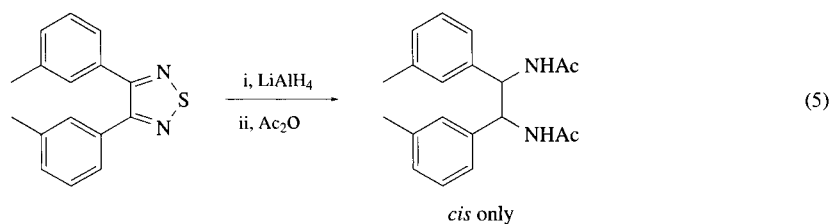
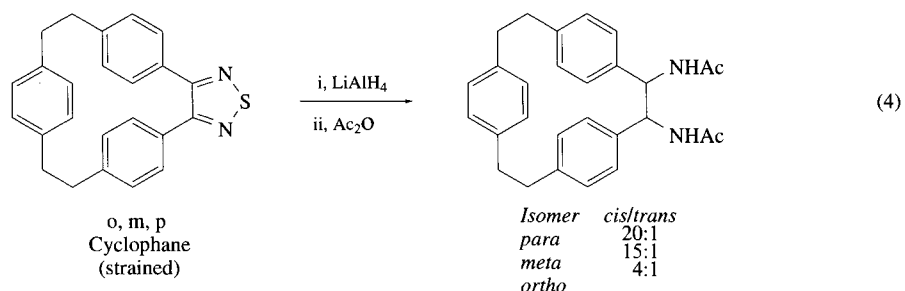
1,2,5-Thiadiazole is a planar, thermally stable, and weakly basic aromatic ring system. Aromatic forms of the 1,2,5-thiadiazole nucleus are generally stable to concentrated mineral acids and are only slightly sensitive to base. Base-catalyzed deuterium exchange of the ring protons can be effected

<67G1870>. Reduced and oxidized forms of the ring, on the other hand, readily undergo hydrolytic fission. The 1,2,5-thiadiazoles are reactive toward nucleophilic attack at carbon, sulfur or a ring proton, the site depending on the structure of the thiadiazole substrate and the nature of the nucleophile. Reductive cleavage and desulfurization also takes place with vigorous reducing agents. The system is very electron poor and is relatively inert in electrophilic substitution reactions, quaternizations, complexation with metal salts, and oxidation. The pronounced acidity of 3-hydroxy-1,2,5-thiadiazole (pK_a 5.1) and the 3-carboxylic acid (pK_a 2.47) reflect the magnitude of the electron-withdrawing effect on substituents.

Even though reductive cleavage of the 1,2,5-thiadiazole ring requires vigorous conditions, the resulting diamines can be isolated in high yield. Reaction of bicyclic thiadiazole (**15**) with LiAlH_4 or Raney Ni produces the corresponding diamine (**16**) in 87% and 77% yield, respectively (Equation (3)). The same compound (**15**) was stable toward treatment with Na/EtOH or $\text{NaBH}_4/\text{EtOH}$ (reflux) <82JHC1481>.



It is noteworthy that the strain introduced by substituents at the carbon atoms C_3 – C_4 can have a dramatic effect on the stereochemical outcome of the thiadiazole reduction (Equations (4) and (5)). In these cases, Na/EtOH will also reduce the 1,2,5-thiadiazole but with a reversal of stereochemistry (*trans*-diamine predominates) <91JHC55, 91JHC289>.

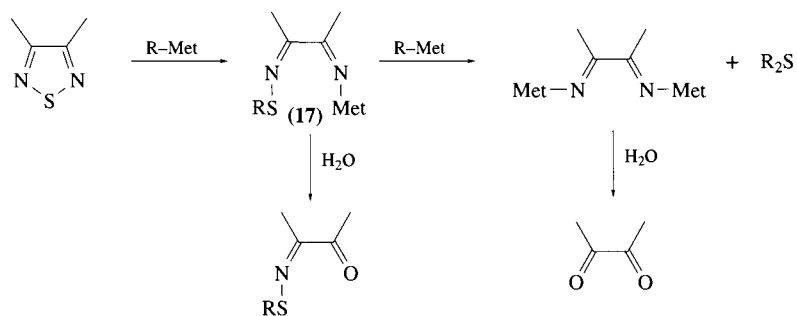


The nucleophilic attack of organometallic species occurs with cleavage of the N—S bond and eventual formation of an α -diketone. This reaction has been shown to proceed through an unsymmetrical diimine (**17**) (Scheme 2) <90JHC1861>. The 4-unsubstituted series (**18**) can be functionalized in this way. The diimine product of ring opening (**19**) can add a nucleophile at carbon (**20**) and then be recycled to a 3,4-disubstituted 1,2,5-thiadiazole (**21**) (Scheme 3) <86H1131>.

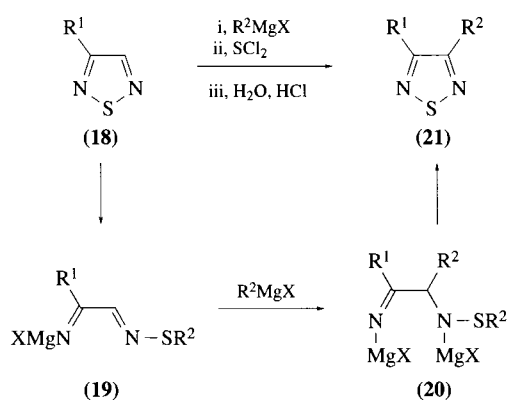
Although 1,2,5-thiadiazoles have been shown to undergo cycloaddition with benzyne <82CC299>, the predominant mode of attack is at sulfur. The result is extrusion of a nitrile and formation of a 1,2-benzisothiazole (**22**) (Scheme 4) <88JCS(P1)2141>.

The relative stability of the 1,2,5-thiadiazole ring makes it an excellent choice for a ligand in the development of novel organometallic reagents. The simple 2,1,3-benzothiadiazole (**1**) has been coordinated to ruthenium, osmium, and iridium. Interestingly, x-ray analysis shows that ligation of the metal occurs at nitrogen not sulfur (**23**) <89JOM(377)151, 90JCS(D)1737>.

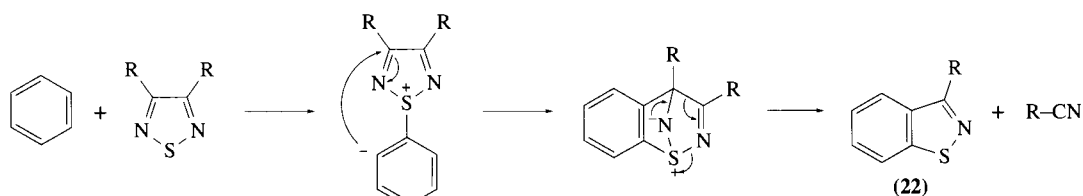
1,2,5-Thiadiazoles



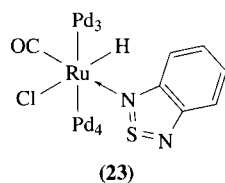
Scheme 2



Scheme 3



Scheme 4



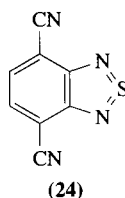
4.09.5.2 Thermal and Photochemical Reactions

The thermal stability of 1,2,5-thiadiazole is remarkable. The parent ring and its alkyl derivatives can withstand heating to at least 250–300°C. Under UV photolytic conditions, the aromatic thiadiazoles slowly fragment to nitriles and sulfur.

Photolysis of 2,1,3-benzothiadiazole-1-oxide produces 1,3-dihydro-2,1,3-benzothiadiazole-2,2-dioxide, shown by flash photolysis to be formed via hydration of the 2-oxide intermediate

<78ACS(B)625>. Independent of this process, 2-thionitrosobenzene is generated reversibly as a short-lived intermediate, analogous to the thermal and photochemical formation of a 1,2-dinitroso intermediate from benzofuroxans.

Photoreduction of 2,1,3-benzothiadiazole-4,7-dicarbonitrile (**24**) in the presence of cationic micelles, produces a radical anion which is stable for more than 48 h <89JCS(F1)3385>.

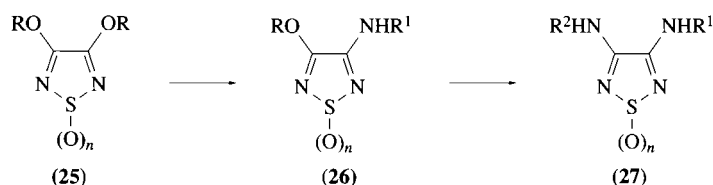


4.09.6 REACTIVITY OF NONCONJUGATED RINGS

4.09.6.1 S-Monoxides and Dioxides

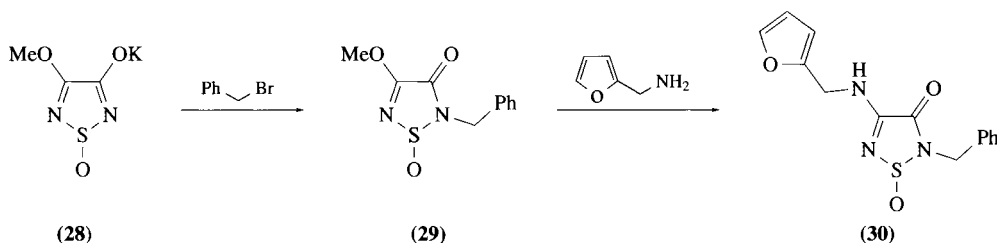
1,2,5-Thiadiazole-1-oxides and -1,1-dioxides are nonaromatic (see Section 4.09.4.2), less thermally stable than the aromatic form <68AHC(9)107, 74S22>, and exhibit greatly enhanced reactivity toward nucleophiles. The observation has been made that these systems behave like strong acyl functions and that chloro, alkoxy, and amino derivatives have chemical behavior resembling an acyl chloride, ester, and amide of a strong acid <70CRV593, 75JOC2743>. The pK_a values of the hydroxy derivatives are in accord with these properties (see Section 4.09.4.1).

In the intense search for inhibitors of gastric acid secretion a new class of potent histamine H_2 -receptor antagonist was discovered. These 1,2,5-thiadiazole-1-oxides (**27**) were prepared by nucleophilic addition of primary amines to 3,4-dialkoxy-1,2,5-thiadiazole 1-oxide (**25**). Sequential addition of two different amines to positions C(3) and C(4), respectively, could be achieved via the 3-alkoxy-4-amino adduct (**26**) (Scheme 5) <82JMC207, 82JMC210>.



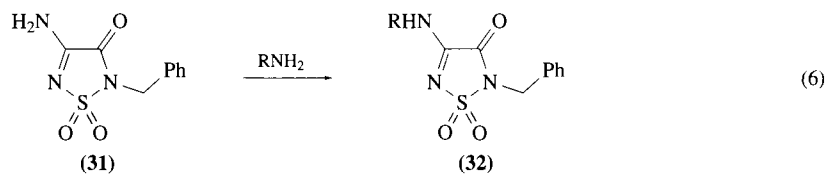
Scheme 5

When a 1,2,5-thiadiazole-1-oxide contains a 3-methoxy-4-hydroxy array (**28**), the system reacts as an amide: alkylation occurs on nitrogen (**29**) allowing selective amination at position C-3 (**30**) (Scheme 6) <85TL6155>.

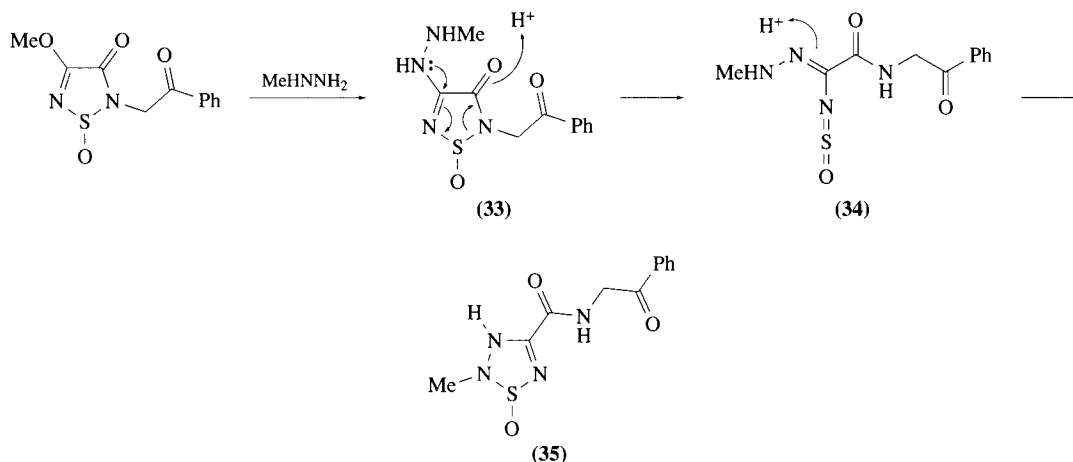


Scheme 6

The chemistry of 4-amino-1,2,5-thiadiazole-1-oxides is directly analogous (**31**) and (**32**) (Equation (6)) <87JCS(P1)955, 88LA337>.

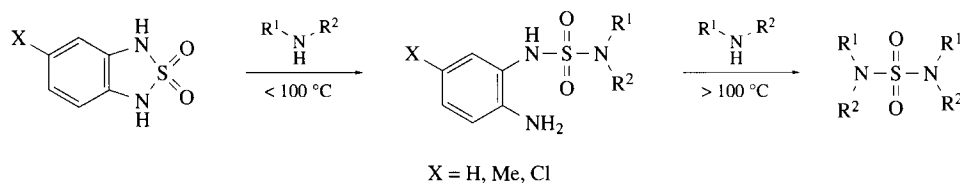


Use of an alkyl hydrazine as the nucleophile followed the expected course of addition. The resulting product (33), however, opened to an N-sulfonylimine (34) which rearranged to a thia-triazoleoxide (35) in 65% yield (Scheme 7) <86H(24)1193>.



Scheme 7

When the 1,2,5-thiadiazole-1,1-dioxide is fused to an aromatic ring, the nucleophilic addition occurs at sulfur not carbon. In these cases, the reduced thiadiazole behaves as a classic sulfamide, readily undergoing amine exchange (Scheme 8) <82JCR(S)84>.

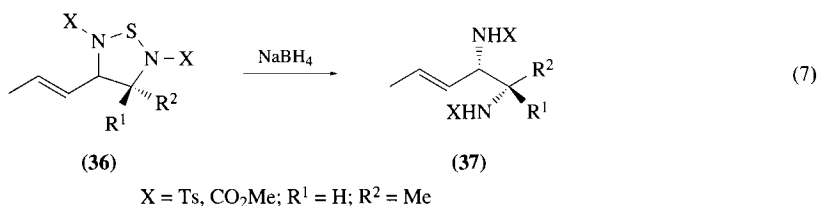


Scheme 8

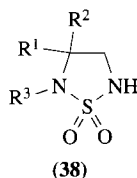
A detailed report has appeared on the electrochemistry of 1,2,5-thiadiazole-1,1-dioxides <91MI 409-01>.

4.09.6.2 Reduced Compounds

The nitrogen-sulfur bond in reduced forms of 1,2,5-thiadiazole is much more labile than in the aromatic analogues. The reduced systems can be hydrolytically desulfurized to the open-chain NCCN portion of the ring <69OPP255, 69T4277, 80JPR273>. Mesoionic thiadiazoles are also sensitive to basic hydrolysis <81JCS(P1)1033>. Reductive cleavage (NaBH_4) has been used to cleanly convert thiadiazolidines (36) into vicinal diamines (37) without loss of stereochemical integrity (Equation (7)) <87H(25)19, 88JOC1116>.



In the case of the thiazolidinedioxides (**38**), the increased acidity of the cyclic sulfamide determines the reactivity. Metallation (NaH) occurs at N—H producing an anion which is readily alkylated <93TL4705>. Treatment with triphenylphosphine produces a stable betaine which can be used to couple alcohols and acids in a variant of the Mitsunobu reaction <94JOC2289>.



4.09.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4.09.7.1 Benzenoid Rings

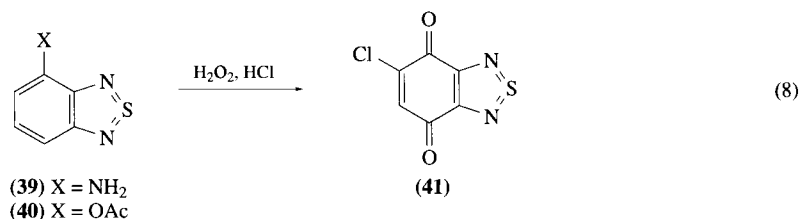
The 2,1,3-benzothiadiazoles readily enter into most classical electrophilic aromatic reactions, e.g. nitration, sulfonation, halogenation, and chloromethylation, but are relatively inert under Friedel–Crafts conditions <70RCR923>. Orientation in these reactions is similar to the naphthalenes, but the reactivity of the heterocycle is lower. Electrophiles attack (**1**) at the C-4 (C-7) position. Substituents in the benzene ring exert a greater orientation effect than the fused thiadiazole ring. The deactivation of position 5(6) to electrophilic attack is overcome by the presence of a donor substituent at position 4. For example, mononitration of 4-methyl- and 4-ethoxy-2,1,3-benzothiadiazole yields a mixture of 5- and 7-nitro derivatives in the proportions 35 : 65 and 50 : 50, respectively, while the 4-hydroxy derivative is nitrated exclusively in position 5. Surprisingly, nitration of 5-ethoxy-2,1,3-benzothiadiazole occurs exclusively at C-4 <82IJC(B)65>. Most of the other electrophilic reactions (sulfonation, halogenation, and chloromethylation) on benzothiadiazoles bearing an electron donor at position 4 take place at position 7 and also readily yield 5,7-disubstituted products. Electron-withdrawing substituents exert the predicted deactivating and *meta*-directing effect, e.g. nitration of either 4- or 5-nitro-2,1,3-benzothiadiazole produces the same 4,6-dinitro derivative <63JGU1714>.

When the benzene ring of (**1**) is strongly activated, the milder electrophilic substitution reactions (nitrosation, azo coupling, and thiocyanation) are readily effected in a manner analogous to the naphthalenes <70RCR923>. Nitrosation of the 4- and 5-hydroxy derivatives of (**1**) occurs at positions 5 and 4, leading to nitroso derivatives that exist predominantly in the quinone monoxime form <74T3839>.

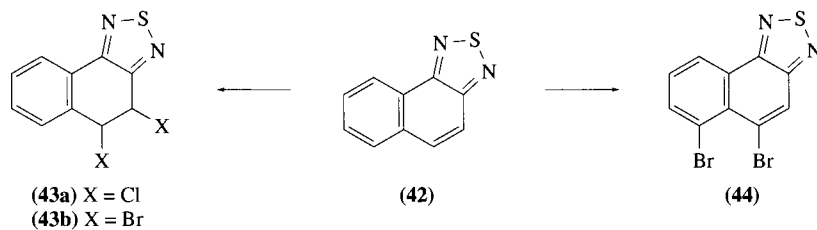
Chlorination of 2,1,3-benzothiadiazoles can take place either by addition or substitution, depending on the reaction conditions, the nature of the substituents in the benzene ring, and the catalyst employed. The uncatalyzed reaction of (**1**) with chlorine is exothermic and produces an isomeric mixture of tetrachloro addition products, which form 4,7-dichloro-2,1,3-benzothiadiazole on treatment with base <70RCR923>. In the presence of an iron catalyst, chlorine substitution in the 4,7-positions predominates.

Bromination of (**1**) leads to the tetrabromide which, when treated with base, forms 4,7-dibromo-2,1,3-benzothiadiazole <70RCR923>. It was subsequently demonstrated that the 4,6-dibromo (20%) and a trace of the 4,5-dibromo derivatives are also produced in this reaction <70JHC629>. In the presence of iron, bromination of a melt of (**1**) yields almost exclusively the 4,7-dibromo derivative even when equimolar quantities of bromine are used. As in the chlorination of (**1**), the process under these conditions cannot be limited to monosubstitution <70RCR923>. Monobromination and subsequent dibromination can be achieved, however, when the reaction is carried out by dropwise addition of bromine to (**1**) in 47% hydrobromic acid at 130°C <70JHC629>.

Oxidation of 4-amino (**39**) or 4-acetoxy-2,1,3-benzothiadiazoles (**40**) to quinones (**41**) has been reported (Equation (8)) <88KGS114>.

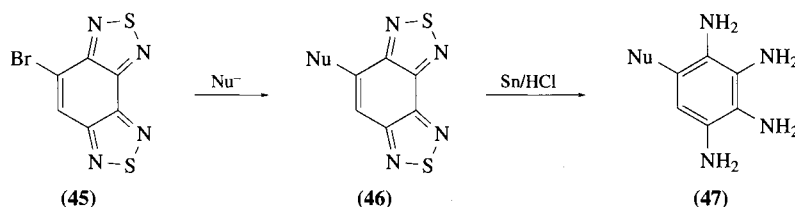


The fusion of a second aromatic ring results in subtle changes in reactivity. Halogenation of naphtho[1,2-*c*]-1,2,5-thiadiazole (**42**) occurs either by 4,5-addition of chlorine (**43a**) or by 5,6-substitution (**44**) by bromine. This heterocyclic analog of phenanthrene behaves like phenanthrene in that it gave the 4,5-addition product (**43b**) when treated with Br₂ in glacial acetic acid (Scheme 9) <91JHC813>.



Scheme 9

Mataka *et al.* have extensively studied the chemistry of bromobisthiadiazoles (**45**) showing that, in general, nucleophiles (Nu⁻) will add smoothly. Elimination of HBr yields the “replacement” product (**46**) which can be converted to a substituted 1,2,3,4-benzenetetraamine (**47**) (Scheme 10) <89BCJ3127, 92H(33)791>.



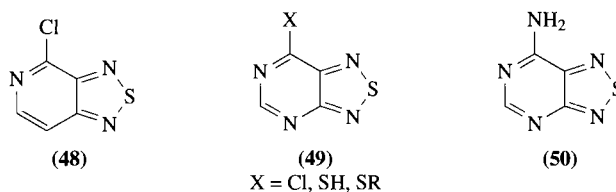
Scheme 10

4.09.7.2 Heterocyclic Rings

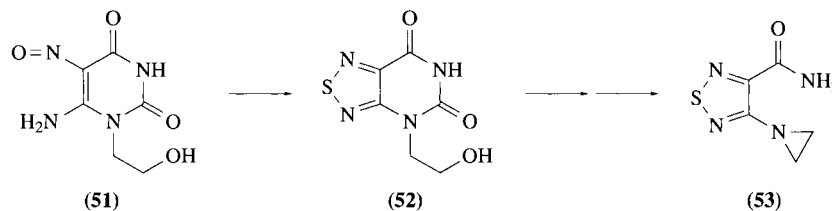
The fusion of the 1,2,5-thiadiazole system to a heterocyclic nucleus greatly enhances the electrophilicity of the substituted ring. These properties are manifested in increased rates of hydrolysis and more facile displacement, Diels–Alder, and cycloaddition reactions. The synthetically useful nucleophilic cleavage of the pyrimidine ring of 1,2,5-thiadiazolo[3,4-*d*]pyrimidines was studied in detail by Shealy and co-workers and previously discussed <68AHC(9)107>.

Leaving groups present in heterocyclic rings fused to the 1,2,5-thiadiazole systems are highly mobile and are displaced readily under substitution conditions <70RCR923, 70RTC5>. The chloro group in (**48**) is extremely reactive and hydrolyzed by aqueous acid much more readily than the corresponding imidazopyridine. Similarly, the substituents Cl, SR, and SH in the 7-position of the pyrimidothiadiazole (**49**) are easily replaced. The amino group in (**50**) can be substituted by heating with secondary amines <68AHC(9)107> and substituted benzylamines <78JOC960>.

The facile hydrolysis of a pyrimidine ring fused to a 1,2,5-thiadiazole (**52**) allowed the use of

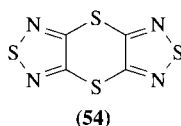


uracil derivatives (**51**) as a scaffold in the preparation of novelly substituted thiadiazoles (**53**) (Scheme 11) <92ZOR422>.



Scheme 11

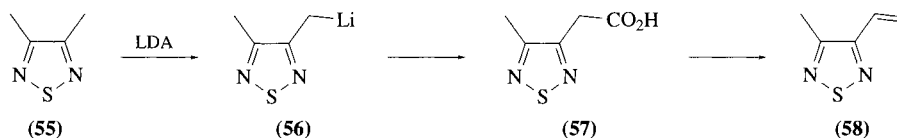
The unusual dithiino-bis[1,2,5]thiadiazole (**54**) has been synthesized and characterized <92JHC439>. No reports have yet appeared on its reactivity.



4.09.7.3 Other C-linked substituents

The effect of the 1,2,5-thiadiazole system on the reactions of carbon-bound substituents can be summarized as follows: (i) stabilization of carbanions; (ii) destabilization of carbenium ions; (iii) enhanced S_N2 reactivity and repressed S_N1 reactivity <68AHC(9)107>. Aryl substituents are rendered more reactive to nucleophiles <72IJS(A)25> and deactivated in reactions with electrophiles, which are directed to the *ortho/para* positions by the thiadiazole ring <72IJS(A)25, 78MI 409-01>.

Metallation of 3,4-dimethyl-1,2,5-thiadiazole (**55**) to the anion (**56**) was accomplished with the use of a nonnucleophilic base, lithium diisopropylamide <82JHC1247>. Nucleophilic attack at sulfur resulted in an alkyl lithium reagent <70CJC2006>. The lithiomethyl derivative (**56**) was carboxylated to (**57**) with carbon dioxide and converted to the vinyl derivative (**58**) via an esterification, reduction, mesylation, and base elimination sequence (Scheme 12).



Scheme 12

The pronounced electron-withdrawing nature of the 1,2,5-thiadiazole system is also evidenced by strong carbonyl electrophilic activation and by enhancement of carboxy acidity. The acid dissociation constants of thiadiazole acids, discussed in Section 4.09.4.1, fall in the range 1.5–2.5. The 1,2,3-thiadiazole carboxylic acids are easily decarboxylated at 160–200°C. This reaction has been used for the synthesis of monosubstituted derivatives as well as the parent ring and deuterated derivatives <68AHC(9)107>. An efficient bromo-decarboxylation of 3-amino-1,2,5-thiadiazole-carboxylic acid has also been reported <70BRP1190359>.

The enhanced acidity of the thiadiazole acids is reflected in the reactivity of the corresponding esters which undergo hydrolysis, aminolysis, and hydrazinolysis with extreme ease. Thiadiazoleamides and -hydrazides behave normally in the Hofmann and Curtius reactions.

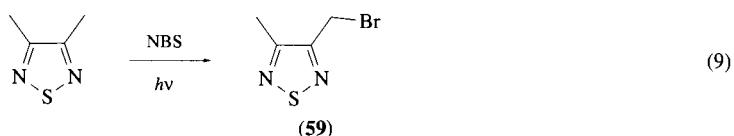
The acid chlorides have served as useful synthetic intermediates leading to ketones via the malonic acid synthesis and Friedel–Crafts reaction, thiadiazole acetic acid derivatives, and halo ketones via the Arndt–Eistert synthesis and carbinols by hydride reduction <68AHC(9)107>. The dialkylcadmium conversion of acid chlorides into ketones fails in the 1,2,5-thiadiazole series. The major product is either a tertiary carbinol or the corresponding dehydration product, by virtue of the high reactivity of the intermediate ketone.

Acetyl thiadiazole also displays enhanced reactivity in both the carbonyl and the methyl groups and enters the aldol condensation, the Mannich reaction, cyanoethylation reaction, the Willgerodt

reaction, the Leukart reaction, and borohydride reduction, all in high yield under very mild conditions <68AHC(9)107>.

Addition of nucleophiles to the cyano group of cyanothiadiazole under basic conditions takes place with unusual ease <88AG(E)434, 94ACS372>. Hydrolysis to the amide, for example, can be effected at 0°C in the presence of a catalytic amount of sodium hydroxide or basic ion-exchange resin. At reflux temperature, hydrazine and monosubstituted hydrazines convert 3,4-dicyano-1,2,5-thiadiazole into the 1,2,5-thiadiazole[3,4-*d*]pyridazines <71JHC441>. The base-catalyzed addition of acetone to cyanothiadiazole forms an enamino ketone, used as a key intermediate for the synthesis of a number of heterocyclic ring systems, e.g. isothiazole, isoxazole, pyrazole, pyrimidine, and thiazole <77H(6)1985>.

Radical bromination of 3,4-dimethyl-1,2,5-thiadiazole (**55**) has been extensively studied. While, under forcing conditions a mixture of mono-, di-, tri-, and tetrabromo derivatives can form, by careful control the monobromide (**59**) can be selectively formed (Equation (9)) <84JHC1157, 87CB1593, 89CCC2176>.



4.09.7.4 N-Linked Substituents

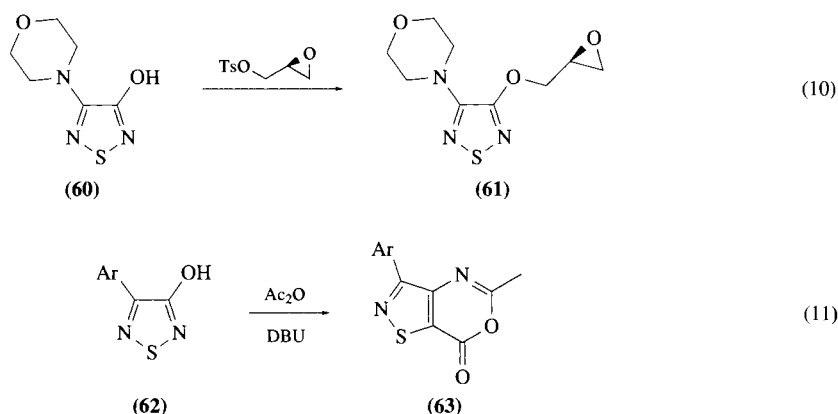
3-Amino-1,2,5-thiadiazole is a weak base but is sufficiently nucleophilic to readily form acyl, aroyl, sulfanyl, and sulfinyl derivatives on the exocyclic nitrogen atom. Similarly, all the observed reactions of diaminothiadiazole <76JHC13> involve the exocyclic nitrogen atoms. IR, UV, and NMR spectroscopic evidence clearly indicate, however, that aminothiadiazole protonates on the ring nitrogen atom <68AHC(9)107>.

Diazotization of the monoamine in acidic aqueous media formed only the diazoamino compound in high yield. In an attempt to generate and trap 1,2,5-thiadiazine via diazotization of the 3-amino-4-carboxylic acid in the presence of anthracene, a mixture comprising 9-nitroanthracene and a small amount of 9-thiocyananthracene was obtained <71TL2143>.

Despite the tendency of the thiadiazole ring to undergo reductive cleavage, milder reducing agents selectively reduce nitro, nitroso, azo, acyl chlorides, and even ester functions without rupture of the ring system. Selective reducing agents include sodium borohydride <67JHC445>, diisobutylaluminum hydride <81JHC1247>, iron in acetic acid, sodium dithionite, sodium sulfide, zinc in calcium chloride, alkaline iron(II) sulfate <69CHE53, 70RCR923>, sodium hydrosulfite <75JHC829>, palladium and sodium phosphinite <78T213>, and palladium on carbon <74JHC835>.

4.09.7.5 O-linked Substituents

Hydroxythiadiazoles exhibit marked acid properties and exist essentially in the hydroxy form <68AHC(9)107>. Alkylation with alkyl halides or sulfates and base in dipolar aprotic solvents usually forms ethers. In media where the oxygen atom is screened by solvation or by formation of ion pairs, mixtures of N- and O-alkylation products are formed. The reaction of 3-chloro-4-hydroxy-1,2,5-thiadiazole with epichlorohydrin catalyzed by piperidine in the absence of a solvent gave a mixture of N- and O-alkylated products in about equal amounts <72JHC651>. Treatment of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**60**) with chloroacetic acid in aqueous sodium hydroxide produced very low yields of O-alkylated product <78CJC722>. In contrast, the same "aromatic" hydroxyl (**60**) is clearly alkylated by glycidyl tosylate. By analogy with phenols, attack comes at the terminal carbon, rather than the epoxide, with retention of stereochemistry to give (**61**) (Equation (10)) <89JOC1295>. An attempt to prepare a mesoionic compound by the alkylation of 3-hydroxy-4-phenyl-1,2,5-thiadiazole (**62**) with dimethyl sulfate and methyl fluorosulfonate in the absence of base produced 2-methyl-4-phenyl-1,2,5-thiadiazole-3-one <81JCS(P1)1033> and attempts to acylate the 3-hydroxyl with acetic anhydride led to ring transformation into the isothiazole (**63**) (Equation (11)) <85JHC1497>. Diazomethane gave a mixture of N- and O-methylation products.



Hydroxythiadiazoles can be converted into chloro compounds by the usual methods, for example with POCl₃. The O-acylation of the sodium salt of hydroxythiadiazoles with dimethylthiocarbamoyl chloride followed by thermal rearrangement of the thiolcarbamate and hydrolysis is a convenient route to 1,2,5-thiadiazole-3-thiones <73CJC2349>.

4.09.7.6 Halogens

The halogens in 1,2,5-thiadiazoles are reactive but 3-chloro-1,2,5-thiadiazole usually does not produce high yields in displacement reactions, probably because of ring decomposition via proton abstractions <68AHC(9)107>.

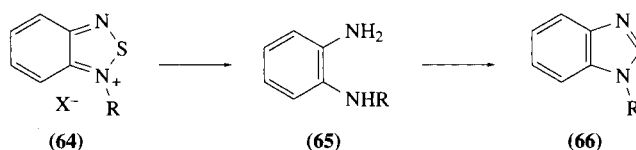
A detailed study of the conversion of 3,4-dichloro-1,2,5-thiadiazole into 3,4-diamino-1,2,5-thiadiazole has been carried out <76JHC13>. Reaction with lithium or sodium amide produces only 4% of the diamine together with cyano-containing by-products, a consequence of direct attack on sulfur. Use of a less powerful nucleophile, ammonia or potassium phthalimide, resulted in an increased attack on carbon and produced the diamine in 24% and 66% yields, respectively. Secondary amines, e.g. morpholine <76JOC3121> and dimethylamine <72JMC315>, produce the normal displacement products. The reaction of dichlorothiadiazoole with potassium fluoride in sulfolane gives a mixture of 3-chloro-4-fluoro and 3,4-difluoro-1,2,5-thiadiazole <82CB2135>.

The presence of an electron-donating group on the thiadiazole ring promotes attack on carbon and good yields of the displacement products. In contrast to 3,4-dichloro-1,2,5-thiadiazole, which is destroyed by caustic hydrolysis, the 3-chloro-4-*N*-morpholino analogue can be hydrolyzed to 3-hydroxy-4-*N*-morpholino-1,2,5-thiadiazole in nearly quantitative yield <76JOC3121>. The alkoxy group behaves similarly; 4-chloro-3-ethoxy-1,2,5-thiadiazole produces 62% of the corresponding sulfanilamido derivative on reaction with sulfanilamide and base <67JOC2823>.

4.09.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

4.09.8.1 N-linked Substituents

Alkylation of the benzothiadiazole ring nitrogen will provide an ammonium halide (64) which is readily hydrolyzed to an unsymmetrically substituted 1,2-benzenediamine (65). Subsequent treatment with formic acid allows access to *N*-alkylbenzimidazoles (66) (Scheme 13) <89SC1381>.



Scheme 13

4.09.9 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

4.09.9.1 Synthesis of 1,2,5-Thiadiazole Rings

There are three classical methods for the synthesis of the 1,2,5-thiadiazole ring system. They are characterized by the combination of atom fragments necessary to form the ring: [4 + 1], [3 + 2] (type A), and [3 + 2] (type B) (Figure 3). These methods will be reviewed in the subsequent sections (Sections 4.09.9.1.1 and 4.09.9.1.2). The synthesis of aromatic and azaaromatic fused 1,2,5-thiadiazole has been reviewed (83H(20)71).

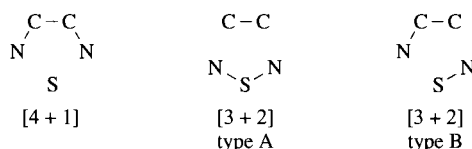
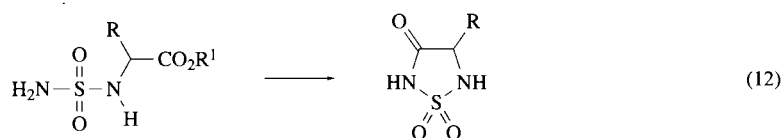


Figure 3 Synthesis of 1,2,5-thiadiazole ring system.

Since the start of the 1990s, a number of novel routes to 1,2,5-thiadiazole-1,1-dioxides have appeared. All involve an intramolecular cyclization of a sulfamide nitrogen onto an ester or its equivalent. The method is general and allows a variety of α -amino acids to be used as starting materials (Equation (12)) (89JOC4471, 89JOC5824, 89JOC3077, 92MI 409-01, 92MI 409-02).



4.09.9.1.1 Synthesis from [4 + 1] atom fragments

The syntheses from [4 + 1] atom fragments, in which the Group 16 heteroatom is introduced between two nitrogen atoms, are the most widely applicable and versatile methods available for construction of the 1,2,5-thiadiazole ring system. These methods have been applied to the synthesis of monocyclic and polycyclic aromatic forms of these ring systems in addition to the direct formation of 1-oxides and 1,1-dioxides, 2-oxides, quaternary salts, and reduced forms. The earliest use of the [4 + 1] synthesis dates back to 1889 when Hinsburg prepared 2,1,3-benzothiadiazole (**1**) from *o*-phenylenediamine and sodium bisulfite.

These reactions have undergone extensive development and have proven to be general for the synthesis of these ring systems from any substituted *o*-diamine (B-61MI 409-01, 70RCR923). The choice of the sulfur reagent, thionyl chloride, sulfur dioxide, sulfinylaniline or sulfur monochloride, depends upon the nature of substituents present.

The mechanism for the formation of 2,1,3-benzothiadiazole from an *o*-diamine and thionyl chloride involves an *o*-sulfinylaniline (59DIS3136, 67CB2170, 68CB371) and not an *o*-sulfinylamine intermediate as proposed by early workers.

1,2,5-Thiadiazoles fused to other heterocyclic systems have attracted considerable attention. These polycyclic systems, obtained either via [4 + 1] syntheses from the corresponding *o*-diamines or via annulation of a heterocycle to a compound already containing a thiadiazole ring, involve fusion to pyridine (70RTC5, 70RCR923, 78JOC960, 79JMC944, 79S687, 80S842), pyridazine (71JHC441, 71CCA101), pyrazine (74JOC1235, 75JHC451, 76JHC13), pyrazole (81JOC4065), 1,2,5-thiadiazole (75JOC2749, 76JHC13), triazole (74BCJ1493), thiadiazine (79JMC944), thiophene (69JA6891), quinoline (76CHE61, 81S316), quinoxaline (76JHC13, 79JHC1617), benzimidazole (81JJC(B)111), benzoxadiazole (78CPB3896, 80CPB1909), benzisothiazole (80JHC537), benzothiadiazole (75JHC829), acridine (72JHC1109), and coumarin (80KGS853, 88KGS977).

Due to the lack of suitable aliphatic starting materials, the synthesis of aromatic forms of monocyclic 1,2,5-thiadiazoles was not accomplished for more than 70 years after the first report of the benzo analogues. General synthetic methodology for monocyclic 1,2,5-thiadiazoles was devised which readily leads to a variety of substituted derivatives, alkyl, aryl, halo, hydroxy, alkoxy, cyano, and amino as well as the parent system. A general model for substrates applicable in these syntheses

can be described in terms of an acyclic NCCN system in which the N—C groups exist at any hybridization, *sp*, *sp*², and *sp*³. Compounds containing these C—N functionalities in any combination react with sulfur monochloride or sulfur dichloride to form an appropriately substituted thiadiazole <67JOC2823, 68AHC(9)107>. These syntheses are summarized in Table 3. In a few limited cases, thionyl chloride <70RCR923>, tetrasulfur tetranitride or sulfur tetrafluoride <76CB2442> served as the thio cyclizing agent but the sulfur chlorides are the most versatile and generally applicable reagents for this purpose. For example, the sulfur chlorides are strongly electrophilic and capable of forming N—S bonds with a wide range of nucleophiles, e.g. amines, imines, amides, nitriles, and oximes, and can also serve as the oxidant, as required in the syntheses of thiadiazoles from reduced substrates (e.g. α -diamines). The sulfur chlorides also readily add to nitrile groups, providing chloro-substituted thiadiazoles.

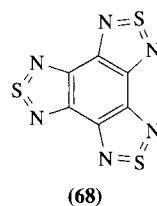
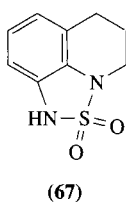
Table 3 Synthesis of 1,2,5-thiadiazoles from aliphatic compounds and sulfur chlorides.

Starting material	R ¹	R ²	Yield (%)	Ref.
R ¹ CH(NH ₂)CH(NH ₂)R ²	H	H, alkyl, aryl CO ₂ H,	50–70	67JOC2823, 68AHC(9)107,
		vinyl		80T1245
(NH ₂)C(CN)=C(CN)(NH ₂) or	CN	CN	60	59DIS1593, 68AHC(9)107
NH ₂ C(CN)=C(CN)NH ₂				
R ¹ CN(NH ₂)CONH ₂	H, alkyl, aryl	OH	40–60	67JOC2823, 68AHC(9)107,
				68CPB544
NH ₂ CH ₂ CONHR ¹	^a		40–80	79JOC1118
R ² NHCH(R ¹)CONH ₂	^b		50–65	81JCS(P1)1033
NH ₂ CH ₂ C(=NH)NH ₂	H	NH ₂	66	67JOC2823
NH ₂ CH(R ¹)CN	H, alkyl, aryl	Cl	50–70	67JOC2823
NCC(=NH)C(=NH)CN	CN	CN	93	72JOC4136
R ¹ C(=NTMS)—C(=NTMS)R ²	Aryl	Aryl	80–100	68LA(711)174,
				79JOM(166)25
R ¹ C(=NH)C(=NH)R ²	Alkoxy	H, alkoxy	50–90	67JOC2823
NH ₂ COCN	OH	Cl	88	67JOC2823
R ¹ C(=NH)CN	Alkoxy	Cl	89–90	67JOC2823
NCCN	Cl	Cl	90	68AHC(9)107, 67JOC2823
NCC(=NOH)CONH ₂	CN	OH	68	64JA2861
R ¹ C(=NOH)CN	Aryl	Cl	15	67JOC2823
R ¹ C(=NOH)C(=NOH)R ²	Alkyl, aryl ^c	Alkyl, aryl	40–45	67JOC2823, 70JOC1165

^a2-Substituted 2*H*-1,2,5-thiadiazole-3-ones are formed. ^bThe products are mesoionic 5-alkyl-4-aryl-1,2,5-thiadiazolium-3-olates.

^c*N*-Oxides have also been detected.

A number of new “thio” cyclizing agents have been reported including piperidine-1-sulfonyl chloride, <84JCS(P1)2591>, *N,N'*-thiobisphthalimide <88MI 409-01>, and *in situ*-generated SO₂ <92T8615>. Additionally, the syntheses of a tricyclic thiadiazole (**67**) and the hexamine derived trithiadiazole (**68**) demonstrate the versatility of the method <90LA203, 92H(34)907>.



Thiadiazole oxides and reduced forms are readily prepared via [4 + 1] cyclizations (Table 4). The reagents employed for this purpose are thionyl chloride, sulfuryl chloride, sulfur tetrafluoride, *N,N'*-bis(*p*-toluenesulfonyl)sulfur diimide, cyclic diimides, pentafluoroethyliminosulfur difluoride and sulfamide.

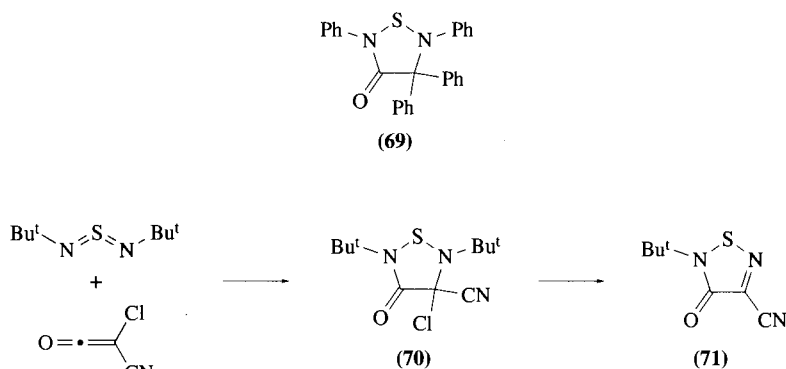
4.09.9.2 Synthesis from [3 + 2] Atom Fragments

The N—S—N grouping in the [3 + 2] (type A) thiadiazole syntheses is functionally equivalent to either an *N,N'*- or *S,S'*-disubstituted sulfur diimide, diaminosulfane, sulfamide or tetrasulfur tetranitride. In the cycloaddition of diphenylketene to *N,N'*-diphenylsulfur diimide the 1 : 1 adduct

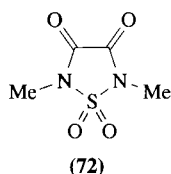
Table 4 Synthesis of 1-oxides and reduced forms of 1,2,5-thiadiazole from [4 + 1] atom fragments.

Starting material	Cyclizing reagent	Product	Ref.
EtOC(=NH)C(=NH)OEt	SOCl ₂	3,4-Diethoxy-1,2,5-thiadiazole 1-oxide	81H(16)1561, 68LA(711)174
H ₂ NCM ₂ CN	SOCl ₂ or SO ₂ Cl ₂	3-Chloro-4,4-dimethyl-Δ ² -1,2,5-thiadiazoline 1-oxide or 1,1-dioxide	75AKZ412
Bu ^t NHCOCH ₂ NHPh	SOCl ₂	2- <i>t</i> -Butyl-5-phenyl-1,2,5-thiadiazolidin-3-one 1-oxide	77JOC1015
TMSNHC ₂ H ₄ CH ₂ NHTMS	SF ₄	3,4-Dihydro-1λ ⁴ ,2,5-thiadiazole	77CB3205
H ₂ NCHMeCH ₂ NH ₂	TosN=S=NTos	3,4-Dihydro-3-methyl-1λ ⁴ ,2,5-thiadiazole	69TL4117
MeNHCH ₂ CH ₂ NHMe	CF ₃ CF ₂ N=SF ₂	1-Pentafluoroethylimino-2,5-dimethyl-1,2,5-thiadiazolidine	79IC213
MeNHCH ₂ CH ₂ NHMe	SO ₂ Cl ₂	2,5-Dimethyl-1,2,5-thiadiazolidine 1,1-dioxide	78CB1915
<i>o</i> -C ₆ H ₄ (NHTos) ₂	SOCl ₂	1,3-Bis(<i>p</i> -toluenesulfonyl)-1,3-dihydro-2,1,3-benzothiadiazole 1-oxide	59DIS3136, 79CB1012
<i>o</i> -C ₆ H ₄ (NH ₂) ₂	NH ₂ SO ₂ NH ₂	1,3-Dihydro-2,1,3-benzothiadiazole 1,1-dioxide	71JCS(C)993
PhNHC(=NPh)C(=NPh)Ph	SOCl ₂	2,5-Diphenyl-3,4-diphenylimino-1,2,5-thiadiazolidine 1-oxide	80JPR273

(69) is formed. With chlorocyanoketene and *N,N'*-di-*t*-butyl sulfur diimide the initial adduct (70) loses HCl and isobutylene to form the dealkylated product (71) in 51% yield (Scheme 14) <83H(20)187>.

**Scheme 14**

S,S-Disubstituted sulfur diimides react with oxalyl chloride to form 1,1-dialkylthiadiazoles in high yield <72LA(759)107>. Sulfamide also readily condenses with bifunctional electrophiles <88LA337, 89LA1135>, α-diketones <68AHC(9)107, 70CRV593>, diethyloxalate <75JOC2743>, and α-ketoesters <83JHC821> producing thiadiazole-1,1-dioxides. *N,N'*-Disubstituted sulfamides react with oxalyl chloride in high yield to produce thiadiazolidinedione dioxides (72) <83IC2095>.



Tetrasulfur tetranitride (S₄N₄) is perhaps the most widely reported reagent for the [3 + 2] (type A or B) formation of the 1,2,5-thiadiazole ring (Table 5) <90MI 409-01>.

The reaction of alkoxy benzenes with S₄N₄ has been shown to be an effective method for conversion of phenols <85JCR(S)346, 88JCS(P1)1869, 89BCJ3127> and naphthols <91BCJ68> to 1,2,5-thiadiazoles. For example, phenol gives (1) and 2-naphthol gives (42).

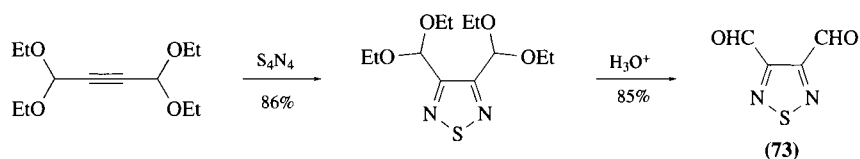
Trithiazyl trichloride (S₃N₃Cl₃) has been shown to be more electrophilic than S₄N₄. It will react

Table 5 Synthesis of 1,2,5-thiadiazole from [3 + 2] atom fragments using S₄N₄.

Starting material	R ¹	R ²	Yield (%)	Ref.
R ¹ CH ₂ CH ₂ R ²	Phenyl	H, phenyl	10–20	67G1614, 65AG(E)239
R ¹ CH ₂ CH(NH ₂)R ²	Phenyl	H, phenyl	60	71G259
R ¹ CH ₂ COR ²	Aryl	Aryl, alkyl	10–60	79S524, 80JHC1681
R ¹ C(=NOH)COR ²	Phenyl	Phenyl	4	79JCS(P1)2905
R ¹ C≡CR ²	Aryl, CO ₂ Me, CN, H	Aryl, CO ₂ Me, CN, phenyl	16 16 7	79JHC1009, B-68MI 409-01, 77H(6)933, 87CC59, 84CC57
α- or β-naphthyl amines			20–60	59DIS3136
R ¹ COMe	Aryl	H	30	85OPP152
ArCOCH ₂ COR	ArCO	R	7–50	82S976
ArC(OTMS)(=CH ₂)	Ar	OH	11–19	83H(20)2047
ArC(=NOH)CH ₂ Cl	Ar	H	80–90	94H(38)1859, 93JCS(P1)2345

with *trans*-stilbene to produce 3,4-diphenyl-1,2,5-thiadiazole <77JCS(P1)916> and with CF₃—C≡C—CF₃ to produce 3,4-bis(trifluoromethyl)-1,2,5-thiadiazole in 58% yield <92CC898>.

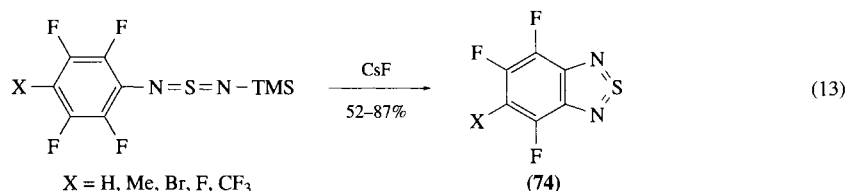
A thorough study of the cycloaddition reactions of S₄N₄ with electron deficient alkynes has appeared <87JCS(P1)1579>. A clear mechanistic hypothesis is proposed along with the report of a high yielding synthesis of the versatile 3,4-diformyl-1,2,5-thiadiazole (**73**) (Scheme 15).

**Scheme 15**

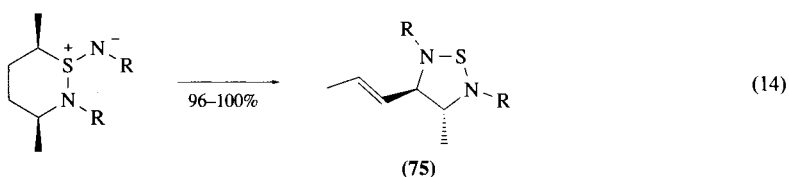
4.09.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

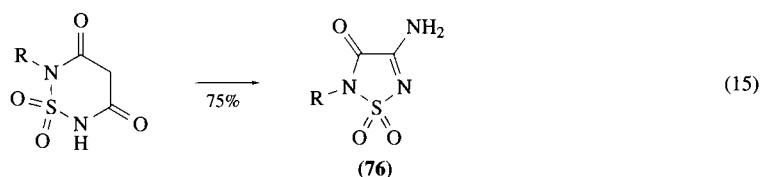
4.09.10.1 Synthesis of 1,2,5-Thiadiazole Rings

While not a general method for thiadiazole rings, the transformation of an existing ring into a thiadiazole can play an important role. It is also possible to use an existing ring as a scaffold for thiadiazole formation <92ZOR422>. One example is the aromatic nucleophilic displacement of fluoride to produce 2,1,3-benzothiadiazoles (**74**) (Equation (13)) <90JFC(50)359>.



Ring contractions of six-membered heterocycles have also been reported to yield both reduced (**75**) <84JA7867> and oxidized (**76**) <86JCS(P1)643> forms of thiadiazole (Equations (14) and (15)).

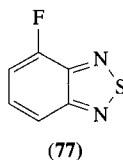




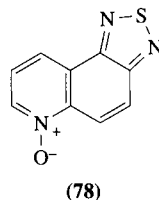
4.09.11 SYNTHESIS OF A PARTICULAR CLASS OF COMPOUNDS AND A CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

4.09.11.1 Miscellaneous Issues

Research on the fluorination of aromatic amines has provided access to 4-fluoro-2,1,3-benzothiadiazole (77). Treatment of 4-amino-2,1,3-benzothiadiazole (1) with nitrosonium tetrafluoroborate (NOBF₄), followed by heating of the resulting diazonium salt, gave the aryl fluoride (77) in 23% yield <92SC73>.



Oxidation of quinoline fused thiadiazoles occurs selectively at the quinoline nitrogen to provide the quinoline-*N*-oxide (78) in 70% yield <86IJC(B)271>.

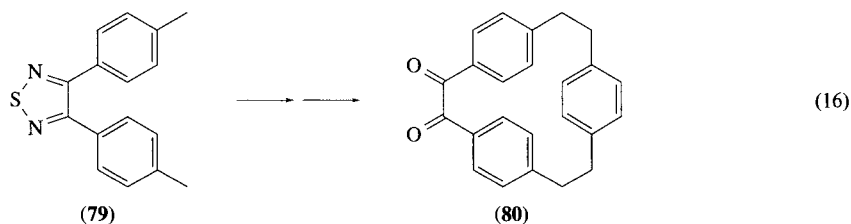


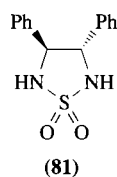
4.09.12 APPLICATIONS OF 1,2,5-THIADIAZOLES

4.09.12.1 Miscellaneous Issues

The 1,2,5-thiadiazoles have found value across pharmaceutical, agricultural, industrial, and polymer chemistry. These uses have been well documented <84CHEC-I(6)513>.

Since the mid-1980s, chemists have begun to use the thiadiazole ring as a synthetic tool in constraining the geometry of a chemical reaction. The simple 3,4-ditoluyl analogue (79) has been used to construct complex cyclophan-1,2-diones (80) (Equation (16)) <86JHC813>. Likewise, the (1*R*,2*R*)-diphenyl-1,2-diaminoethane-derived thiadiazole dioxide (81) is extremely useful as a chiral auxiliary in the Evans aldol reaction <92TL6661>.





In the search for structural diversity, and novel therapeutic agents, unique ring structures like the 1,2,5-thiadiazole have always captured the imagination of chemists. Often, as in the case of timolol (4), the interest is rewarded. In the early 1990s, a simple thiadiazole was appended to a penem in the development of the structure–activity relationships for a series of β -lactamase inhibitors. The result was enhanced penetration of the bacterial membrane and a broader spectrum of activity versus clavulanic acid <91JAN331>.

4.10

1,3,4-Thiadiazoles

GABE I. KORNIS

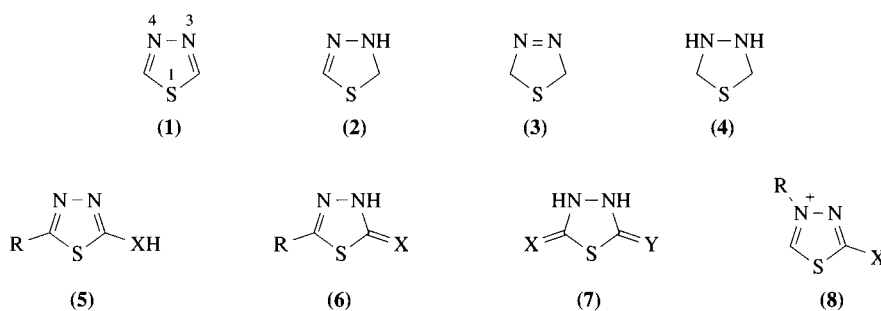
The Upjohn Company, Kalamazoo, MI, USA

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4.10.1 INTRODUCTION

1,3,4-Thiadiazole and its derivatives continue to be of great interest to a large number of researchers. A *Chemical Abstracts* search between 1982 and 1994 based on structure (1) in which the nature of the bonds and substituents were not defined, yielded 6621 records. By limiting the search to only three *Chemical Abstracts* sections, 831 publications and 386 patents were located. Surprisingly, no comprehensive review articles were written since 1984 although some aspects of thiadiazole chemistry were covered in the *Progress in Heterocyclic Chemistry* series (91PHC149, 92PHC130, 93PHC167). For the literature prior to 1982 and the history of 1,3,4-thiadiazole the reader is referred to Kornis (84CHEC-I(4)545). The main classes of the 1,3,4-thiadiazole system covered in this review are the aromatic 1,3,4-thiadiazoles (1), the non-aromatic Δ^2 -thiadiazolines (2), Δ^3 -thiadiazolines (3), and the thiadiazolidines (4). Systems such as (5) are aromatic but the tautomeric forms such as (6) and (7) are not aromatic. The mesoionic systems (8) represent a further class of thiadiazoles. Benzo fusion in 1,3,4-thiadiazoles is not possible.

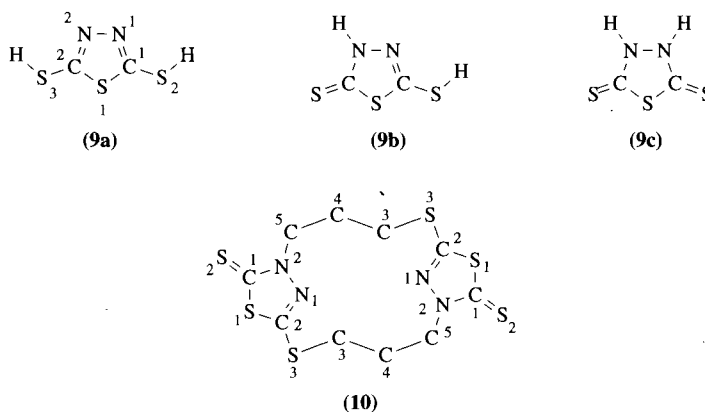


4.10.2 THEORETICAL METHODS

The reaction of 2,5-dithio-1,3,4-thiadiazole (9) with dibromo alkanes $[\text{Br}(\text{CH}_2)_n\text{Br}]$ under alkaline conditions yielded macrocyclic compounds connected by one or more methylene groups. Due to the three possible tautomeric forms ((9a), (9b), and (9c)) several macrocycles can be obtained. Compound (10) was such a product, formed by the thermal dimerization of an intermediate. The molecular geometry of (10) was optimized by the AM1 method. Its electronic spectrum was calculated at CNDO/S level. Based on the UV bands observed and the calculated electronic transition, the thiol–thione structure of (9) shows the greatest stability, and the electronic transitions of (10) are almost the same as for (9) (90BCJ2991). Self consistent field configuration interaction calculations (SCF-CI) on 1,3,4-thiadiazoles suggest that the electronic state of the sulfur atom is best described by $s^2p_xp_y p_z^2$ in which the two p_z electrons are conjugated with the π -electron system of the rest of the molecule. The SCF eigenvalues and the molecular geometries have also been published (69JIC779).

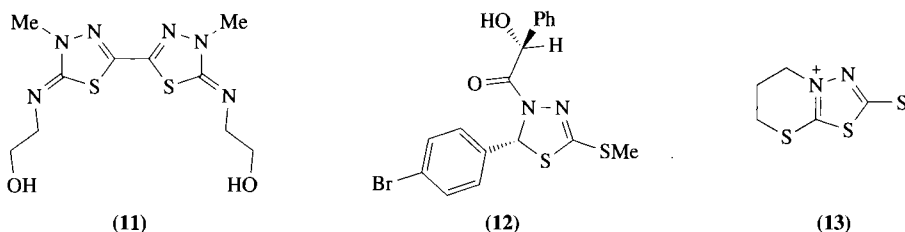
4.10.3 EXPERIMENTAL STRUCTURAL METHODS

The use of NMR, MS, IR spectroscopy, and to a lesser extent x-ray crystallography has become routine since the mid-1980s. Particularly, the use of sophisticated NMR techniques such as NOE, COSY, HETCOR, HMBC etc., has become indispensable for structure elucidation, and has provided much insight into the field of reaction mechanisms.



4.10.3.1 X-ray Diffraction

X-ray diffraction techniques have been extensively utilized for the elucidation of many 1,3,4-thiadiazoles. 5-Amino-1,3,4-thiadiazole-2-thiol is planar and in the solid state exists in the thione and not the thiol form. The ring shows aromatic character with a localized C(1)=N(1) double bond of 1.305 Å. Other C—N bond lengths are 1.334 Å and 1.339 Å and the N—N bond is 1.382 Å. The cyclic C—S distances are 1.746 Å and 1.748 Å and the exocyclic C—S bond is 1.678 Å. Pairs of molecules are joined across centers of symmetry by hydrogen bonding <72AX(B)1584, 84CHEC-I(4)547>. Crystals of compound (11) were described in a P(1) cell, with an internal crystallographic inversion center <91JCS(P)1159>. The crystal structure of the chiral thiadiazoline (12) was solved by direct methods using the multan program, and the absolute configuration was obtained from the intensity examination of the Bijvoet pairs <89H(29)1233>. Pappalardo and co-workers utilized x-ray diffraction to ascertain the structure of (13) previously thought to be a sulfur bridged heterophane containing two thiadiazole molecules. The zwitterionic character of the molecule was deduced from the planarity of the thiadiazole ring and the characteristic bond length between the carbon and heteroatoms <89JOC2024>.

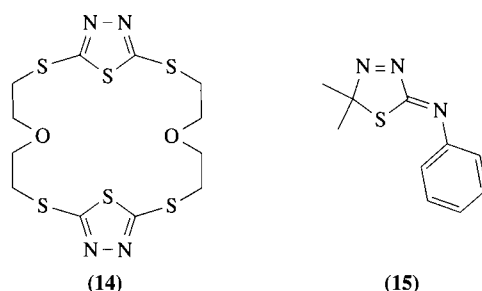


The Pappalardo group also used x-ray diffraction to establish the geometry and modes of binding sites of 1,3,4-thiadiazolo thia crown ethers (14). It was concluded that the thiadiazole molecules are stacked in parallel *anti* fashion and that no cavity is present. The discrete dimeric molecules lie on centers of symmetry; the thiadiazole ring is planar with the bridgehead sulfur atoms somewhat out of plane <88JCR(S)56>. X-ray diffraction established that the Δ^3 -thiadiazoline (15) has the *Z* configuration, the ring is planar, and that the —N=N—, C—N and C—S bonds were the expected lengths; the angles however differed substantially from the normal 108° expected. The *ortho* hydrogen on the phenyl ring is repulsed by the sulfur atom, causing the phenyl ring to be out of plane with respect to the thiadiazoline ring <87CJC1154>.

The synthetic routes to some of the compounds mentioned in this section are discussed in Section 4.10.10.

4.10.3.2 Microwave Spectroscopy and Neutron and Electron Diffraction

The complete substitution pattern of normal, mono-deuterated and perdeuterated 1,3,4-thiadiazoles was established with the aid of double-resonance modulation microwave spectroscopy. Bond lengths and angles were determined with uncertainties covering all three molecular forms. It



was concluded that the position of the near-axis atoms could be refined from the shift and swing of inertial axes from the different parent forms $\langle 89ZN(A)29 \rangle$. Microwave spectroscopy was also useful in measuring relative aromaticity $\langle B-85MI\ 410-01 \rangle$.

Electron diffraction studies on 1,3,4-thiadiazole (1) in the vapor phase are consistent with a planar molecule having C_{2v} symmetry. Bond angles and distances correspond with the values obtained from microwave spectroscopy studies. Bond lengths and bond angles follow, with values in parentheses being estimated error limits: (C—H) = 1.081 (± 0.028) Å, (N—C) = 1.304 (± 0.010) Å, (N—N) = 1.381 (± 0.016) Å, (S—C) = 1.722 (± 0.006) Å; CSC = 86.4 (± 0.4)°, SCN = 114.8 (± 0.5)°, CNN = 112.0 (± 0.4)°, SCH = 124.1 (± 3.0)°, HCN = 121.1 (± 3.0)° $\langle 70ACS2525 \rangle$.

No publications relating to neutron diffraction experiments were found.

4.10.3.3 Nuclear Magnetic Resonance

Proton, ^{13}C , ^{14}N , and ^{15}N NMR values for 1,3,4-thiadiazoles were discussed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and some representative chemical shifts are summarized in Figure 1 $\langle 84CHEC-I(4)549 \rangle$.

A comparison between the ^{13}C NMR chemical shifts of thiadiazole, oxadiazole, and isosydnone derivatives indicates that the effect of substituents was more pronounced for thiadiazoles than for oxadiazoles $\langle 82OMR(18)159 \rangle$. Proton and ^{13}C NMR spectroscopy was useful in establishing the influence of the $-N=S^+-O^-$ moiety on the thiadiazole ring $\langle 89JCS(P2)1855 \rangle$ and the changes occurring on oxidizing the 2-alkylthio group to a sulfoxide or sulfone $\langle 88MI\ 410-01 \rangle$.

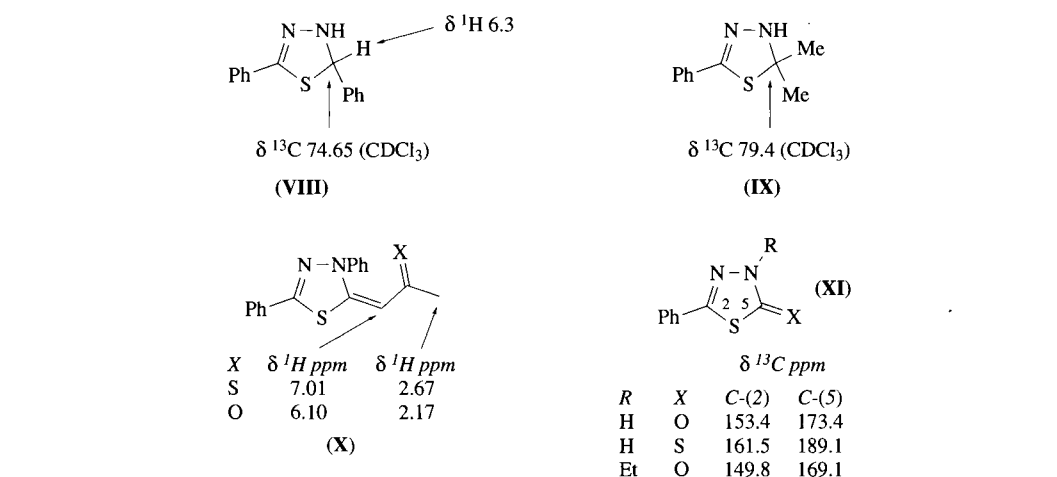
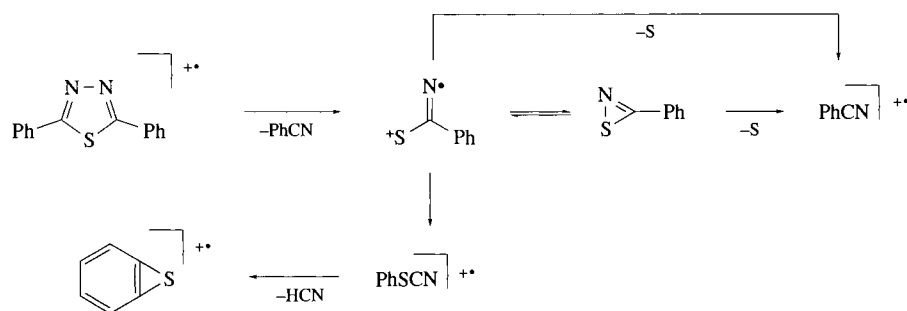
Nitrogen-15 NMR spectroscopy was very useful in establishing unequivocally that the 1,3,4-thiadiazol-2(3H)-ones (16) exist in the oxo rather than the enol form (17). Use was made of the large differences in chemical shifts to distinguish between the N-methyl group in (18) and the O-methyl group in (19). Fritz *et al.* give several tables with accurate chemical shifts for all the compounds described $\langle 83HCA1755 \rangle$.

4.10.3.4 Mass Spectrometry

The principal fragmentation of 1,3,4-thiadiazoles in the mass spectrometer is loss of a nitrile group as shown in Scheme 1. In the presence of a methylthio substituent, the major process is loss of $\cdot SH$ and fragmentation at the heterocyclic sulfur atom (Scheme 2). In 1,3,4-thiadiazolines the major pathway is loss of $PhS\cdot$ (Scheme 3) while 1,3,4-thiadiazolidinediones decompose by fragmentation of the ring $\langle B-85MI\ 410-02 \rangle$.

Pappalardo and co-workers studied the mass spectral characteristics of alkyl and aryl substituted 2,5-dithio-1,3,4-thiadiazoles. Selected ions in the mass spectra of SH, S-CH₃, and S-aryl thiadiazoles were tabulated. The S-aryl thiadiazoles form stable cyclic ions yielding additional fragments. The fragmentation pattern is dependent on the structural characteristics of the substituents. If both tautomers—thiol and thione—are present, the molecular ion will also lose CS₂. Besides the base peak, intense peaks observed in the MS spectrum are due to extensive fission of the thiadiazole ring. Some of the fragments formed are shown in Scheme 4 $\langle 82OMS(17)335 \rangle$.

While most other techniques failed, MS was quite successful in distinguishing between the two isomers (20) and (21) (Scheme 5). While the 7-one (20) undergoes a *retro* Diels–Alder process and exhibits a diagnostic fragmentation pattern at m/z 203 and 102, these peaks are lacking in (21)


$$\begin{array}{ccccccc}
 \begin{array}{c} \text{H} \\ | \\ \text{4 N}-\text{N 3} \\ // \quad \backslash \\ \text{R} \quad \text{S} \quad \text{C=O} \end{array} & \rightleftharpoons & \begin{array}{c} \text{4 N}-\text{N 3} \\ // \quad \backslash \\ \text{R} \quad \text{S} \quad \text{C=OH} \end{array} & & \begin{array}{c} \text{Me} \\ | \\ \text{4 N}-\text{N 3} \\ // \quad \backslash \\ \text{R} \quad \text{S} \quad \text{C=O} \end{array} & & \begin{array}{c} \text{4 N}-\text{N 3} \\ // \quad \backslash \\ \text{R} \quad \text{S} \quad \text{C=OMe} \end{array} \\
 \text{(16)} & & \text{(17)} & & \text{(18)} & & \text{(19)}
 \end{array}$$


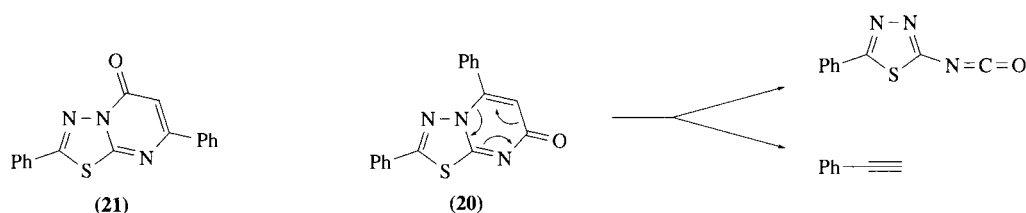
Scheme 1

Scheme 2

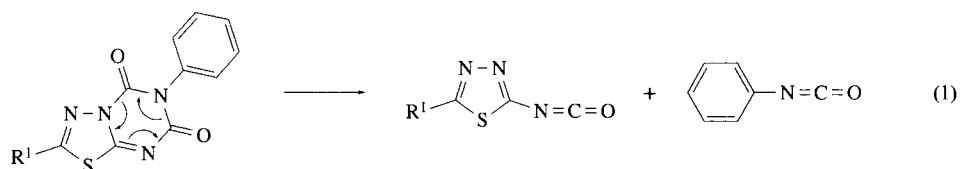
Scheme 3

Scheme 4

(85JHC297). In a continuation of the above work, 1,3,4-thiadiazolo[3,2-*a*][1,3,5]-triazines were also analyzed by electron impact mass spectrometry. A *retro* Diels–Alder process gave two fragments (Equation (1)) which in turn were further fragmented into smaller molecules. The mass spectral data for the 11 compounds analyzed has been tabulated in great detail (89OMS(24)379).



Scheme 5



4.10.3.5 UV, CD, Photoelectron, and Fluorescence Spectroscopy

UV Spectroscopy has had limited application as a tool for structure determination or reaction mechanism elucidation since the mid-1980s. Unconjugated 1,3,4-thiadiazoles have no absorption above 220 nm. Some UV data for substituted thiadiazoles was given in <84CHEC-I(4)545> and little additional data has since appeared. Toyooka *et al.* <91CPB777> employed circular dichroism (CD) to confirm the absolute configuration of (12) already mentioned in Section 4.10.3.1 <89H(29)1233>. Russian workers employed photoelectron spectroscopy to study the differences between oxadiazoles and thiadiazoles when various fluorinated alkyl groups were introduced in the 2,5 positions. A shift of the first band to higher energies was noted. This was approximately the same for both classes of compounds and was explained by the fact that first bands correspond to ring π and nitrogen unshared pair orbitals. The alkyl groups and the oxygen or sulfur atoms influence the bands in the 13–14 eV region <89ZOB2698>.

Photoelectron spectroscopy was used by French workers to follow the thermolysis of 2-azidothiadiazoles <88CJC2830> (see also Section 4.10.6.1). No publications related to fluorescence were found.

4.10.3.6 IR and Raman Spectroscopy

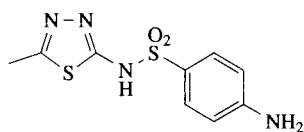
The characteristic bands for 1,3,4-thiadiazoles are as follows: 1230–1165, 1190–1120, 1075–1045, 1040, 975–905, 905–875, 850, 775–750 <84CHEC-I(4)25>. The only publication mentioning Raman spectroscopy concerns vibrational analysis of 2-(*p*-aminobenzenesulfonamid)-5-methyl-1,3,4-thiadiazole <90MI 410-01>.

4.10.3.7 Dipole Moments and Electron Spin Resonance

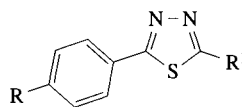
Using a combination of techniques 1,3,4-thiadiazole was shown to have a dipole moment of 3.0 D directed from the sulfur atom toward the center of the N—N bond. Dipole moment measurements were useful for proving the mesoionic structure and the large negative charge of an exocyclic sulfur atom for certain 1,3,4-thiadiazole derivatives <84CHEC-I(4)545>.

4.10.4 THERMODYNAMIC ASPECTS

Gupta and co-workers have measured the energy, entropy, and enthalpy of activation for the oxidation of sulfamethizole (22) with periodate. The reaction obeyed the Arrhenius equation and a correlation of the results with the nature of the transition state was attempted <83MI 410-01>.



(22)

(23) R = H, Cl, NO₂; R¹ = SO₂Et
R = H, Cl; R¹ = NHNHCO₂CH₂CH=CH₂

4.10.4.1 Melting and Boiling Points, Solubility, and Chromatographic Behavior

The melting and boiling points and solubilities of many thiadiazoles have been summarized $\langle 84\text{CHEC-I(4)545} \rangle$ and comprehensive tables are available $\langle 52\text{HC(4)81} \rangle$. 1,3,4-Thiadiazole melts at 43 °C and the 2-methyl analog at 201 °C. Thiadiazoles substituted with a primary amine melt in the 200 °C region while the corresponding alkyl amino derivatives have usually a lower melting point. 1,3,4-Thiadiazole, the 2-amino, 2-aminomethyl, 2-aminomethyl-5-methyl, and 2,5-dimethyl derivatives are all soluble in water. Generally, as the size of the substituents on carbon increases, the aqueous solubility decreases and the solubility in organic solvents increases.

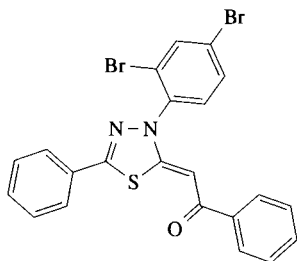
4.10.4.2 Aromaticity and Stability

Microwave spectroscopy indicates that aromaticity diminishes in the order 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole > 1,2,4-oxadiazole $\langle 84\text{CHEC-I(4)545, B-85MI 410-01} \rangle$. The aromaticity of heterocycles has been discussed by Katritzky and Barczynski $\langle 90\text{JPR885} \rangle$ and by Bird $\langle 94\text{H(37)249} \rangle$. The thermal stability of 2,5-substituted thiadiazoles (**23**) was studied by differential scanning calorimetry and shown to increase as the π -contribution of the substituents becomes greater $\langle 89\text{MI 410-01} \rangle$.

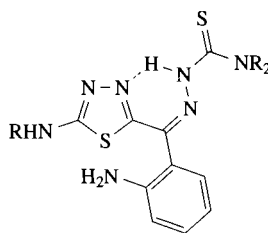
4.10.4.3 Conformation

Older literature has been reviewed $\langle 84\text{CHEC-I(4)545} \rangle$. The energy barrier to internal rotation of the dimethylamino group in 1,3,4-thiadiazoles is greater by 1.7–2.9 kJ mol⁻¹ than for the corresponding 1,3,4-oxadiazoles $\langle 77\text{SST431} \rangle$. The stereochemistry of thiadiazolines has also been extensively discussed $\langle 78\text{JCS(P1)45} \rangle$.

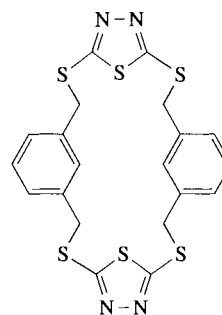
In a 1993 study, the conformation of 2-acylidene-2,3-dihydro-thiadiazoles (**24**) was studied by x-ray crystallography and NMR spectroscopy. Common features are a short S...O contact of 2.463–2.691 Å and planar thiadiazole rings with the dibromophenyl ring almost perpendicular to the heterocyclic ring. This last feature was unexpected, because as a rule, phenyl rings twist only slightly out of the plane of a second delocalized ring system. NMR Data suggest that the conformation of (**24**) in solution is the same as in the crystalline state $\langle 93\text{CJC561} \rangle$. Russian workers found the conformation of (**25**) to be stabilized by intramolecular hydrogen bonding in solution $\langle 89\text{ZOR846} \rangle$. Pappalardo and co-workers studied the conformational preferences of macrocycles containing 2,5-dithio-1,3,4-thiadiazole units of the type (**26**) utilizing NMR spectroscopy at room and elevated temperatures and concluded that the preferred conformation is “saddle” shaped $\langle 82\text{T665} \rangle$.



(24)



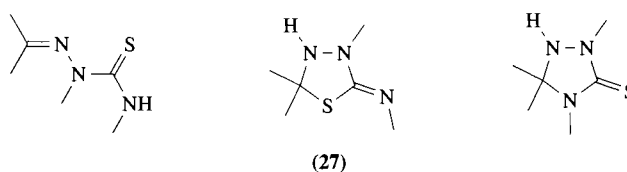
(25)



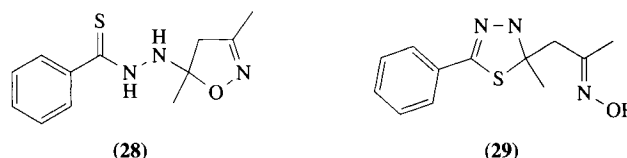
(26)

4.10.5 TAUTOMERISM

This section has been reviewed quite extensively <84CHEC-I(4)545> and only some salient points will be repeated here. Substituted thiadiazoles can exist in several tautomeric forms: 2-one and 2-thiones exist in the oxo and thione forms, respectively; amino thiadiazoles show the presence of amino and not imino groups <76AHC380>. There is an equilibrium between thiadiazoline-2-thiones and the open-chain hydrazones; it shifts towards the hydrazone salt under basic conditions <70LA(731)142>. Zelenin *et al.* have published a series of papers on ring tautomerism in thiosemicarbazones and thiadiazoles. Reaction of oxo compounds with thiosemicarbazide can lead to three compounds which may exist as single entities or as a mixture of tautomers. NMR experiments in saturated solutions of CF_3COOH have established that all three forms (27) are present in proportions dependent on the nature of the substituents <93T5327>. The most stable tautomeric form of 5-arylamino-3-*H*-thiadiazole-2-thiones was the thione and not the thiol form as determined by extensive ^{13}C studies <93JHC397>.



Proton, ^{13}C , and ^{15}N NMR spectroscopy has been employed to demonstrate the existence of ring-chain tautomerism between protonated forms of thiosemicarbazones and protonated 2-aryl-5-amino-2,3-dihydro-1,3,4-thiadiazoles <92KGS1689>. The use of NMR in various solvents, indicates that the isoxazoline (28) contains between 24% and 34% of the thiadiazoline (29) <85KGS1001>. Tautomerism was also discussed in Sections 4.10.2 <90BCJ2991> and 4.10.3.3 <83HCA1755>.



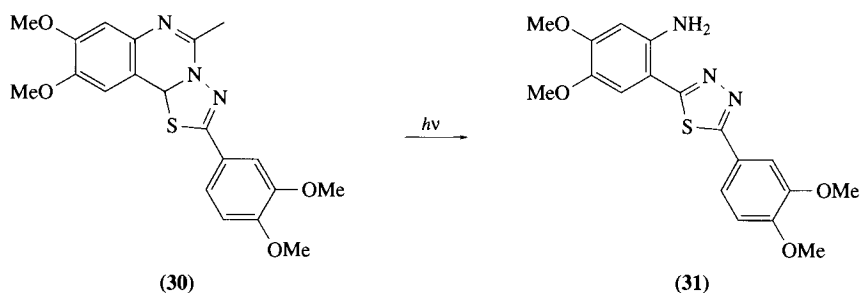
4.10.6 REACTIVITY OF FULLY CONJUGATED RINGS

1,3,4-Thiadiazoles form mesoionic compounds with electrophiles and can undergo ring opening under basic conditions. As expected, the substituents on C(2) and C(5) control the reactivity of the molecule as a whole. 2-Aminothiadiazoole has two nucleophilic centers of similar reactivity often causing difficulties in allocating the correct structure of the products. Bridging these two nitrogen atoms leads to many heterocyclic fused thiadiazoles. The reactivity of 2-thiothiadiazole is similar to benzenethiol while C(2) and C(5) methyl groups have commonality with the methyl groups of picoline. The C(2) and C(5) carbon atoms have a low electron density due to the high electronegativity of N(3) and N(4). This explains the lack of electrophilic attack on unsubstituted thiadiazoles, the ease of decarboxylation, and nucleophilic displacement of halogen atoms <84CHEC-I(4)545>.

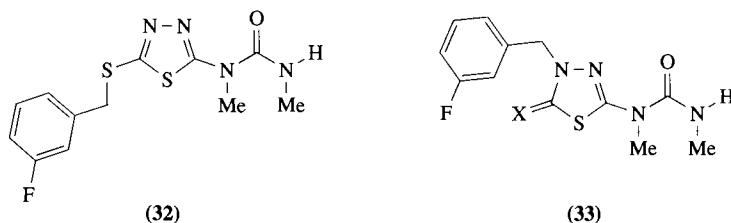
4.10.6.1 Unimolecular Thermal and Photochemical Reactions

1,3,4-Thiadiazoles often undergo photochemical fragmentation similar to the fragmentation observed in a mass spectrometer (see Section 4.10.3.4). An ethanolic solution of thia-

diazoloquinazoline (**30**) was photolyzed to yield a mixture of products from which the 2,5-diarylthiadiazole (**31**) was isolated <84JCS(P1)1143>.

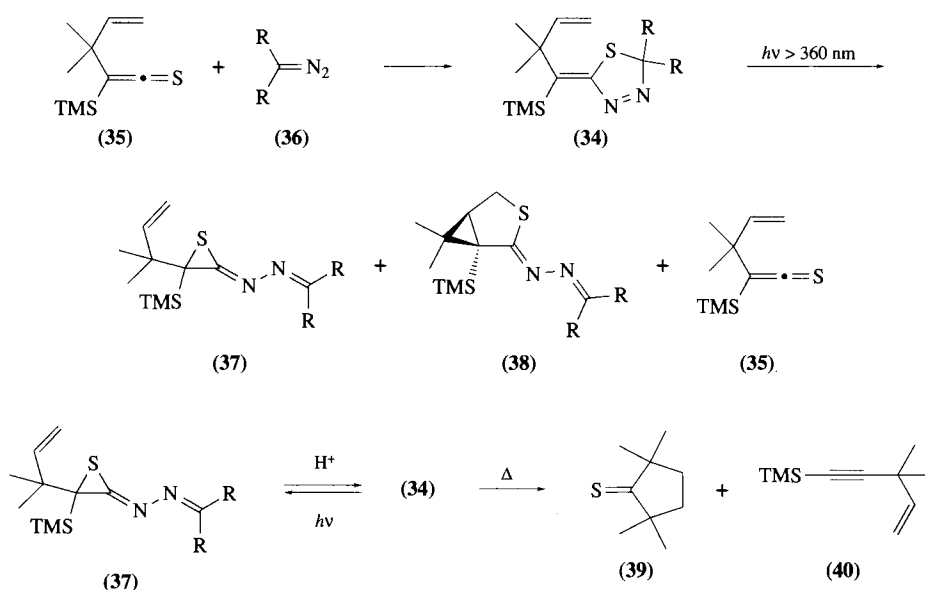


The photodegradation of the urea herbicide (**32**) in solution or as a thin film yielded via a sulfur to nitrogen migration the thione (**33**; X = S) and the corresponding oxo analog (**33**; X = O) <85JHC915>.



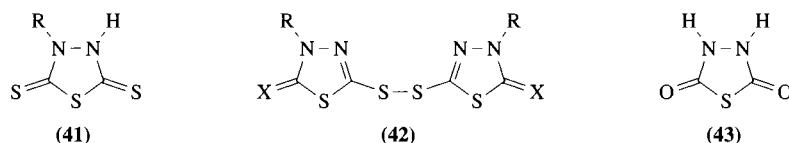
Ando and co-workers have carried out photolysis and thermolysis on 2-alkylidene-1,3,4-thiadiazolines (**34**) synthesized from the thioketene (**35**) and diazo compounds (**36**). Irradiation of a benzene solution of (**34**) (R,R = —Me₂C(CH₂)₂CMe₂—) with a medium pressure mercury lamp produced (**37**) in a 51% yield, the bicyclo derivative (**38**) in a 15% yield, and a smaller amount of (**35**). In contrast, thermolysis of (**34**) at 130°C gave the thioketone (**39**) and the ethyne (**40**) in a quantitative yield. The episulfide (**37**) was isomerized quantitatively into the thiadiazoline (**34**) when treated with a trace of acid. A number of mechanisms were suggested for these transformations <90TL3571>.

Irradiation of 1,3,4-thiadiazolidine-2,5-dithione (**41**; R = H, Me, Ph) yielded the disulfides (**42**;

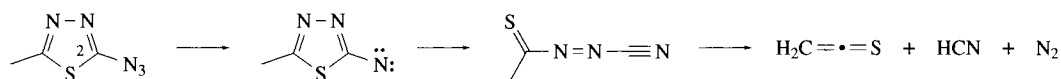


Scheme 6

X = S). Photooxygenation of (41; R = Me, Ph) yielded (42; X = S, O) while (41; R = H) gave a mixture of (42; X = S, O) and (43) <91PS(57)51>.



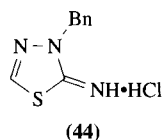
Photolysis of 1,3,4-thiadiazolidine-2,5-dione yielded diimide (HN=NH) under neutral conditions at room temperature. The diimide thus produced was used to hydrogenate double bonds with high stereospecificity <93TL4137>. Substituted thiadiazolidine-2,5-diones on photolysis yielded azo compounds which underwent Diels–Alder reactions and also acted as dinucleophiles towards alkylating agents <94JOC3564>. French workers have studied the thermolysis of 2-azido-5-methyl-1,3,4-thiadiazole at 873 °C with the aid of UV photoelectron spectroscopy (Scheme 7). Initial nitrene formation is followed by cleavage of the S—C(2) bond to yield an azothione which at elevated temperature breaks down spontaneously, with expulsion of nitrogen, to yield thioketene and hydrocyanic acid. MNDO calculations are in agreement with the products observed <88CJC2830>.



Scheme 7

4.10.6.2 Electrophilic Attack at Nitrogen

As a rule, the annular nitrogen atoms in 1,3,4-thiadiazoles are very reactive towards electrophiles as shown by facile alkylation reactions and quaternary salt formation. A thorough study on the quaternization of 2,5-disubstituted thiadiazoles, and its comparison with pyridazines has been published <84CHEC-I(4)545>. Electrophilic attack by benzyl chloride on 2-aminothiadiazole to give (44) in a regiospecific manner was utilized in the synthesis of an antiviral candidate <92MI 410-01>.



4.10.6.3 Electrophilic Attack at Carbon

As discussed in Section 4.10.6.1, due to low electron density at the carbon atoms, electrophilic reactions such as acylation, sulfonation, and nitration do not occur readily. In the presence of an amino group at C(2), the 5-bromo derivative can be prepared <84CHEC-I(4)545>.

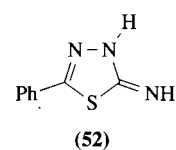
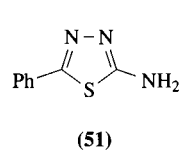
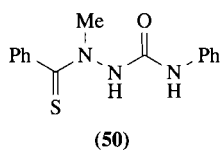
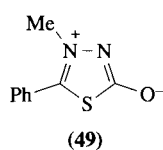
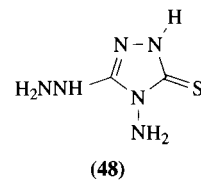
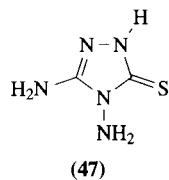
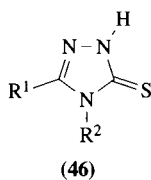
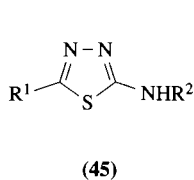
4.10.6.4 Electrophilic Attack on Sulfur

The direct oxidation of thiadiazoles to form sulfoxides or sulfones has not been reported.

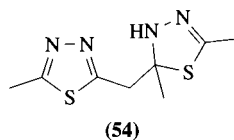
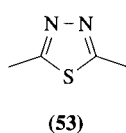
4.10.6.5 Nucleophilic Attack on Carbon

Unsubstituted thiadiazole is unstable under basic conditions, and will decompose. 2-Aminothiadiazole derivatives (45) react with amines to yield triazolinethiones (46). 2-Amino-5-halo-thiadiazole reacts with hydrazine to give a mixture of (47) and (48). 2,5-Dihalo and 2,5-dithiothiadiazoles yield only (48) under the same conditions. Even a weaker nucleophile such as aniline

will cause ring fission at C(2) of the mesoionic thiadiazole (49) to give the open-chain compound (50). Treatment of 5-phenylthiadiazole with hydroxylamine leads to the direct introduction of an amino group to give the aminothiadiazole (51), most likely via the imine (52) <84CHEC-I(4)545>.

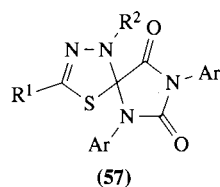
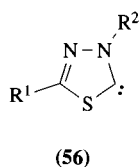
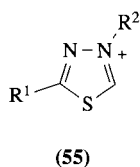


The 2-alkyl anion derived from 2,5-dimethylthiadiazole (53) and sodium hydride adds to the annular carbon of (53) to give (54) <89CZ217>. Examples of nucleophilic displacement of leaving groups from the 2- and 5-positions of thiadiazoles are discussed in Section 4.10.8.



4.10.6.6 Nucleophilic Attack at Hydrogen Attached to Carbon

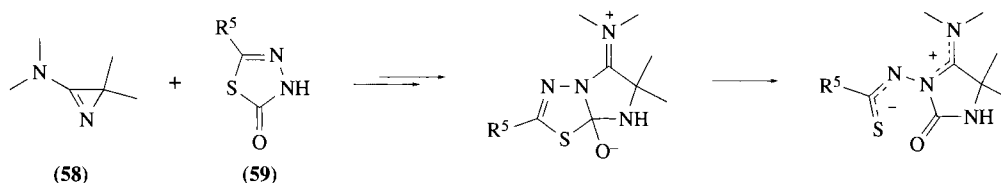
In the presence of strong base, thiadiazole undergoes rapid exchange with deuterium in the 2 position. Thiadiazolium salts are deprotonated 10000 times faster than thiazolium salts <B-85MI 410-03>. Haug *et al.* allowed various alkylating reagents to react with unsubstituted and 5-substituted thiadiazoles to yield 3-alkyl-1,3,4-thiadiazolium salts (55); these were deprotonated to produce a carbene (56) which was trapped with aromatic isocyanates to yield spirocyclic compounds (57) <88LA605>.



4.10.6.7 Reaction with Radicals and Cyclic Transition States

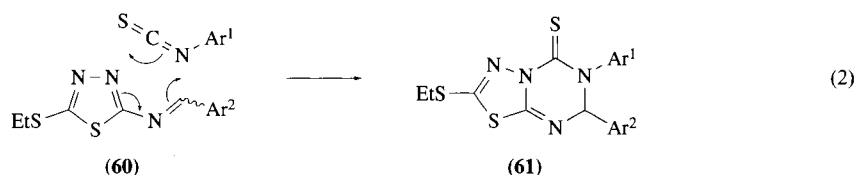
The reaction of 2-amino-2H-azirines (58) with 5-substituted 1,3,4-thiadiazol-2(3H)-ones (59) yields dipolar 1:1 adducts as shown in Scheme 8. The reactions were carried out at room temperature in 2-propanol and the percentage yields (in parentheses) were somewhat dependent on the nature of the substituent at C(5) as follows: CF₃ (76), CN (83), MeSO₂ (95), CCl₃ (54), MeO (84) and CF₃

(54). These dipolar adducts are donor–acceptor stabilized azomethine imines and their structure was ascertained by x-ray crystallography <90HCA492>.



Scheme 8

Indian workers described the synthesis of 1,3,4-thiadiazolo[3,2-*a*]-*s*-triazine-5(*H*)-thiones (**61**) by a hetero Diels–Alder reaction between 2-(arylideneamino)-5-ethylthio-1,3,4-thiadiazoles (**60**) and aromatic isothiocyanates (Equation (2)) <94MI 410-01>. Thiadiazoles can be reduced with sodium amalgam to the aldehyde thiosemicarbazone while lithium aluminum hydride will reduce mesoionic thiadiazoles all the way to the hydrazine <84CHEC-I(4)545>.



L'abbé *et al.* studied the ring chain equilibria of diazomethyl and diazoester substituted thiadiazole derivatives (**62a**) and (**62b**) with the aid of NMR spectroscopy. The former was shown to be in the triazole form (**63a**), although at 75°C in C₆D₆ the proportion of (**62a**) increased to about 12%. In contrast, 70% of the diazoester was present in the thiadiazole form (**62b**), but in more polar solvents such as acetonitrile and dimethyl sulfoxide (**62b**) decreased to about 45%. The following conclusions were drawn concerning the equilibrium of various azoles: (a) the preference of azoles carrying a diazo moiety to exist in the triazole form declines in the order: thiazole > 1,3,4-thiadiazole > 1,2,4-thiadiazole and diazomethyl > diazoester; (b) substituents which are electron donors and benzo fusion favor the triazole form; (c) the percentage of the diazo form is higher in less polar solvents and at higher temperature <92JHC713>.

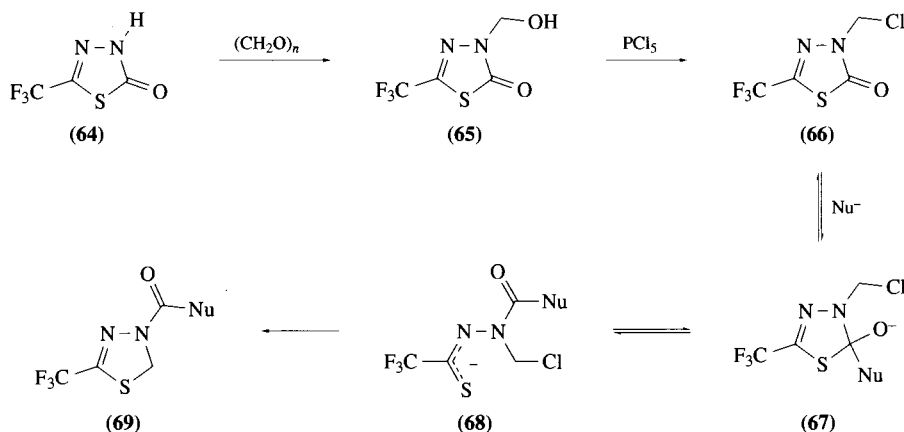


4.10.7 REACTIVITY OF NONCONJUGATED RINGS

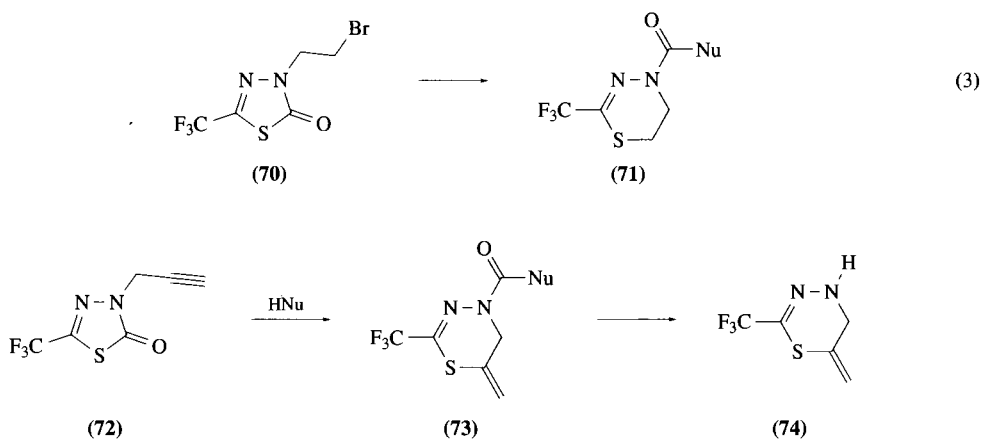
4.10.7.1 Thiadiazolines

Dihydrothiadiazoles undergo many interesting reactions which are illustrated in a Swiss publication (Scheme 9) <83HCA2714>. Treatment of the 5-trifluoromethylthiadiazol-2-one (**64**) with formaldehyde gave the methanol derivative (**65**) in high yield, and this was chlorinated with PCl₅ to (**66**). Treatment of this with various nucleophiles in ethanol caused a rearrangement to provide in high yield 3-acylated 2,3-dihydro thiadiazoles (**69**). The probable mechanism is fission of the C—S bond in (**67**) followed by reclosure on the CH₂ group and elimination of chloride ion (**68**). By replacing the chloromethyl group on N(3) with bromoalkyl groups of various lengths, ring enlargement took place. Thus treatment of the 2-bromoethyl derivative (**70**) with various nucleophiles such as pyrrolidine or dimethylamine gave in yields of over 80% the dihydro-1,3,4-thiadiazines (**71**) (Equation (3)). When the bromoalkyl chain was homologated to propyl, treatment with the same nucleophiles gave a mixture consisting of the tetrahydrothiadiazepines and the thiadiazolone, in

which the bromine atom was replaced by the incoming nucleophile. Introduction of a propargyl chain at N(3) (**72**) and treatment with nucleophiles followed by acidification, afforded the 1,3,4-thiadiazine (**73**) (Scheme 10). With aqueous NaOH, a carbamic acid was formed (**73**; Nu = OH), which decarboxylated to give (**74**) <83HCA2714>.



Scheme 9



Scheme 10

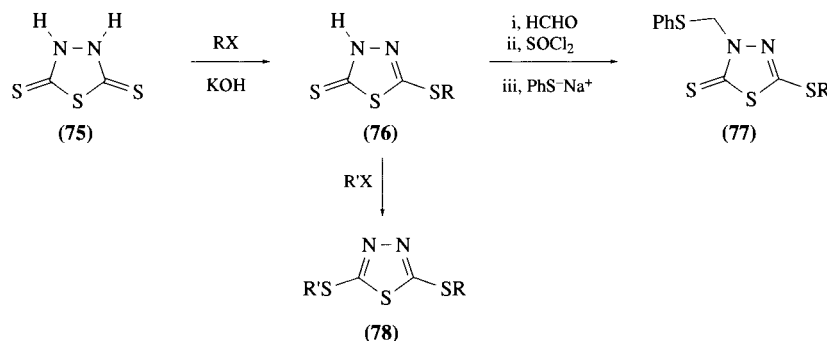
The problem associated with defining correct structures in the field of thiadiazolines is illustrated in the product obtained from the methylation of 2-phenylamino-1,3,4-thiadiazole. At least four structures have been published, the one most likely to be correct is 4-methyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline <87JHC521>.

Thermal decomposition of thiadiazolines is discussed in Section 4.10.10.2.2.

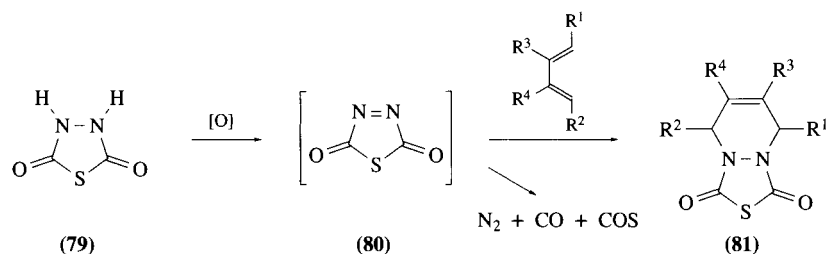
4.10.7.2 Thiadiazolidines

3*H*,4*H*-1,3,4-Thiadiazolidine-2,5-dithione (**75**) (Scheme 11) was monoalkylated in the presence of ethanolic potassium hydroxide to provide (**76**). Treatment with formaldehyde provided the hydroxymethyl derivative which was chlorinated with thionyl chloride and then reacted with sodium thiophenylate to yield the *S,N*-disubstituted thiadiazole dithione (**77**). Further alkylation of (**76**) gave the *S,S*-disubstituted analogs of 1,3,4-thiadiazole dithiones (**78**) <90JHC139>. Many other derivatives of (**78**) prepared in a similar way have been reported <91JHC1139>. The 1,3,4-thia-

diazolidine-2,5-dione (**79**) on oxidation yielded the thiadiazoline (**80**) which was trapped with reactive dienes to give Diels–Alder adducts of the type (**81**) (Scheme 12). The thiadiazoline (**80**) was unstable and in the absence of a diene yielded N_2 , CO and carbon oxysulfide $\langle 74JOC2951 \rangle$.



Scheme 11



Scheme 12

4.10.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO A RING CARBON

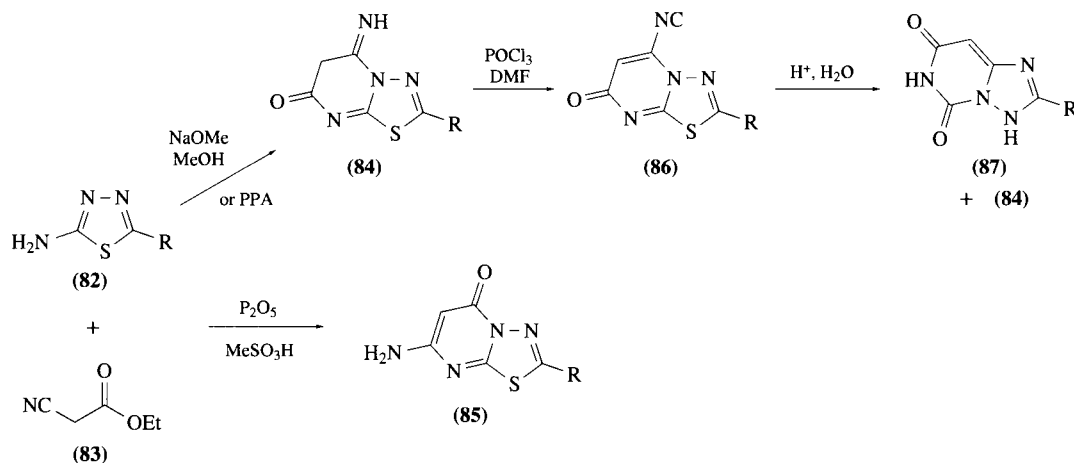
As mentioned in Section 4.10.6.5, substituents on C(2) and C(5) are strongly activated and control the reactivity of the thiadiazole molecule as a whole. The amino group is by far the most popular substituent for further modifications, due to its nucleophilicity and ease of ring formation with the annular N(3). To a somewhat lesser extent, the thiol group has also been utilized in further derivatizing, with the carbon and halogen substituents being the least amenable to further reactions.

4.10.8.1 Nitrogen

This section has been thoroughly reviewed and only a bare outline of the work published before 1982 will be presented. Amino thiadiazoles react with nitrous acid to yield *N*-nitroso compounds, and with acid chlorides and esters to give acyl derivatives, although not always regioselectively. Methylation and base treatment gives thiadiazolines with the methyl group on the annular nitrogen. 2-Aminothiadiazoles react with keto esters and malonates to yield pyrimidinothiadiazoles; depending on the nature of the reagent, some rearrangement may occur. Haloaldehydes and halo ketones also react with aminothiadiazoles in a bidentate fashion to give imidazothiadiazoles, while 2,5-diaminothiadiazoles and β -keto esters yield pyrimidinothiadiazoles with an amine on the thiadiazole ring. 5-Substituted thiadiazoles carrying a hydrazine moiety in the 2-position react with α -keto acids in a two-step reaction producing thiadiazolotriazines; with α -cyanoacetophenone, pyrazolylthiadiazoles are formed $\langle 84CHEC-I(4)545 \rangle$.

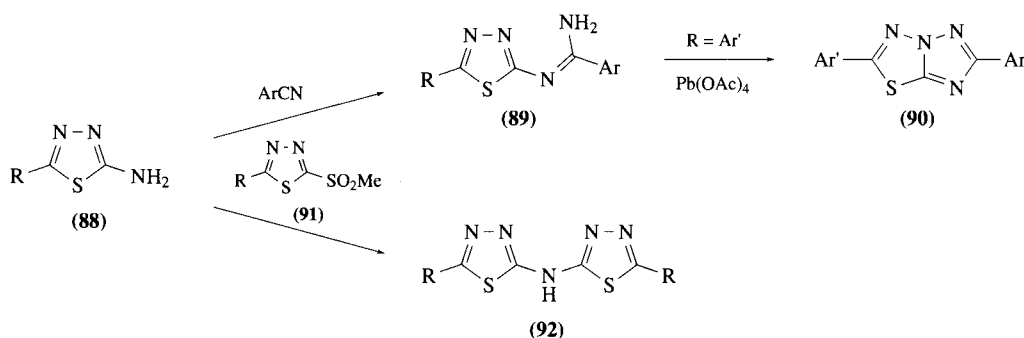
Tsuji obtained two isomeric 1,3,4-thiadiazolo[3,2-*a*]pyrimidino compounds by changing the pH (Scheme 13) $\langle 91JHC489 \rangle$. Thus treatment of 2-amino-5-substituted-thiadiazoles (**82**) with ethyl cyanoacetate (**83**) in the presence of sodium methoxide gave the 2-substituted 5-imino-6*H*-[1,3,4]-thiadiazolo[3,2-*a*]pyrimidine-7-one (**84**). When the same reaction was carried out in the presence of P_2O_5 and CH_3SO_3H instead of sodium methoxide, 7-amino[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-5-one

(85) was obtained. Reaction of (84) with DMF/POCl₃ yielded the 5-isocyanide derivative (86) which on HCl hydrolysis gave a mixture of (87) and (84), providing further support for the structural assignment of the two isomers (84) and (85) <91JHC489>.



Scheme 13

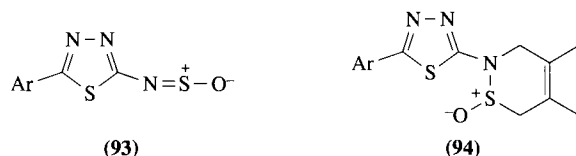
Reaction of the 5-substituted aminothiadiazoles (88; R = Bu^t) with aryl nitriles produced amidines (89) in yields dependent on the reactivity of the nitriles (Scheme 14). Decreasing the electron density of the cyano group by such electron-withdrawing groups as *p*-nitrophenyl-, and 2- and 4-cyanopyridyl, led to higher yields as compared to unsubstituted benzonitrile. A bis thiadiazole (92; R = Bu^t) was prepared by reacting the sodium salt of (88) with 2-methanesulfonyl-5-*t*-butyl-1,3,4-thiadiazole (91) <84JHC1377>.



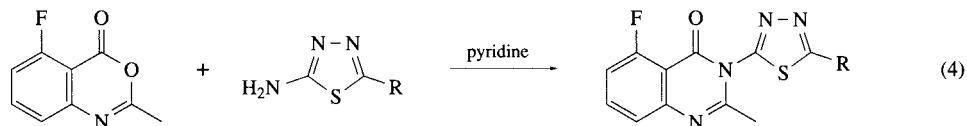
Scheme 14

Reaction of 2-amino-5-aryl-1,3,4-thiadiazole (88; R = Ar) with aryl nitriles in the presence of aluminum chloride produced the aryl amidine (89) which was oxidized with lead tetraacetate to yield the 2,6-diaryl-[1,2,4]-triazolo[5,1-*b*]-1,3,4-thiadiazoles (90) <91JJC(B)435>.

2-Amino-5-aryl-1,3,4-thiadiazole was treated with thionyl chloride in dry benzene to yield the N-sulfinylamine (93) an unstable compound, characterized by NMR and further derivatization. The sulfinylamine moiety caused an upfield shift on C(2) (4–6 ppm) comparable to a carbonyl or sulfonyl group, indicating the double-bond character of the N—S bond. Reaction of (93) with 2,3-dimethylbuta-1,3-diene yielded (94) via thermal cycloaddition <89JCS(P2)1855>.

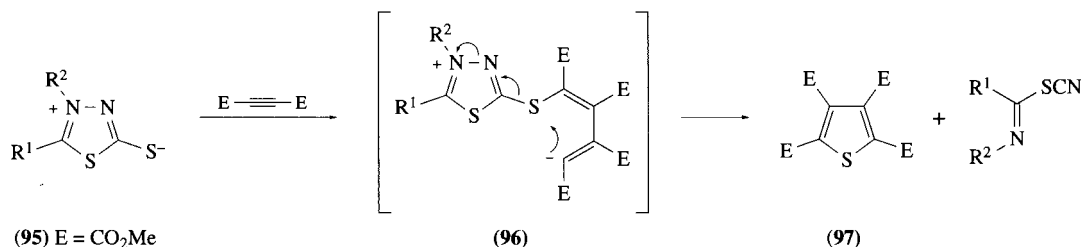


2-Aminothiadiazoled (**88**; $R = CF_3$) condenses with 5-fluoro-2-methylbenzoxazin-4-one in refluxing pyridine to give 5-fluoro-2-methyl-3-(2-trifluoromethyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone in about 60% yield (Equation (4)) <92JHC749>.



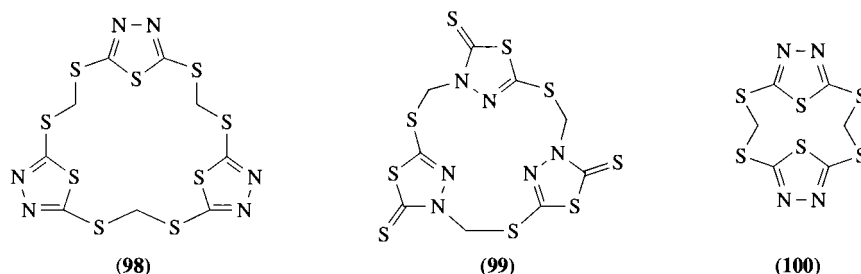
4.10.8.2 Sulfur

Thiadiazoles having one or two thio groups in the 2- and/or 5-positions react with metals to form bidentate ligands; they are widely used as antioxidants. An interesting reaction of mesoionic (**95**) with acetylene dicarboxylate is the formation of thiophene (**97**) via the intermediate (**96**) (Scheme 15) <84CHEC-1(4)545>.

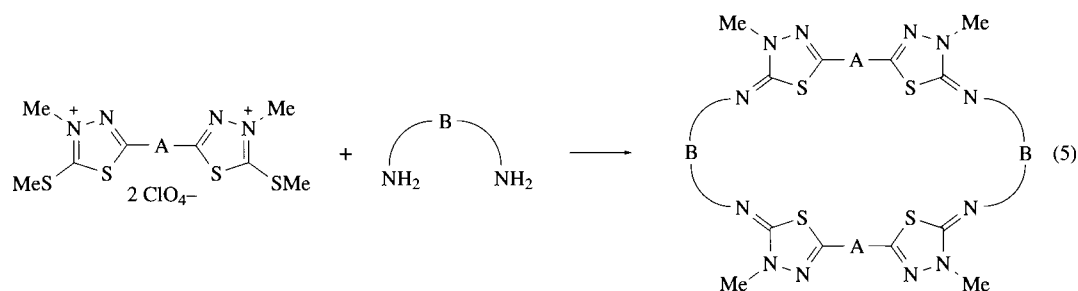


Scheme 15

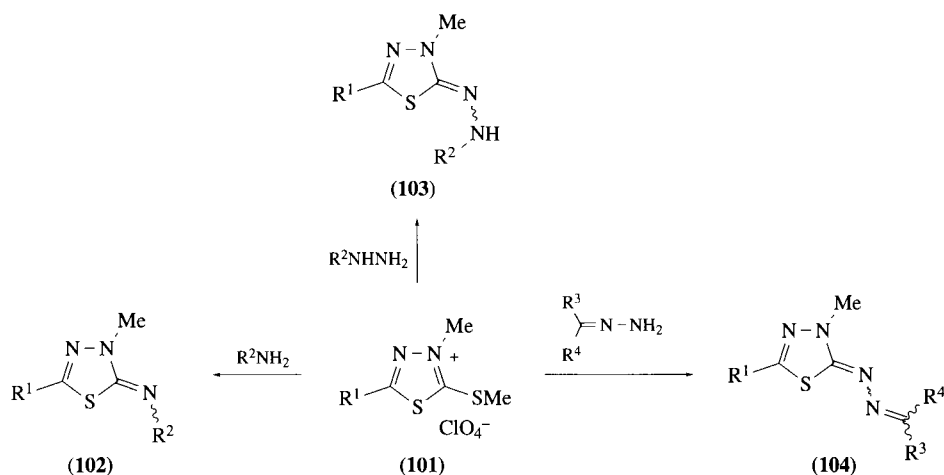
1,3,4-Thiadiazoles have also been utilized in the construction of macrocycles. Although (**9**) exists mainly in the 2-thiol-5-thione form (**9b**) it (and its *S*-alkyl derivative) undergoes regioselective *S*-alkylation under basic conditions. Thus treatment of (**9**) with 1 equivalent CH_2Br_2 and NEt_3 in a very dilute ethanolic solution gave a low (6%) yield of the macrocycle (**98**). However, replacement of NEt_3 with 1 equivalent KOH gave (**99**), also in a low (15%) yield. Treatment of (**9**) with CH_2Br_2 and 2 equivalents KOH led to (**100**), a compound also prepared by treatment of (**9**) with 2,5-bis chloromethylthio thiadiazole in the presence of 2 equivalents KOH . Utilizing this procedure, several other macrocycles were prepared and their structure ascertained by ^{13}C NMR, a method which distinguishes between substitution on sulfur and/or nitrogen. In some cases, due to lack of solubility in solvents suitable for NMR, structure proof was obtained by a stepwise synthesis <87JOC405>.



Molina *et al.* prepared macrocycles containing two, four, or six 1,3,4-thiadiazole moieties by reacting bis[4-methyl-5(methylthio)-1,3,4-thiadiazolium] diperchlorates with diamines. They used multiple reaction conditions, varied the size of the spacer (A) between the thiadiazole units, and increased the chain length (B) of the diamine units. Equation (5) depicts a macrocycle accommodating four thiadiazole moieties; other macrocycles containing two or six thiadiazole units were also synthesized <94JOC3665>.

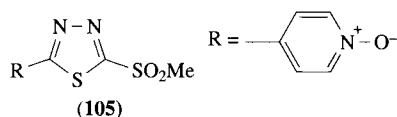


The good leaving properties of the thiomethyl group can be utilized for the introduction of various nitrogen functionalities into the 5-position (Scheme 16). Thus, treatment of 2-methylthiothiadiazolium cation (**101**) with various amines led to the imines (**102**) while hydrazines and hydrazones yielded (**103**) and (**104**), respectively. Reaction with unsubstituted hydrazine, 1,2-diaminoethane or phenylene diamine gave molecules containing two thiadiazole rings <89H(29)2301>.



Scheme 16

Japanese workers have also displaced a methyl sulfone group with a variety of nucleophiles. Thus they were able to introduce, ethoxy, thiophenyl, aniline, and malonic acid groups into the pyridine *N*-oxide derivative (**105**). Acid hydrolysis produced the 2-one compound, while reduction with sodium borohydride cleaved off the methylsulfone group <87CPB1030>.

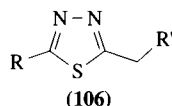


Also taking advantage of the good leaving properties of the $-\text{SMe}$ group, French workers were able to introduce two allylic groups by reacting 2,5-dithiomethyl thiadiazole with allylic Grignard reagents. Introduction of only one allylic group was achieved by carrying out the reaction with the 5-thiomethyl-2-thione analog <94JOM(464)1>.

4.10.8.3 Carbon

In 1974, 2-methyl-5-phenylthiadiazole (**106**; $\text{R} = \text{Ph}$; $\text{R}' = \text{H}$) was converted into the 2-ethyl analog (**106**; $\text{R} = \text{Ph}$; $\text{R}' = \text{CH}_3$) by treatment with butyl lithium followed by methyl iodide <74JOC1189>. Almost 20 years later, the same reaction was applied to 2-methyl-5-thiothiadiazole (**106**; $\text{R} = \text{SH}$; $\text{R}' = \text{H}$). Treatment with butyllithium gave the dianion, which on reaction with

alkyl bromides or iodides yielded regioselectively the 2-homologated thiadiazoles (**106**; $R = SH$; $R' = \text{alkyl}$) <93SL533>. The anion from 2,5-dimethylthiadiazole underwent acylation with esters and also nucleophilic attack on the annular carbon atom of a thiadiazole ring <89CZ217>.

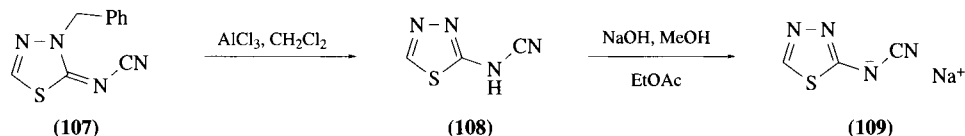


4.10.8.4 Halogen

2-Chloro-5-aryl-substituted thiadiazoles react with amines and hydrazines with expulsion of the chlorine atom. Reaction of the 2-bromo analog with diethyl malonate in the presence of sodium ethoxide gives the 2-malonate ester derivative which on hydrolysis is decarboxylated to the 2-acetic acid derivative of thiadiazole <83JHC73>. Piperidine was used as a substrate to study the nucleophilic reactivity of 2-aryl-5-halothiadiazoles. The nature of the group on the aryl ring affected the rate of nucleophilic exchange with a Hammett ρ value of 1.47 at 50°C in ethanol. The reactivity order in ethanol is $OMe < H < Cl \ll NO_2$ and is also solvent dependent <68T3209>.

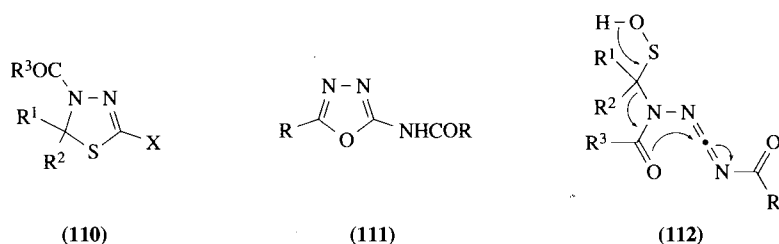
4.10.9 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Very few publications are available on the reactivity of substituents attached to the ring nitrogen and sulfur atoms of thiadiazole. The N-benzyl group in (**107**) can be removed with $AlCl_3$ to give the cyanamide (**108**) and the antiviral compound (**109**) on further treatment with base <92MI 410-01>.



Scheme 17

The sulfur in dihydrothiadiazoles of the type (**110**) can be oxidized to an *S*-oxide with MCPBA and hydrolysis of such sulfoxides (when $R^2 = H$, $X = SO_2Me$, $NHCOR$, CH_2CO_2Et) leads to removal of the acyl group (COR^3) and the oxygen on sulfur to give the corresponding thiadiazole <86H(24)21, 91CPB2837>. Interestingly, on heating in DMSO (100°C/3 h) the *S*-oxide from (**110**; $R^1 = Ph$, $R^2 = H$, $X = NHCOR$) gives a mixture containing oxadiazole (**111**) (74%), benzaldehyde, *trans*-stilbene and sulfur, probably via the ring-opened intermediate (**112**) <86H(24)21>.



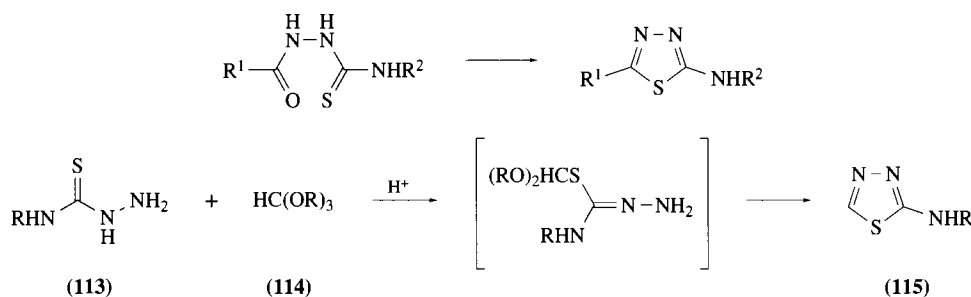
4.10.10 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

Since the 1,3,4-thiadiazoles are compounds of great pharmaceutical and industrial importance, it is not surprising that synthetic publications far outweigh in numbers those relating to all other fields. This section will be discussed in terms of the number of bonds being formed to construct the thiadiazole nucleus. Section 4.10.10.1 will deal with one-bond formation, while two-bond formation

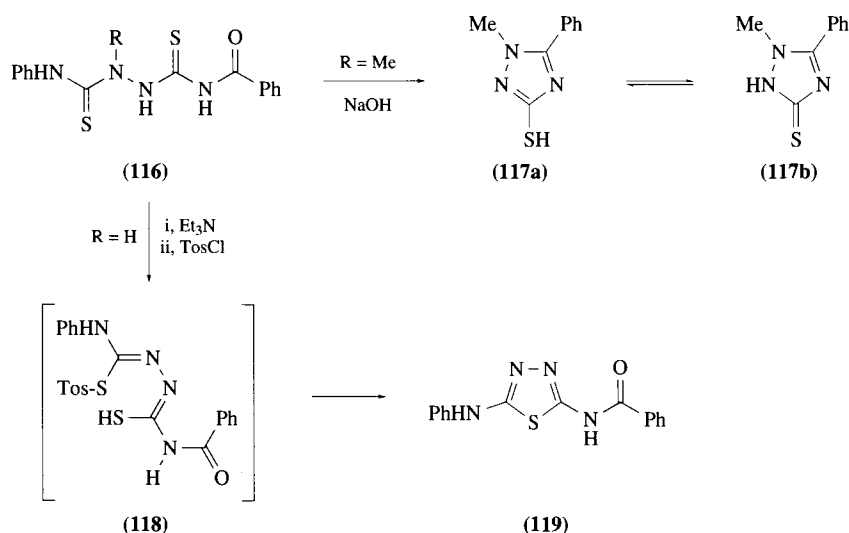
will be presented in Section 4.10.10.2, and will be further subdivided into bond formation by cyclization, dipolar addition, and the synthesis of thiadiazolines and mesoionic compounds. Section 4.10.10.3 will deal with ring formation by three bonds; the synthesis of thiadiazoles by transformation of other ring systems are discussed in Section 4.10.11.

4.10.10.1 Formation of One Bond

A very large number of 2-amino-1,3,4-thiadiazoles have been prepared in high yield by acylation of thiosemicarbazides followed by dehydration with sulfuric, polyphosphoric, or methanesulfonic acids (Scheme 18). 5-Alkyl-2-methylaminothiadiazoles have been prepared by reaction of a carboxylic acid and 4-methylthiosemicarbazide in the presence of a mixture of polyphosphoric and sulfuric acids. The reaction of 4-alkylthiosemicarbazides (**113**) with orthoformate esters (**114**) provides an entry into alkylaminothiadiazoles carrying no substituent in the 5-position (**115**) <84CHEC-I(4)545>. A synthetic procedure which furnishes both 1,3,4-thiadiazoles and 1,2,4-triazoles depending on the conditions used, starts with acylthioureas (**116**) (Scheme 19). Okawara *et al.* treated (**116**; R = Me) in a 5% NaOH-CH₂Cl₂ solution with the phase-transfer catalyst benzyltriethylammonium chloride and were able to isolate the triazole (**117**) which exists as a mixture of tautomers. Reacting compound (**116**; R = H) with *p*-TosCl in the presence of NEt₃ provided a 90% yield of the benzoylated thiadiazole (**119**), presumably via the intermediate (**118**) <88JHC1071>.



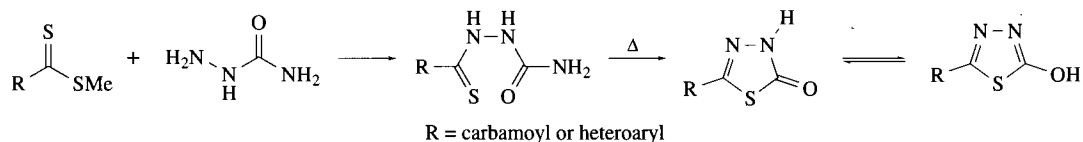
Scheme 18



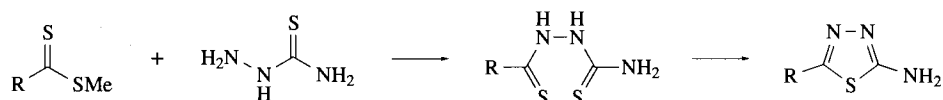
Scheme 19

The synthesis of numerous thiadiazoles substituted in the 5-position with carbamoyl or heteroaryl moieties and hydroxyl or amino groups in the 2-position (Scheme 20), was achieved by reacting dithioesters with semicarbazide or thiosemicarbazide and cyclizing the resulting acylated sem-

icarbazide under the usual conditions (Scheme 21). Examples of heteroaryl groups substituted at the C(5) position of 1,3,4-thiadiazoles are benzoxazoles, benzimidazoles, benzthiazoles and imidazoles <90JPR55>.



Scheme 20



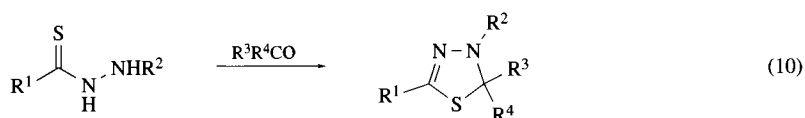
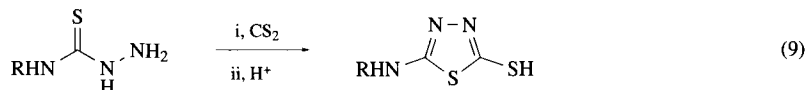
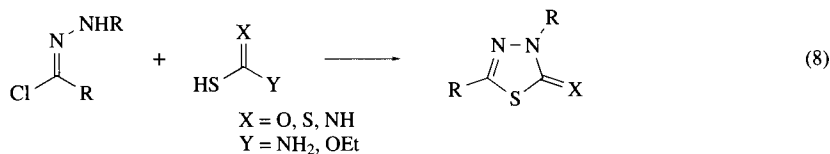
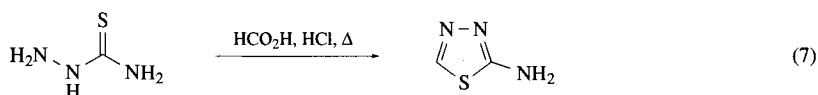
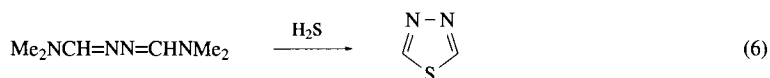
Scheme 21

4.10.10.2 Formation of Two Bonds

A very large number of thiadiazole derivatives have been synthesized by this procedure and therefore the section is further subdivided.

4.10.10.2.1 Cyclizations

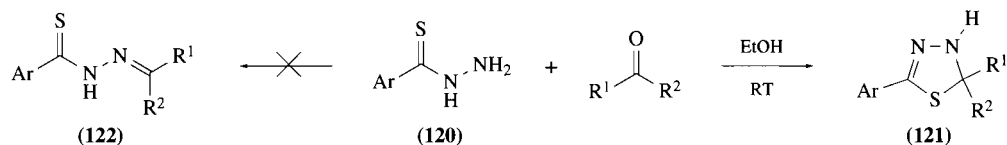
The more important methods from <84CHEC-I(4)545> are summarized in Equations (6) to (10).



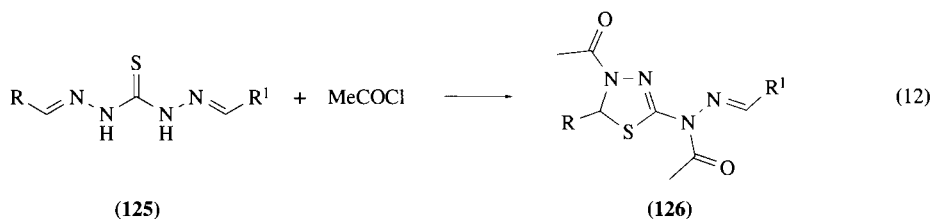
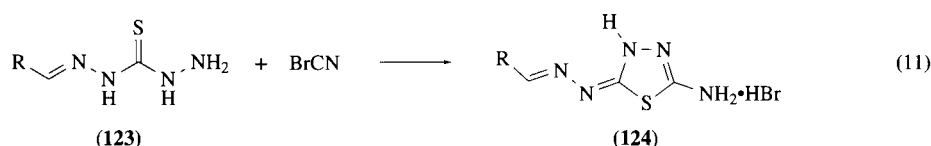
A newer and general procedure for synthesizing 2,5- and 2,2,5-substituted 2,3-dihydrothiadiazoles (**121**) involves the reaction of a ketone or aldehyde with thioaroylhydrazines (**120**) (Scheme 22). With benzaldehyde, the reaction proceeds simply on mixing the aldehyde with (**120**) in ethanol at room temperature; after 15 minutes, a single product was isolated in 88% yield. Previous workers have assigned the acyclic structure (**122**) to these compounds, but based on NMR measurements, it

seems unlikely. The reaction appears to work equally well with ketones such as cyclohexanone, acetone, acetophenone, and 1-methyl-4-piperidone <86JCS(P1)1499>.

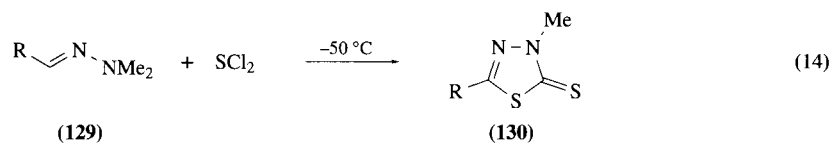
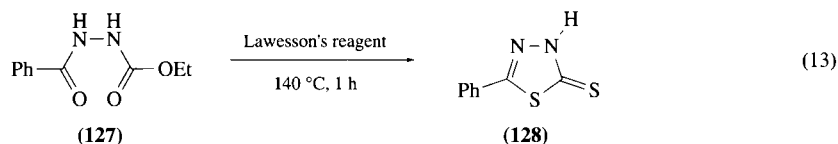
Japanese workers prepared 2-amino-5-substituted thiadiazolines (**124**) by reacting alkylidene-thiocarbohydrazides (**123**) with cyanogen bromide at room temperature for 24 hours (Equation (11)). Similarly, treatment of thiocarbohydrazones (**125**) with acetyl chloride (Equation (12)) yielded the 3-acetyl-4,5-dihydrothiadiazole (**126**) <90H(31)1129>.



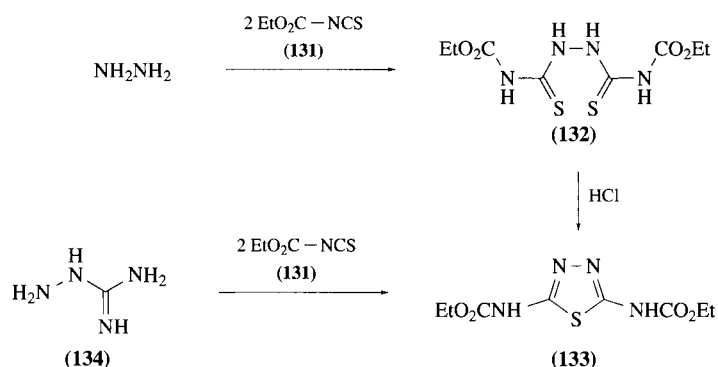
Scheme 22



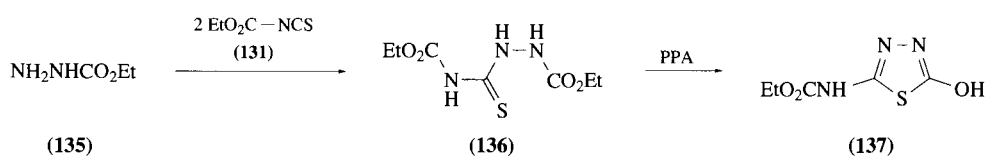
Lawesson and co-workers heated under reflux *N*-benzoyl-*N'*-ethoxycarbonyl hydrazine (**127**) in xylene for 1 h with his own reagent to prepare in a 78% yield the thiadiazolothione (**128**) <83CL809>. The reaction of *N,N*-dimethylhydrazones (**129**) with sulfur dichloride (Equation (14)) also produced thiones of the type (**130**) <85ZC323>. Kurzer and Secker utilized the bifunctional character of ethoxycarbonyl isothiocyanate (**131**) to prepare a variety of thiadiazoles (Scheme 23). The reaction of hydrazine with 2 moles of (**131**) produced the 1,6-bis(ethoxycarbonyl)bithiourea (**132**) in high yield, which on treatment with ethanolic HCl gave an almost quantitative yield of the 2,5-bis(ethoxycarbonyl)-1,3,4-thiadiazole (**133**). The same compound (**133**) was obtained from the reaction of (**131**) with (**134**), although in a lower yield. The reaction of ethoxycarbonylhydrazine (**135**) with (**131**) produced the dicarboethoxy derivative (**136**) (Scheme 24) which required the use of polyphosphoric acid (PPA) for cyclization to the 2-hydroxythiadiazole (**137**). Treatment of (**132**) or (**136**) with base yielded triazoles <89JHC355>.



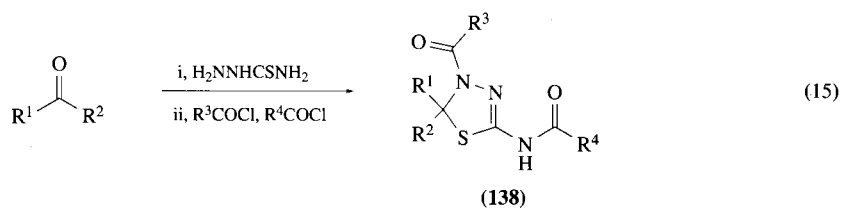
German workers have prepared a very large number of 4-acyl-2-acylamino-4,5-dihydro-1,3,4-thiadiazoles (**138**) by the condensation of substituted thiosemicarbazones with acid chlorides (Equation (15)) <86JPR205>.



Scheme 23



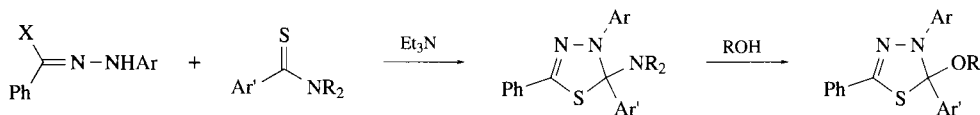
Scheme 24



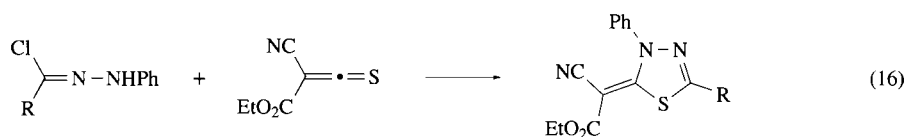
The synthesis of 2-alkylidene-1,3,4-thiadiazolines from thioketene and diazo compounds was discussed in the photochemical Section 4.10.6.1 <90TL3571>.

4.10.10.2.2 Dipolar cycloaddition

This method was extensively reviewed in <84CHEC-I(4)545> and a brief summary is presented here; interestingly, since the mid-1980s, this reaction has become less popular. *N*-Aryl benzhydrazone chlorides react with thiobenzamides to form trisubstituted thiadiazolines which on treatment with alcohols furnish the 2-alkoxy derivative (Scheme 25). *N*-Arylbenzhydrazone chlorides also react with thioketenes to yield 5-methylene thiadiazolines (Equation (16)). Other examples involve the addition of the nitrileimine generated from *N*-trifluoroacetobenzhydrazone bromide to the C=S of potassium isothiocyanate and methyl isocyanate <87JHC1391>.



Scheme 25

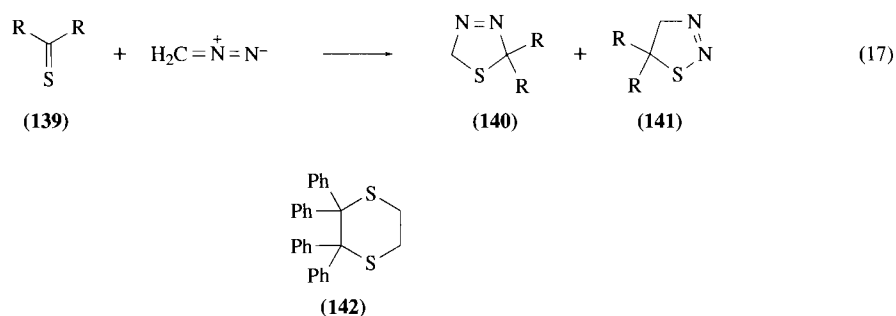


(16)

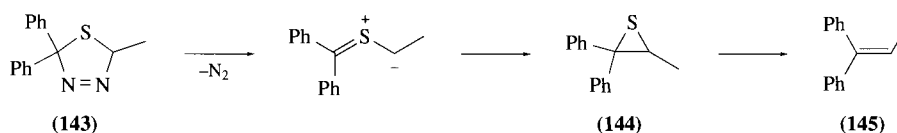
A second well-known dipolar cycloaddition reaction which is useful for the synthesis of thiadiazoles utilizes diazomethane and its derivatives.

Reactions of aliphatic thiones (**139**) with diazomethane yields a mixture of isomers via a 1,3-dipolar cycloaddition reaction. Larger R groups lead to the formation of 1,3,4-thiadiazolines (**140**), while an increase in solvent polarity yields more of the 1,2,3-thiadiazolines (**141**). *Ab initio* calculations relating to the reaction of thioformaldehyde with diazomethane favor the formation of both isomers via a concerted reaction. The AM1 and MNDO-PM3 however, indicate the formation of (**140**) by a concerted reaction, while a two step reaction is more favorable for the formation of (**141**). The formation of (**141**) in more polar solvents is probably due to the higher dipole moment of the transition state. It is concluded that *ab initio* calculations are closer to experimental findings, than the AM1 or MNDO-PM3 results <89TL7045, 93JOC82>.

Diazomethane also reacts with thiobenzophenone to form the thiadiazoline (**140**; R = Ph) (Equation (17)) which decomposes at -30°C to yield the dithiane (**142**) <84CHEC-I(4)545>.

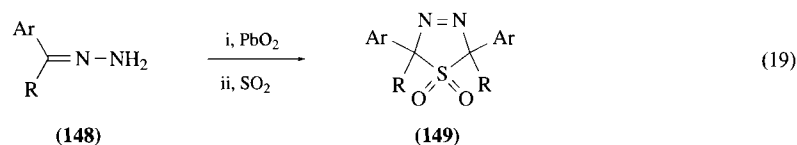
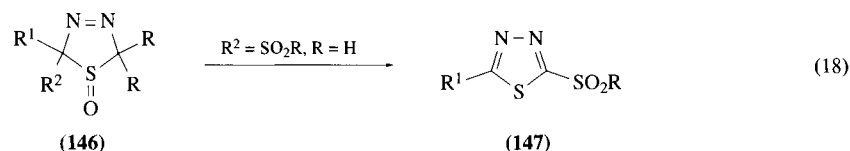


Treatment of thiobenzophenone with 1 equivalent of diazoethane in CH_2Cl_2 at -78°C produced 5-methyl-2,2-diphenylthiadiazoline (**143**) which actually crystallized from a concentrated solution; however, when the crystals were warmed to room temperature, they exploded. In a THF solution at -45°C (**143**) decomposed with nitrogen evolution following first-order kinetics with a half-life of 18 minutes. The product was 2-methyl-1,1-diphenylthirane (**144**) which slowly lost sulfur to yield 1,1-diphenylpropene (**145**) <83H(20)2363>.



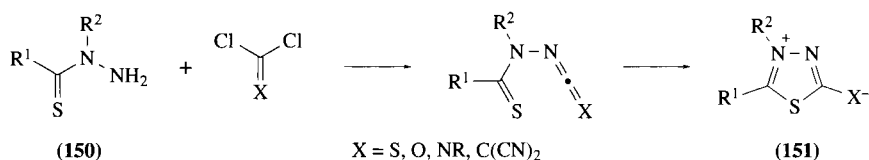
Scheme 26

Δ^3 -1,3,4-Thiadiazoline-1-oxides (**146**) (Equation (18)) are formed by addition of diazo compounds ($\text{R}_2\text{C}=\text{N}_2$) to sulfoxes ($\text{R}^1\text{R}^2\text{C}=\text{S}=\text{O}$). The adducts from diazomethane and aryl substituted sulfoxes are unstable and give the thiadiazole (**147**) via a Pummerer-type aromatization <84CHEC-I(4)545>. The Δ^3 -thiadiazoline-1,1-dioxide (**149**) has been produced by oxidation of the hydrazone (**148**) (Equation (19)) and treatment with sulfur dioxide <84CHEC-I(4)545>. 2-Alkylidenethiadiazolines can be obtained from the dipolar addition of diazo compounds to thioketenes <83CB66, 90TL3571, 92HCA1825>.

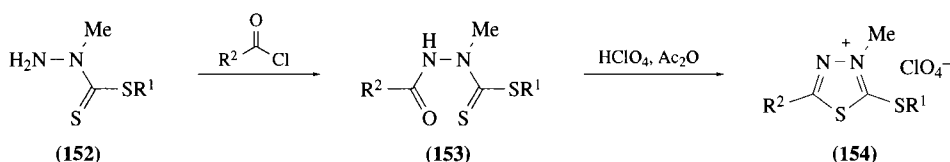


4.10.10.2.3 Mesoionic compounds

Some general methods of synthesis are shown in Schemes 27 and 28. Thioacylhydrazines (**150**) react with thiophosgene and related derivatives and with 3,3-dichloromethylenemalononitrile to give the 2,5-substituted mesoionic derivatives (**151**) (Scheme 27). Alkyl-2-methyldithiocarbazates (**152**) and acyl chlorides (Scheme 28) gave high yields of alkyl 3-acyl-2-methyldithiocarbazate (**153**) which on treatment with a mixture of acetic anhydride and perchloric acid at 0°C cyclized to 2-alkylthio-3-methyl-1,3,4-thiadiazolium salts (**154**) in >90% yield [88S690].



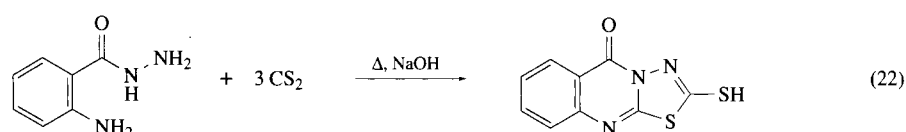
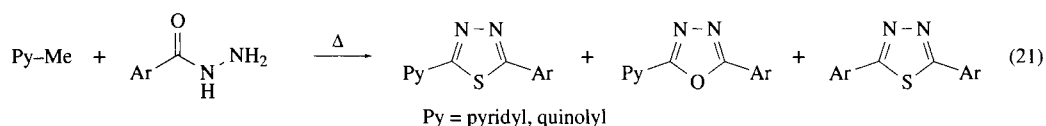
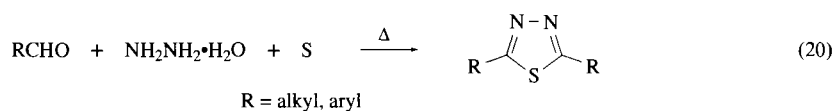
Scheme 27



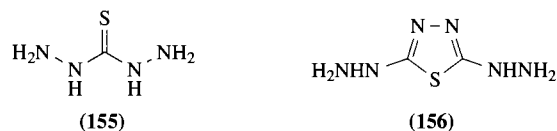
Scheme 28

4.10.10.3 Formation of Three Bonds

There are several one-pot syntheses of 1,3,4-thiadiazoles. 2,5-Dialkyl- and diaryl-1,3,4-thiadiazoles are formed in high yields by combining an aldehyde with hydrazine hydrate and sulfur (Equation (20)) [80LA1216, 83JHC1399]. 2-Heteroaryl-5-phenyl-1,3,4-thiadiazoles have also been produced by heating sulfur, methyl pyridines and alkoxybenzoylhydrazines but the yields were mediocre, and the products were contaminated by small amounts of the dialkylated oxadiazoles and symmetrical diaryl thiadiazoles (Equation (21)) [84JHC181]. Chinese workers have reported the one-pot synthesis of 2-thio-5H-1,3,4-thiadiazolo-[2,3-*b*]quinazolin-5-one (68% yield) (Equation (22)) from the hydrazide of *o*-aminobenzoic acid and carbon disulfide in refluxing sodium hydroxide solution [90MI 410-02].

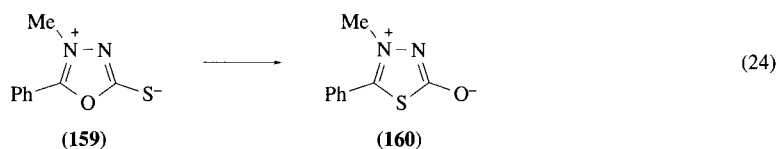
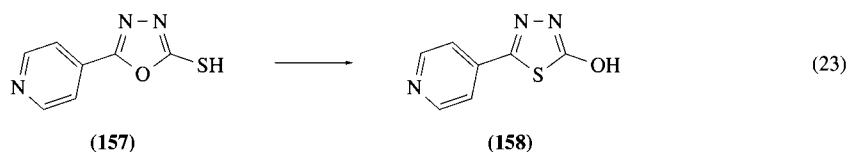


Investigations on the nature of a colored impurity that occurs during the manufacture of the triazine herbicide metribuzin led to an unusual synthesis of 2,5-dihydrazino-1,3,4-thiadiazole (**156**). Addition of H_2O_2 to the dihydrazide (**155**) in aqueous hydrochloric acid, and storage overnight followed by a complex workup, gave (**156**) in a crude yield of 28% <90JHC1053>.



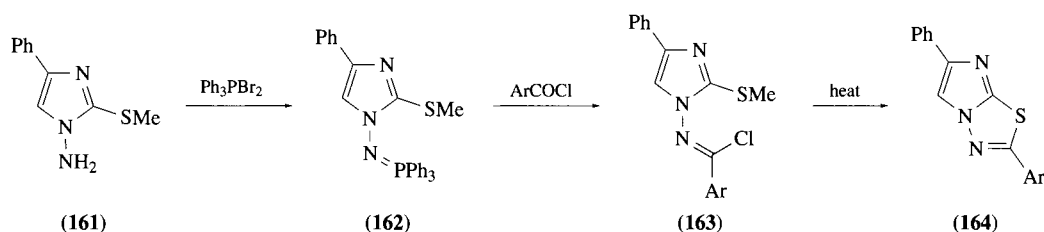
4.10.11 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

1,3,4-Thiadiazoles and 1,3,4-oxadiazoles are closely related in their reactivity, and can also be prepared from common precursors. They also undergo ring transformations and the thiadiazoles can be obtained directly from the oxadiazoles. 2-Thio-5-(4-pyridyl)-1,3,4-oxadiazole (**157**) (Equation (23)) when heated under reflux in ethanolic HCl rearranges to the 2-hydroxythiadiazole derivative (**158**). The mesoionic oxadiazole (**159**) also rearranges to the thiadiazole (**160**) when heated in ethanol (Equation (24)) <84CHEC-I(4)545>.



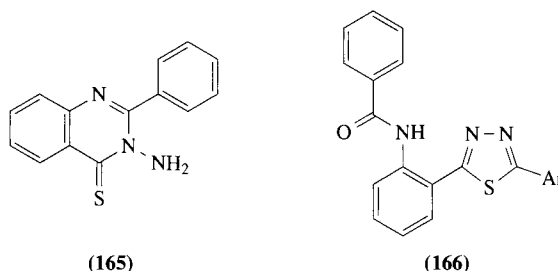
There are many heterocyclic molecules in which 1,3,4-thiadiazoles are fused to other ring systems. For example, Molina *et al.* developed a procedure for building a thiadiazole ring on to a properly substituted imidazole moiety (Scheme 29). Reaction of 1-amino-2-methylthio-4-phenylimidazole (**161**) with triphenylphosphine dibromide in dry benzene furnished the 2-methylthio-4-phenyl-1-triphenylphosphoranylideneamino imidazole (**162**) in a 95% yield. With aroyl chlorides at elevated temperature, this gave the 2-aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles (**164**) in yields between 50% and 70% via the imidoyl chloride intermediate (**163**) which could be isolated and shown to cyclize to the thiadiazole. The method developed for the imidazole ring was also applicable to the thiadiazolotriazine ring system <88H(27)1935>.

Molina *et al.* also synthesized 2,5-disubstituted thiadiazoles (**166**) by prolonged heating of 3-

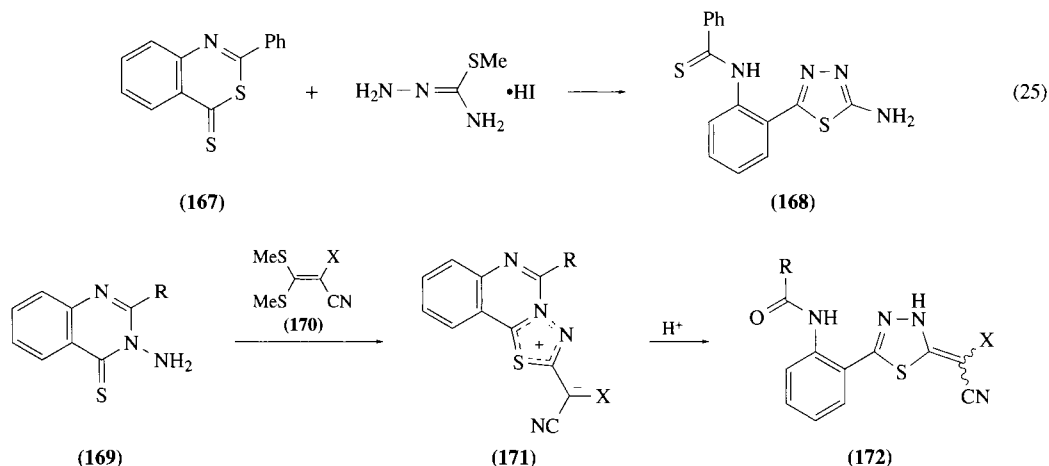


Scheme 29

amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**165**) with aromatic aldehydes in ethanol in the presence of HCl <82S944> or by reaction with acid chlorides <83JHC983>.



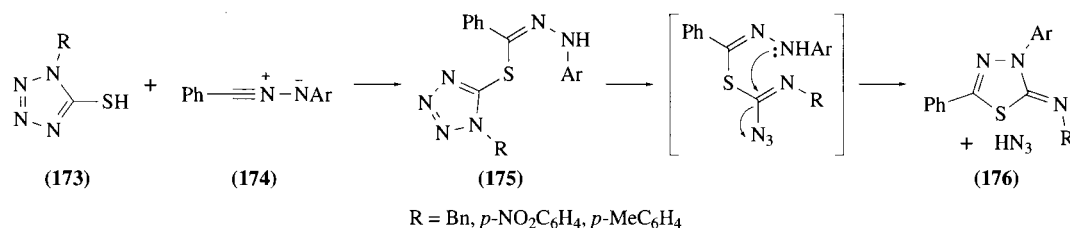
In a fourth paper from the Molina school, 4*H*-3,1-benzothiazine-4-thione (**167**) was treated with *S*-methylisothiosemicarbazide hydroiodide in ethanol containing sodium acetate, to yield the 5-aryl-2-amino-1,3,4-thiadiazole (**168**) (Equation (25)). A plausible mechanism for this transformation requires the addition of one of the amino groups from the thiosemicarbazide to the thiocarbonyl group of the benzothiazine-4-thione (**167**) followed by ring opening and recyclization with elimination of CH₃SH to give the thiadiazole (**168**). Mesoionic 1,3,4-thiadiazolo[3,2-*c*]quinazolinylum-2-methanides (**171**) were produced in moderate to good yields (Scheme 30) by treating the amino quinazoline thione (**169**) with the ketene dithioacetal (**170**) in a DMF solution containing potassium *tert*-butoxide. A large number of these mesoionic compounds were prepared; on treatment with mild acid, the thiadiazole ring is unmasked to yield (**172**) <88LA133>.



Scheme 30

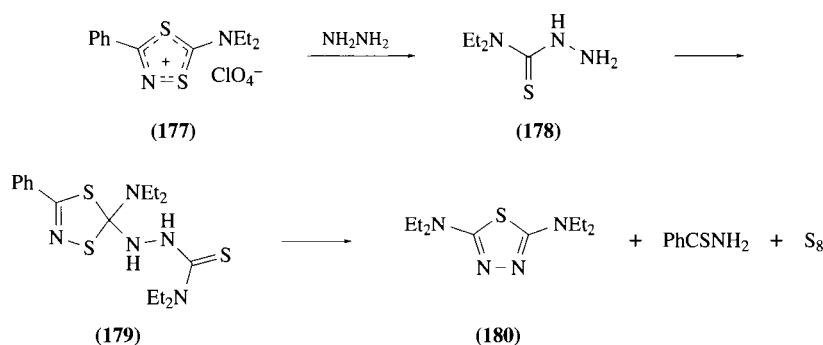
The reaction of a nitrile imide with 1-aryltetrazoles substituted at C(5) with a hydroxyl, thiol or amino group provides means of transforming a tetrazole ring into a 1,3,4-thiadiazole. For example, electrophilic attack by benzonitrilium *N*-4-nitrophenylimide (**174**) on the exocyclic sulfur atom of tetrazole (**173**) (Scheme 31) gave the benzothiohydrazone (**175**) which on heating in toluene or dry DMSO is converted to the 2-imino-5-substituted thiadiazole (**176**). The hydrazone (**175**) is presumed to have a *Z* structure because the nucleophilic addition to the nitrilium ion should place the nitrogen lone pair *trans* to the entering nucleophile. The ¹³C NMR spectrum of (**175**) in deuterated DMSO indicated *E*-*Z* isomerization. When R is phenyl, the signals from one of the isomers were four times stronger than from the second one; on heating to 90°C, the signals due to the minor isomer disappeared, but reappeared on cooling to room temperature. Based on models, the *Z* form is favored for the major isomer <93JCR(S)306>.

The reaction of 1,4,2-dithiazolium salts with amines also leads to thiadiazoles. Thus treatment of the *N,N*-diethylamino dithiazolium salt (**177**) with an excess of hydrazine (Scheme 32) afforded 2,5-bis(diethylamino)-1,3,4-thiadiazole (**180**) together with thiobenzamide. The mechanism postulated is as follows: in the first step, hydrazine causes rupture of the ring to liberate *N,N*-diethylthiosemicarbazide (**178**) which in turn reacts with another molecule of (**177**) to give the intermediate



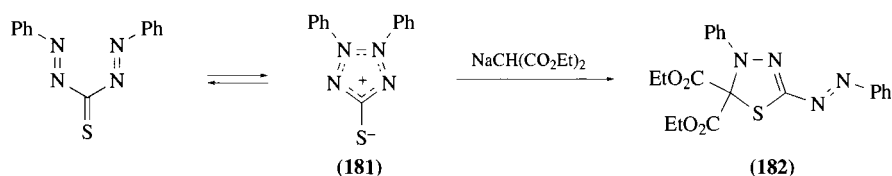
Scheme 31

(179). Opening of the ring and expulsion of thiobenzamide and sulfur leads to the thiadiazole (180). The preferential attack of (177) on (178) instead of the excess hydrazine present in the reaction mixture is partially explained by differences in solubilities <88BCJ4043>.



Scheme 32

Thiadiazolines were also obtained by a 1,5-dipolar ring reconstruction of mesoionic ylides. The bromine adduct of 2,3-diphenyltetrazolium-5-thiolate (181) reacts with the sodium salt of diethyl malonate to yield as the only product 5,5-bis(ethoxycarbonyl)-4-phenyl-2-phenylazo-2,3-dihydro-1,3,4-thiadiazole (182) (Scheme 33). The same type of product was obtained from reactions with ethyl cyanoacetate and ethyl acetoacetate <88BCJ2979>.



Scheme 33

4.10.12 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

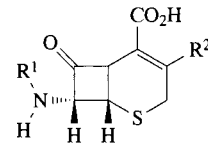
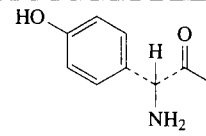
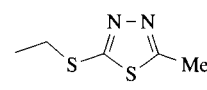
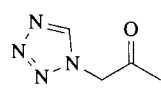
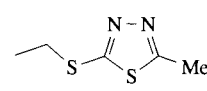
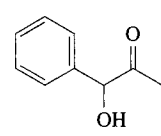
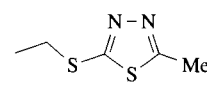
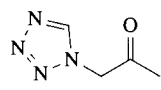
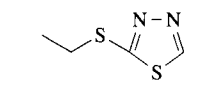
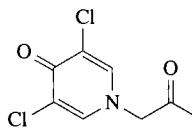
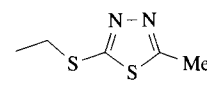
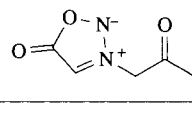
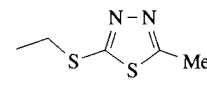
2,5-Symmetrically substituted thiadiazoles are best synthesized by combining aliphatic or aromatic aldehydes, hydrazine hydrate, and elemental sulfur, and heating the reaction mixture at high temperature, sometimes in an autoclave. Although the yields are not optimal and work-up can be difficult due to the presence of sulfur, the method is attractive due to its low cost and simplicity (Section 4.10.10.3). 2,5-Unsymmetrically substituted thiadiazoles can be obtained by many procedures, most of them satisfactory; a very popular one is by acylating a thiosemicarbazide followed by dehydration with acid. In the past, harsh acids such as sulfuric acid have been used, but in the 1990s methanesulfonic acid has gained favor. This method is also applicable to the synthesis of triazoles and oxadiazoles, and has been discussed in Section 4.10.10.1. The reaction of 4-alkylthiosemicarbazide with orthoformate esters gives good yields of 2-alkylaminothiadiazoles. The reaction of heteroaryl dithiocarboxylic esters with semicarbazide followed by cyclocondensation yields thiadiazoles with an heteroaryl group substituted at the 5-position (Schemes 20 and 21). A

great variety has been prepared, and the yields appear to be good <90JPR55>. Thiadiazolines are readily available from the reaction of *N*-alkyl and *N*-aryl benzhydrazonyl chlorides with thio-benzamide derivatives. The yields are satisfactory, but not in all cases <76ACS(B)837>. Thiadiazolodithiones can be prepared from hydrazine and carbon disulfide in good yields <90JHC139>.

4.10.13 IMPORTANT COMPOUNDS AND APPLICATIONS

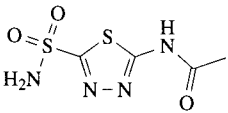
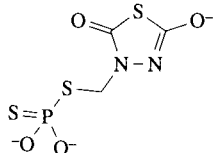
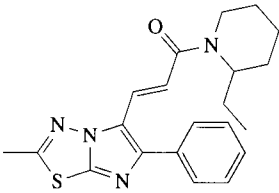
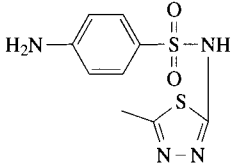
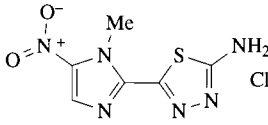
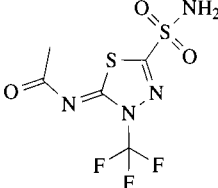
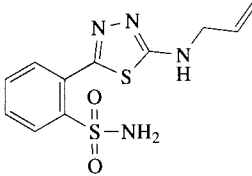
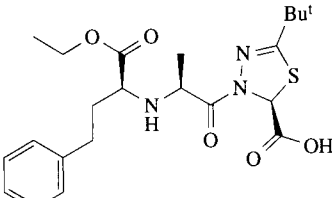
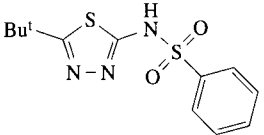
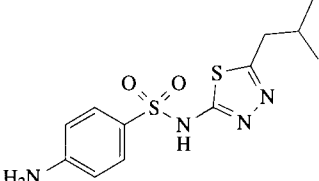
1,3,4-Thiadiazole and its derivatives have become very useful compounds in medicine, agriculture and in many fields of technology. Between 1967 and 1982, *Chemical Abstracts* listed 242 patents. From 1982 to August 1994 well over 400 patents were found in a *Chemical Abstracts* search in which the nature of the bonds in the thiadiazole nucleus were not defined, and substituents were allowed on all atoms. Although very few patented compounds become marketed products, patents do give a rough indication of utility. Some of the technological uses involve dyes, lubricating compositions, optically active liquid crystals, photographic materials, epoxy resins, and many others. A large number of thiadiazoles have been patented in the agricultural field as herbicides, insecticides, fungicides, bactericides, and anthelmintics. In the medical field they have been patented for almost every disease known to man, and quite a few of them have become commercial products. One of the best known drugs based on the thiadiazole molecule is acetazolamide, also called acetazola which is a carbonic anhydrase inhibitor. Its indications and usage are many, including glaucoma, epilepsy, and congestive cardiac failure. Although it is an old drug, attempts to improve its efficacy and decrease its side effects continue <92JMC2697>. In a series of publications from British workers, thiadiazole derivatives were found to have antihypertensive and anticonvulsive activities

Table 1 Cephalosporins linked to thiadiazoles <B-93MI 410-01>.

		Name
R^1	R^2	
		Cefaparole
		Cefazolin Sodium
		Cefcanel
		Ceftezole
		Cefazedone
		Cefanone

<88JMC7>. Derivatizing 2-amino thiadiazole with the phenylsulfonyl group imparts good anti-microbial activity while the *N,N*-dialkylated carbamoyl group bestows herbicidal properties to Spike, a product marketed for a number of years. Table 1 presents antibacterial cephalosporin-thiadiazole derivatives <B-93MI 410-01>, while Table 2 illustrates various biological activities attributed to 1,3,4-thiadiazoles <B-94MI 410-02>.

Table 2 Biological activity of some thiadiazoles <B-93MI 410-02>.

 (Acetazola: Epilepsy, Gloucoma, Congestive Cardiac-Failure)	 (Methidath: Insecticides)
 (Bayn-1468: Diuretics)	 (Sulfameti: Urinary-tract Infections)
 (CL-75805: Anthelmintics)	 (Trifluorm: Diuretics)
 (G-445: Virucides)	 (Utibapril: Hypotensives)
 (Glybuzole: Type-2 Diabetes)	 (2256-RP: Antidiabetics)

4.11

1,2-Oxa/thia-3-azoles

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Russian Academy of Sciences, Moscow, Russia

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4.11.1 INTRODUCTION

Development of the chemistry of 1,2,3-dithiazoles, 1,2,3- and 1,2,5-oxathiazoles has been more or less uniform up to 1995.

In the post-1980 period more attention has been paid to heteropentalene structures. An abundance of new chemistry has been revealed for 4,5-dichloro-1,2,3-dithiazolium chloride ("Appel's salt"),

the Herz reaction mechanism has been intensively studied, and novel synthetic routes to the heterocycles reviewed in this chapter have been found. Stable radicals of 1,2,3-dithiazoles have been discovered and investigated. Thermolysis of 1,2,3-dithiazoles and their radicals was another new development.

Known 1,2,3-dithiazoles are represented by the structures in row (a) of Figure 1. Strictly, these are 1,2,3-dithiazolines, the first one being 1,2,3-dithiazoline-5-one. 1,2,5-Oxathiazoles are represented by 1,2,5-oxathiazolidine-4-ones (b) and 3-methylene 1,2,5-oxathiazolines (c). 1,2,3-Oxathiazoles have been obtained only in the form of their *S*-oxides (d), which should rather be termed -azolidines and -azolidinones. Experimentally prepared *S*-oxides of 1,2,3-dithiazoles and 1,2,5-oxathiazoles are depicted in row (e) and should be termed dithiazolines and oxathiazolines. 1,2,3-Dithiazolyl radicals (f) are known, as well as 1,2,3-dithiazolium cations (g) which are the only formally aromatic examples of the ring system and which may be represented by a number of resonance structures (h).

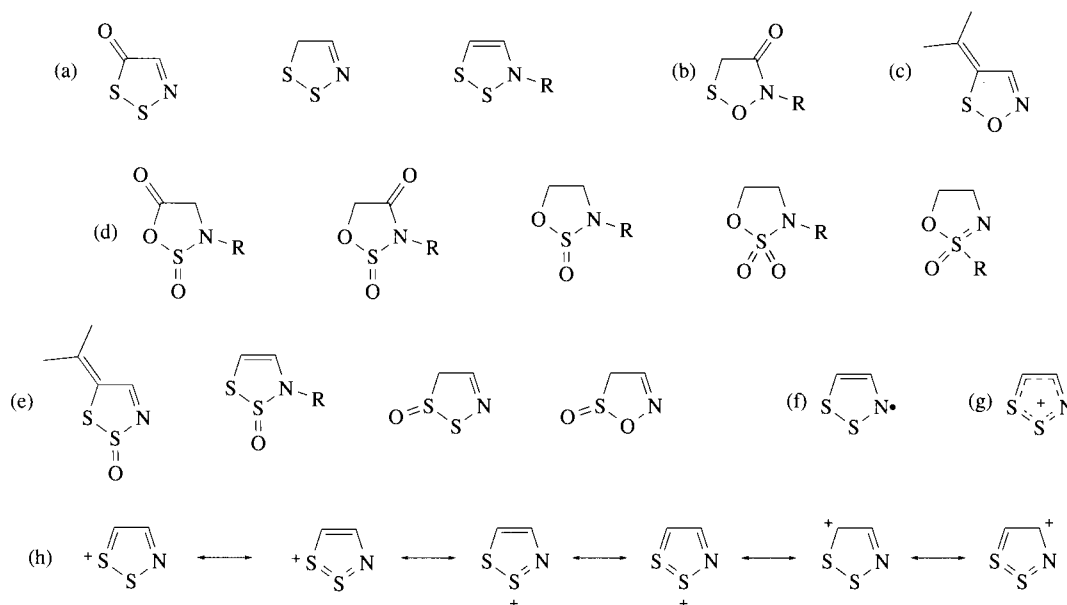
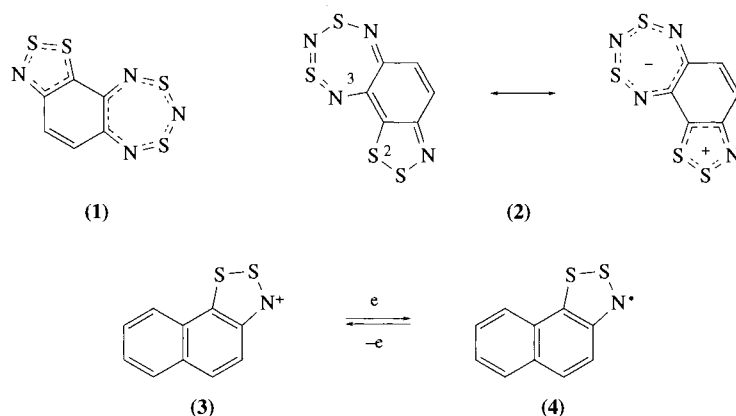


Figure 1 Known 1,2-oxa/thia-3-azoles.

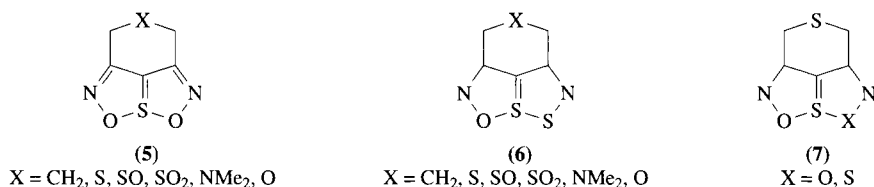
4.11.2 THEORETICAL METHODS

Extended Hückel MO calculations for (1) showed the charge distribution to be in the sense of the dipolar formulation (2), a net π -charge excess of ≈ 0.6 electrons on the large ring compared with the small one being estimated $\langle 83CJC1562 \rangle$. A relative splitting of the degenerate pairs of the parent perimeter HOMOs and LUMOs of (1) was calculated by the Pariser Parr Pople (PPP) method $\langle 86IC3194 \rangle$. A small splitting of the HOMOs and the large splitting of the LUMOs was found suggesting (1) to be a negative hard chromophore. Calculated transition states energies agree well with experimental values of UV and MCD spectra. π -Charges and π -bond orders were calculated by the SCF-LCI Longuet-Higgins method and the Pople method in π -approximation for the cation (3) and radical (4) in ground and excited states. Changes in π -electron distribution effected by excitation of (3) and (4) were found to be similar. The calculated UV spectral characteristics are close to the experimental UV spectra $\langle 82PS(13)107 \rangle$.

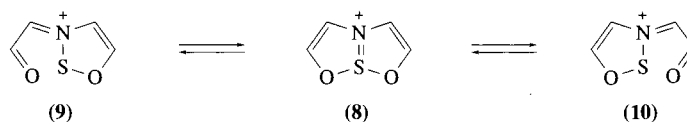
Heteropentalenes (5) with proven or potential herbicidal activity were subjected to calculation by a standard MNDO method to estimate the electron-accepting properties of the molecules. The adiabatic electron affinity (the difference between calculated standard enthalpies of formation of the molecule and its anion radical) was found to correlate with measured reduction potentials (the greater the affinity the easier the reduction) and thus serves to predict the ease of reduction of (5) with various X. The calculated LUMO energy E_{LUMO} for X = O is slightly lower (by 0.056 eV) than for X = S and the calculated half-peak reduction potential $E_{1/2}$ is slightly less negative (by 10 mV) indicating a slightly more difficult reduction $\langle 89JCS(P2)469 \rangle$. A more pronounced effect ensues when



oxygen is substituted for sulfur in the heteropentalene part of the molecule, i.e. nearer to the reaction site; (5; X = S) is more difficult to reduce than (6; X = S) (and (7; X = O) than (7; X = S)) ($E_{1/2}$ more negative by 200 mV) and has E_{LUMO} higher by ≈ 0.2 eV [85JCS(P2)1797].



Ab initio calculation of energy changes accompanying distortions of the dioxathiaazapentalene cation (8) showed structure (8) not to have the lowest energy but to be rather a transition state between the two valence bond structures (9) and (10). This process corresponds to an in-plane bend parallel to the 3c,4e-hypervalent bond at sulfur. An out-of-plane bend about the SN bond also leads to an energy minimum but this is at a much higher level and is therefore less realistic [91PS(55)35].



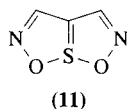
Scheme 1

4.11.3 EXPERIMENTAL STRUCTURAL METHODS

4.11.3.1 X-ray, Neutron, and Electron Diffraction

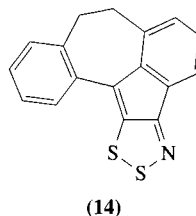
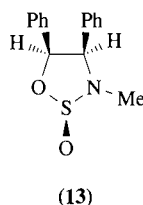
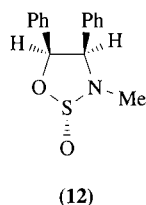
2,5-Diaza-1,6-dioxa-6a-thiapentalene (11) was studied by x-ray [82ACS(A)673, 88AX(B)522, 89JA5728], neutron [88AX(B)522], and electron [88ACS(A)71] diffraction methods. Both rings are planar as is the disposition of bonds around the central carbon atom. However, the sum of bond angles around the sulfur atom (343° instead of 360°) indicates a slight deviation from planarity, the rings forming an angle of 2.5° [89JA5728]. Electron density distribution determined by x-ray study at 11 K [89JA5728] coincides well with the calculated density map [B-86MI 411-01]. The S atom is hypervalent, its four electrons are accommodated on a three-center bond O—S—O, which is close to linear ($\angle \text{OSO} = 171^\circ$). One electron is in a p_x orbital (along S—O), one is in a (sp_y) hybrid orbital toward the central carbon, and one σ lone pair is in the orthogonal (sp_y) hybrid (one σ -electron takes the $d_{x^2-y^2}$ and one π -electron the p_z orbital). The π -electronic structure of the molecule involves one electron from sulfur, two electrons from each oxygen, and one electron from each nitrogen. Strong $p(\text{S})$ — $p(\text{O})$ coupling is additionally stabilized by inclusion of sulfur d -orbitals. Nevertheless, the SO bond (1.836 Å) is longer than a usual covalent bond, 1.56–1.65 Å [B-85MI 411-01], or the sum of sulfur and oxygen covalent radii, 1.71 Å [82ACS(A)673]. Since nitrogen is more electronegative

than sulfur, the oxygen electron lone pair is delocalized more on nitrogen than on sulfur and this enhances the ability of $d(S)$ -orbitals to π overlap with the central carbon producing a shortened carbon–sulfur bond (1.682 Å vs. 1.81 Å and 1.71 Å for standard single and double sulfur–nitrogen bonds, respectively) $\langle 89JA5728 \rangle$. If carbon is substituted for nitrogen, the sulfur–oxygen bond lengthens (1.875 Å) and the carbon–sulfur bond (1.706 Å) becomes less double bonded $\langle 88ACS(A)71, 88AX(B)522 \rangle$. An elevated electron density at nitrogen may be responsible for $N \cdots H-C$ intermolecular H-bond contacts ($N \cdots H$ is 2.30 Å, $\angle NHC = 159^\circ$) $\langle 88AX(B)522 \rangle$, this is supported by IR spectra (Section 4.11.3.5). The charges on the atoms are estimated to be +0.41(S), +0.29(C central), +0.02 (C others), –0.90 (O) and –0.18 (N). The geometry at 11 K and 122 K is virtually the same, but for the charge density study the lower temperature was crucial $\langle 89JA5728 \rangle$. The nitrogen atom appears to form a weak intermolecular H-bond, whereas sulfur makes a close intermolecular contact with oxygen (1.88 Å) $\langle 88AX(B)522 \rangle$.

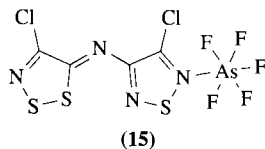


Fusion of a six-membered cycle on to (11) to produce a tri-cyclic thiapentalene structure (5) brings only negligible changes in geometry of the heterocyclic part. Both rings remain planar with strict planarity around all three carbon atoms, and as before the three bonds around sulfur deviate from planarity (bond angle sum is 338°). The geometry is practically the same for $X = S, SO, SO_2$ $\langle 89JCS(P2)469 \rangle$, and CMe_2 $\langle 72JCS(P2)2001 \rangle$.

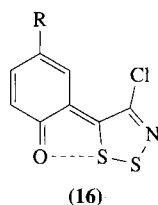
X-ray analysis confirmed the stereochemistry of nonplanar (12) and (13) $\langle 86BSF397 \rangle$ and helped to elucidate the complicated structures (14) $\langle 91JCS(P1)311 \rangle$ and planar (2) $\langle 83CJC1562 \rangle$. A short nonbonded intramolecular contact $S2 \cdots N3$ (2.850 compared with van der Waals' radii sum 3.35 Å) appears to cause a very slight buckling at these two sites in (2). The geometry parameters indicate a π -delocalization, which necessitates the use of the dipolar formulation in addition to the neutral valence structure to adequately describe the molecule. This is also substantiated by packing of the molecules such that the five-membered ring of one molecule is located over the seven-membered ring of the other, the pattern repeating throughout the stack $\langle 83CJC1562 \rangle$.



In the arsenicum adduct (15) the $N-As$ bond (2.001 Å) lies in the ring plane and compares in length with that in other $N \cdots AsF_5$ adducts; both rings are completely planar and the length of the SS bond (2.077 Å) is within the expected range $\langle 86ZN(B)162 \rangle$.

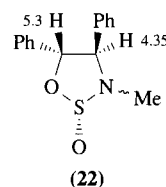
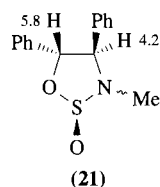
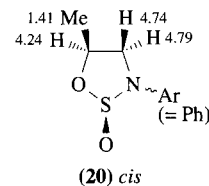
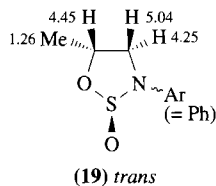
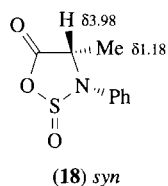
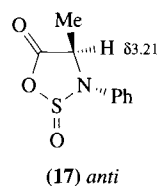


Formation of a very close intramolecular contact (2.16 Å) between the carbonyl oxygen and the ring sulfur was found in the quinonoid derivative of 4-chloro-1,2,3-dithiazole (16). The contact is much less than the sum of van der Waals' radii (3.2 Å) and not much longer than the SO bond in oxathiazoles (≈ 1.8 Å). Other bond lengths are intermediate between single and double bonds indicating a great deal of delocalization in this entirely planar molecule. Moreover, in the crystal the molecules are stacked so that the SS entities of one stack make a close (shorter than van der Waals') contact with oxygen atoms of the adjacent stack to form a "winding staircase" twisted alternately right and left from stack to stack. This possibly causes the metallic lustre of the crystals $\langle 85CB1632 \rangle$.



4.11.3.2 ^1H NMR Spectroscopy

Substituted 1,2,3-oxathiazolidine 2-oxides display regular differences of ring proton chemical shifts depending on structural surroundings, and this was extensively used for solution of various conformational and configurational problems. *Anti* (17) and *syn* (18) isomers were assigned by fine differences in the C4-H signals (benzene) $\langle 90\text{PS}(53)411 \rangle$, as were pairs of isomers (19)–(20) (CDCl_3) $\langle 90\text{JHC195} \rangle$ and (21)–(22) (CDCl_3) $\langle 86\text{BSF397} \rangle$. The differences stem from *cis*-Me group shielding (≈ 0.44 ppm) and *cis*-SO bond acetylenic-like anisotropic deshielding (≈ 0.36 ppm) effects.

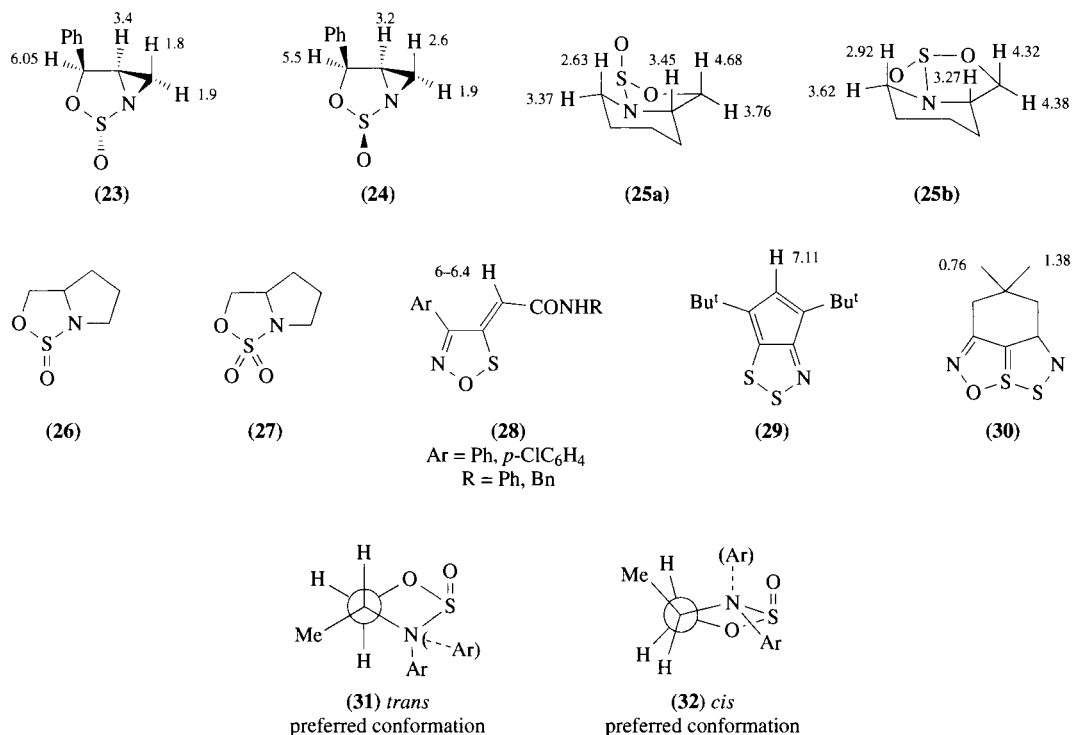


The assignment is more complex in bicyclic structures such as (23) and (24) $\langle 86\text{BSF397} \rangle$, especially in cyclopenta- and cyclohexacondensed systems exemplified by (25); a *trans*-junction of the rings was proposed for (25) and *cis*- for (26) and (27), the heterocycle having a twist-envelope like conformation with sulfur as a flap $\langle 90\text{TA885} \rangle$. Chemical shifts for 1,2,5-oxathiazoles are represented by (28) (CDCl_3 , $(\text{CD}_3)_2\text{SO}$) $\langle 84\text{JHC1679} \rangle$ and for 1,2,3-dithiazoles by (29) (CDCl_3) $\langle 85\text{TL189} \rangle$. The delocalized 10π -electron system of the latter is the cause of a downfield shift of its signal as compared with pentafulvalenes. For the heteropentalene (30) the separate signals from the two methyl groups were clearly observed only at -110°C , they had coalesced at -80°C and merged into one clear peak (δ 1.12) at -70°C . These changes are characteristic of a simple conformational transition ($\text{A} \rightleftharpoons \text{B}$). The low activation free energy 36.5 kJ mol^{-1} (-80°C) compares with that for boat-chair flipping in cyclohexane (42.8) and cyclooctane (32.3) $\langle 85\text{JCS(P2)1797} \rangle$.

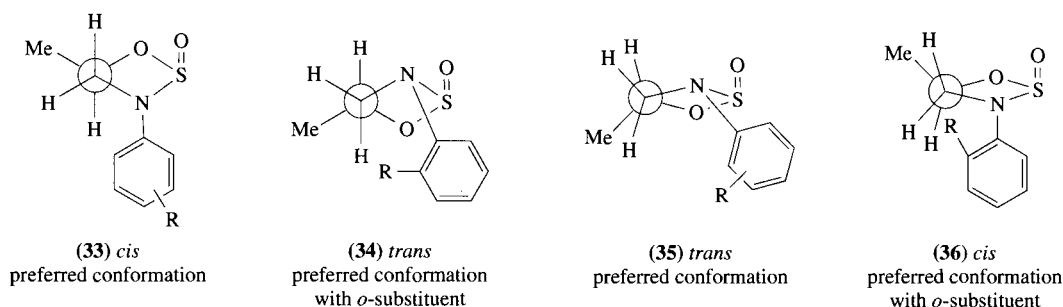
4.11.3.3 ^{13}C NMR Spectroscopy

In five 3-aryl-4-methyl-1,2,3-oxathiazolidine 2-oxides the average chemical shift for C(4) of *trans* isomers (19) is $\delta 52.7 \pm 0.1$ without an *o*-substituent and $\delta 54.4 \pm 0.1$ with an *o*-substituent, whereas in *cis* isomers (20) the values are $\delta 55.8 \pm 0.3$ and $\delta 60.0 \pm 0.2$, respectively. The downfield signal displacement in *o*-substituted isomers is due to a δ -effect of *o*-substituents. The chemical shift for C(5) is far less affected: the average δ -value for 10 compounds being 76.4 ± 0.8 . NMR spectroscopy was used for a conformational analysis. Both *trans* and *cis* isomers (31) and (32) are considered to adopt conformations with strong deviation of the methyl group from an axial towards an equatorial position to avoid its interaction with the sulfoxide group; an *o*-substituted aryl group in *cis* isomers (32) avoids the axial position because of steric interaction with both methyl and $\text{S}=\text{O}$ groups. The *trans* isomer always predominates in synthesis (Section 4.11.8.3) $\langle 90\text{JHC195} \rangle$.

An essentially analogous relationship, if with some peculiarities, was found with seven 5-methyl derivatives $\langle 82\text{JHC1553} \rangle$. Again, the methyl group prefers to adopt an equatorial position because



of steric repulsion from the S=O group in *cis* isomers (33) and from the *o*-substituent in *trans* isomers having *o*-substituted aryl groups (34). The difference in chemical shifts for C(4) carbon in both cases is therefore substantial: δ 50.72 $\pm$ 0.05 in the first case and δ 54.55 $\pm$ 0.24 in the second. The upfield signal displacement by 3.8 ppm in the first case is considered to be induced by a *gauche* relationship between C(4) and sulfoxide oxygen. Without an *o*-substituent the repulsion between methyl and aryl in *trans* isomers becomes only moderate so that methyl moves closer to the axial position (35). An *o*-substituent in *cis* isomers causes a moderate repulsion from the axial hydrogen to turn methyl closer to its axial position (36). Chemical shifts for C(4) in these cases are very similar: δ 52.82 $\pm$ 0.04 and δ 52.95 $\pm$ 0.24, respectively, just halfway between the chemical shifts in (33) and (34). C(5) has chemical shifts $\delta \approx 83.5$ in (33) and (35), $\delta \approx 79.5$ in (34) and (36); the difference stems from a *gauche* relationship in the latter pair between C(5) and sulfoxide oxygen. A similar behavior was found for seven 5-ethyl derivatives. The heterocycle has a twist-envelope conformation.



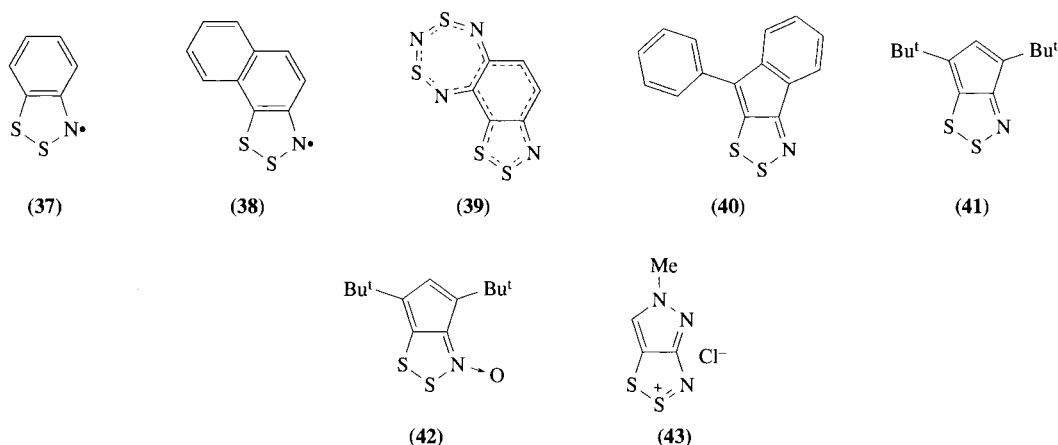
4.11.3.4 UV and ESR Spectroscopy

UV spectra of some 1,2,3-dithiazoles are presented in Table 1. Absorption for (41) is similar to that for pseudo azulenes <85TL189>. The wavelength associated with the first excited singlet state for (6; X = S) (λ 451 nm, ϵ 8040 dm⁻³ mol⁻¹ cm⁻¹) is red-shifted relative to (5; X = S) (λ 353 nm, ϵ 6580 dm⁻³ mol⁻¹ cm⁻¹) and this is taken to imply that the latter more readily accepts an electron

<85JCS(P2)1797>. The magnetic circular dichroism spectrum of (39) contains eight bands, of which the first six are centered at UV bands and the two remaining are near 265 nm and 242 nm; the signs of the B terms are $-$, $+$, $-$, $+$, $-$, $+$, $+$, $-$ in order of increasing energy <86IC3194>.

Table 1 UV Absorption maxima for 1,2,3-dithiazoles.

Structure	$\lambda_{\max}$ (nm) (log ϵ)	Solvent	Ref.
(37)	$\approx 340, 390\text{--}400, 500\text{--}520$	<i>c</i> -hexane, benzene	82PS(13)107, 84CCC684
(38)	$\approx 375, 420\text{--}450, 570\text{--}600$	<i>c</i> -hexane, benzene	82PS(13)107, 84CCC684
(39)	301(3.9) sh, 318(4.0) sh, 352(4.18), 385(3.8) sh, 585(4.08), 714(3.3) sh	CH_2Cl_2	86IC3194
(40)	280(3.84), 315(3.62), 352(3.34)	EtOH	91JCS(P1)311
(41)	246(3.08) sh, 332(3.83) sh, 339(3.88) sh, 343(3.89), 352(3.82) sh, 358(3.71) sh, 525(3.16)	hexane	85TL189
(42)	247(3.9), 373(2.81), 560(2.73)	hexane	85TL189
(43)	326(4.01), 452(3.20)	$\text{CF}_3\text{CO}_2\text{H}$	84JOC1224



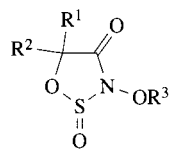
ESR spectra of 1,2,3-dithiazole radicals fused to benzene, naphthalene, anthraquinone, pyridine, thiophene, and thiazole show ^{14}N coupling constants $a_{\text{N}} = 0.65\text{--}0.87$ mT and g -factors 2.0075–2.0084 independent of solvent and temperature. Relatively low a_{N} values are associated with an electron delocalization over the entire radical. ^{14}N coupling constants correlate with σ_{p} constants for variously substituted (37) (inversely proportional) <84CCC684>. The ESR spectrum of the radical anion of (5; X = S) is a quintet ($a_{\text{H}} = 0.18$ mT) of quintets ($a_{\text{N}} = 0.41$ mT) arising from the interaction of electron lone pairs of two nitrogens with the four hydrogen atoms of the CH_2 groups. A somewhat reduced a_{N} value may be also explained by an extensive delocalization <85JCS(P2)833>. The hyperfine coupling constants $a_{\text{N}(\text{O})}$, $a_{\text{N}(\text{S})}$, $a_{\text{H}(\text{O})}$, and $a_{\text{H}(\text{S})}$ (mT) for the radical anions of (6; X = CMe₂) and (6; X = S) are 0.31, 0.40, 0.08, 0.24 and 0.29, 0.40, 0.14, 0.15, respectively (subscripts in brackets indicate nitrogen or hydrogen position on oxygen or sulfur side of the molecule) <85JCS(P2)1797>.

4.11.3.5 IR Spectroscopy

The absorption band at 1121 cm^{-1} in dithiazole (40) is assigned to an N—S ring bond stretching frequency <91JCS(P1)311>. Five 3-alkoxy-1,2,3-oxathiazolidine-4-one 2-oxides (44) show strong bands at 1200 cm^{-1} (S=O) and $1750\text{--}1735\text{ cm}^{-1}$ (C=O) <86AP(319)1084>. Intermolecular H-bonding was observed for (11) in solution (a narrow 3104 cm^{-1} band) and in the solid state (a broadened $3104\text{--}1084\text{ cm}^{-1}$ band) <88AX(B)522>.

4.11.3.6 Mass Spectrometry

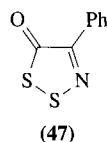
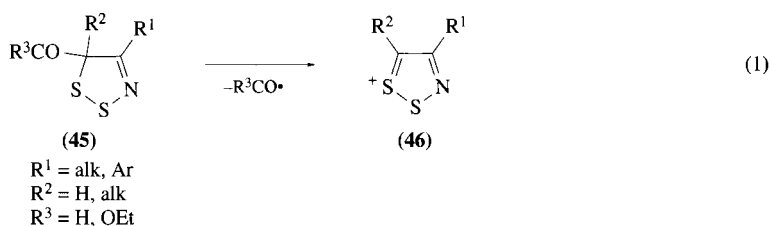
5-Carbonyl substituted 5*H*-1,2,3-dithiazoles (45) lose the carbonyl substituent to give a stable aromatic ion (46) as a main peak in their mass spectra (Equation (1)) <81BCJ3541>. The ring carbonyl



(44)

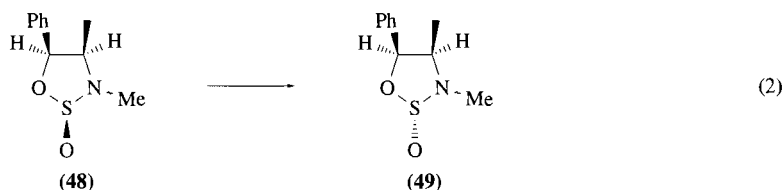
$R^1, R^2 = \text{H, alk, Ar}; R^3 = \text{Me, Bn}$

in the 5*H*-1,2,3-dithiazole (47) is expelled affording a main peak $(\text{PhCNSS})^+$ and then $(\text{PhCN})^+$ $\langle 89\text{JCS(P1)2489} \rangle$. The platinum derivative of 5*H*-1,2,3-dithiazole (59) (Section 4.11.7) gives two main peaks: $(\text{M}-\text{Ph}_3\text{PS})^+$ and $(\text{C}_4\text{Cl}_2\text{N}_4\text{S}_3)^+$ $\langle 86\text{CB366} \rangle$.



4.11.4 THERMODYNAMIC ASPECTS

Chiral substituted 1,2,3-dithiazolidine (48) converts slowly at RT into its stereoisomer (49) by $\text{S}=\text{O}$ group inversion which relieves the steric interaction with both methyl and phenyl groups (Equation (2)). The freshly prepared mixture (48): (49) = 4.4: 1 (Section 4.11.8.3), when kept at 0°C in the presence of $\text{Et}_4\text{N}^+\text{Cl}^-$, exhibits a change of the equilibrium to 9: 1 in 24 h and to 34: 1 in the next 24 h, further progress being hampered by slow decomposition of (49) $\langle 91\text{TL5885} \rangle$.



4.11.5 REACTIVITY OF FULLY CONJUGATED RINGS

Reactivity is considered for conjugated and nonconjugated 1,2,3-dithiazole type structures separately.

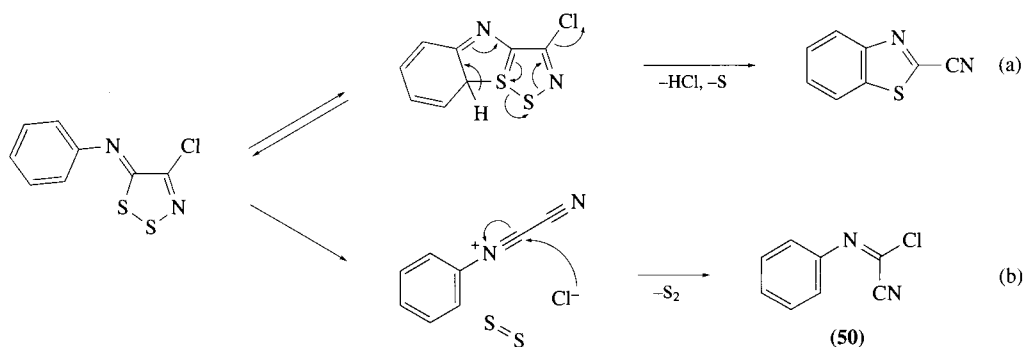
For conjugated structures thermolytic reactions with loss of sulfur have been studied since 1980 and afford various types of cyclic and acyclic products (Section 4.11.5.1). Nucleophilic attack at ring carbon is very characteristic of 1,2,3-dithiazoles (Section 4.11.5.4). This type of reaction was especially prolific with Appel's salt, studied mostly by Appel, Rees and their co-workers. The preferential site of attack is C(5) but nucleophilic substitution may occur at C(4) when the C(5) site is blocked by poorly leaving substituents, see the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) for examples of 1,2,3-dithiazoles $\langle 84\text{CHEC-I(6)924} \rangle$ and 1,2,3-oxathiazoles $\langle 84\text{CHEC-I(6)930} \rangle$. Nucleophilic attack at ring sulfur in 1,2,3-dithiazoles occurs on S(2) (Section 4.11.5.5), see

also CHEC-I (84CHEC-I(6)916). Examples of electrophilic attack at ring sulfur are limited to oxidation by various agents on the S2 site in 1,2,3-dithiazoles and -oxathiazoles (Section 4.11.5.3; 84CHEC-I(6)927). Oxidation at S1 occurs rarely (84CHEC-I(6)927). Electrophilic reactions at carbon and nitrogen ring atoms of 1,2,3-dithiazoles are also rare and are often accompanied by breakdown of the ring (Section 4.11.5.2). This is also caused by reducing agents (Section 4.11.5.6). Electrochemical reduction of oxadithia- and dioxathiaheteropentalene to anion radicals proceeds easily and reversibly revealing the effectiveness of these compounds for electron transfer to O₂.

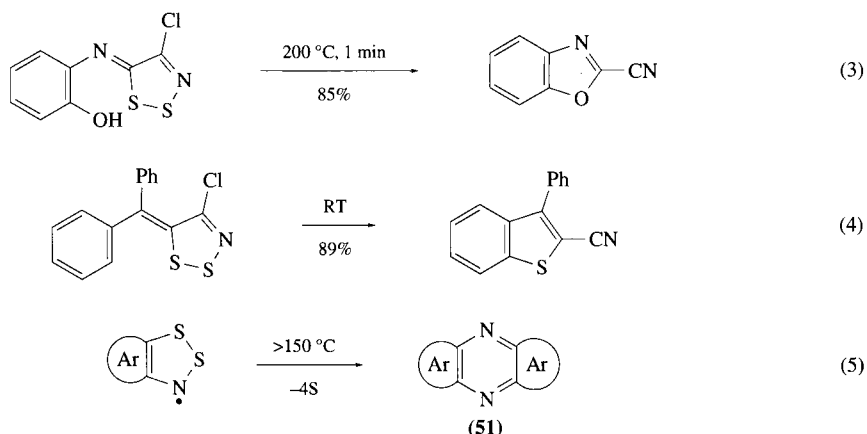
The reactivity of nonconjugated structures is confined to 1,2,3-oxathiazolidines *S*-oxides (Section 4.11.6; 84CHEC-I(6)925). Nucleophiles open the ring to afford 1,2-hydroxyaminoethane derivatives. Heat leads to extrusion of SO or SO₂, for example (104) (84CHEC-I(6)296); in the case of *S*-aryl substituted *S*-oxides C—O bond cleavage occurs to give an *N*-sulfonyl open chain derivative (84CHEC-I(6)925).

4.11.5.1 Thermal Formally Unimolecular Reactions

Readily accessible 5-(*N*-arylimino)-4-chloro-1,2,3-dithiazoles undergo a thermal rearrangement to 2-cyanobenzothiazoles (Scheme 2, pathway(a)) (92JHC639). Electron-releasing substituents enhance the reaction whilst electron-withdrawing groups retard this particular course but promote the formation of cyanoimidoyl chlorides (50) (pathway (b)). A direct loss of S₂ in the latter case is implied in the proposed mechanism (Scheme 2). An *o*-hydroxy substituent leads to the formation of cyano benzoxazoles (Equation (3)). When the nitrogen in the arylimino group is replaced by a carbon atom the rearrangement proceeds much more easily (Equation (4)) (92JHC639). Stable areno-1,2,3-dithiazolyl radicals decompose to give diarenopyrazines (51) on heating above 150 °C (Equation (5)) (85PS(23)277).

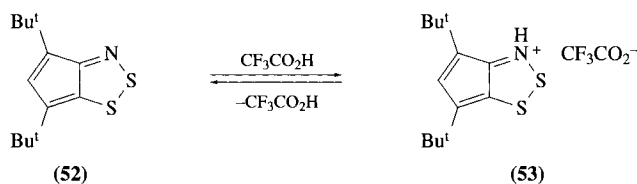


Scheme 2



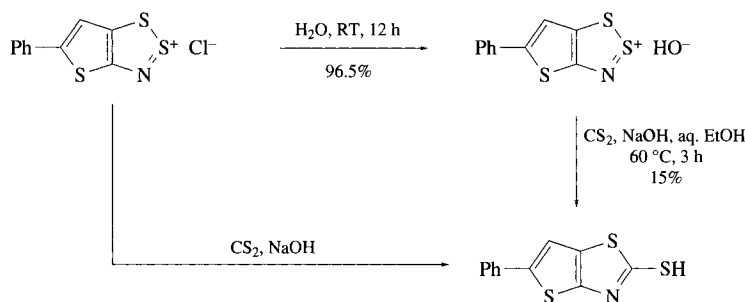
4.11.5.2 Electrophilic Attack at Ring Nitrogen and Carbon

4,6-Di-*t*-butylcyclopenta-1,2,3-dithiazole (52) is protonated reversibly on nitrogen by trifluoroacetic acid in CDCl₃ to produce a violet solution of salt (53) (Scheme 3) (85TL189).



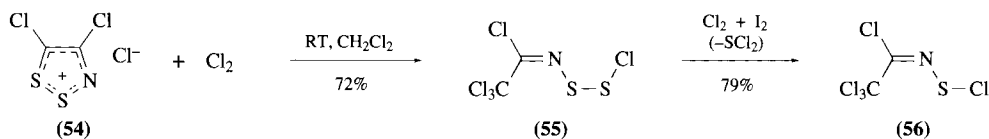
Scheme 3

The 1,2,3-dithiazolium ring is transformed to a thiazole ring by reaction with CS_2 which presumably attacks at ring N through its C atom (Scheme 4) <79KGS477>.

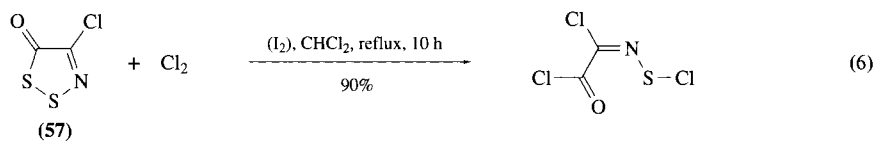


Scheme 4

Appel's salt (**54**) is exhaustively chlorinated by chlorine with ring opening to sulfenyl chloride (**55**). In the presence of I_2 as catalyst the sulfenyl chloride (**56**) is produced (Scheme 5) <85CB1632>. The similar iodine catalyzed chlorination of chlorodithiazolinone (**57**) occurs less readily (Equation (6)) <85CB1632>. Without the iodine catalyst, chlorination proceeds slowly to give a mixture containing chlorodisulfides of the type (**55**).

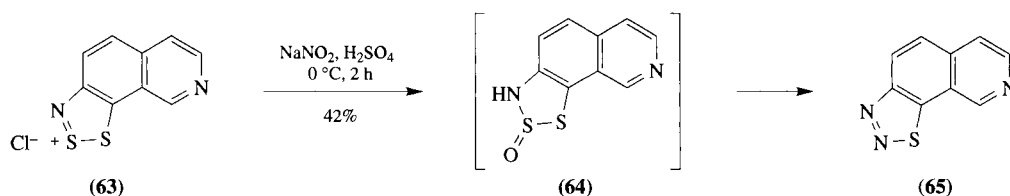
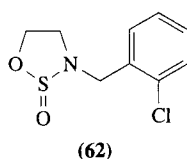
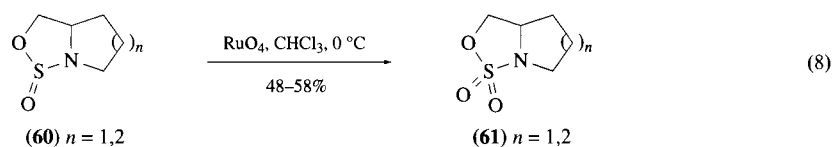
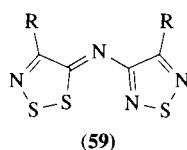
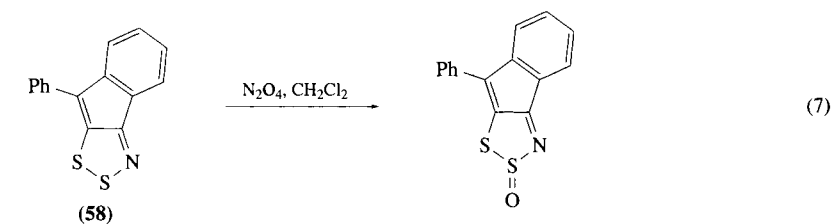


Scheme 5



4.11.5.3 Electrophilic Attack at Ring Sulfur

The 1,2,3-dithiazole ring in the fused system (**58**) is oxidized to an *S*-oxide on S(2); S(1) appears to be less nucleophilic due to electron shift towards imino nitrogen (Equation (7)) <91JCS(P1)311>. When 1,2,3-dithiazole and 1,2,5-thiadiazole rings are interconnected by imino nitrogen as in (**59**; R = Ph) the former ring is oxidized first to an *S*-oxide with MCPBA <89JCS(P1)2489>. Additional MCPBA (4 mol) at 0 °C is consumed to oxidize the second ring to the *S*-dioxide. Ruthenium tetroxide, made from sodium periodate and ruthenium dioxide, is known to oxidize sulfides to sulfoxides and sulfones and transforms bicyclic sulfamidites (**60**) to sulfamidates (**61**) (Equation (8)) <90TA885>. Ruthenium dioxide in combination with sodium hypochlorite similarly oxidizes monocyclic sulfamidites (**62**) <92EUP497695> and this type of sulfamidite is also effectively oxidized by sodium periodate in the presence of a catalytic amount of ruthenium trichloride <90TA881, 91JOC3177>. The use of MCPBA or TPAP/NMO gives considerably lower yields <90MI 411-01>. Reaction of the isoquinolino-1,2,3-dithiazolium salt (**63**) with sodium nitrite in an acid medium

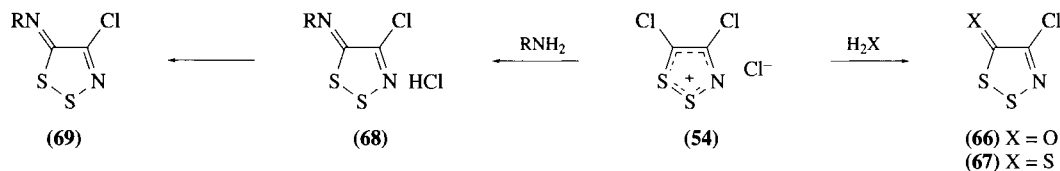


Scheme 6

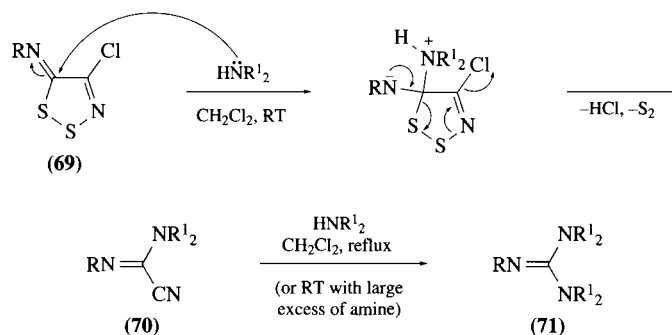
4.11.5.4 Nucleophilic Attack at Ring Carbon

Appel's salt (**54**) is rather susceptible to nucleophilic attack at C(5) <85CB1632>. Water and hydrogen sulfide in acetonitrile easily convert (**54**) into ketone (**66**) and thione (**67**); and indeed, (**54**) undergoes conversion into (**66**) on exposure to atmospheric moisture for a few hours. Even as weak a nucleophile as nitrate anion readily reacts with (**65**) to give (**66**) (other products being NaCl and NO₂Cl). Arylamines and aryl (or alkyl)sulfamides readily give the corresponding imines (**69**) (initially in the form of HCl-salts (**68**)) on reaction with (**54**). The more basic alkylamines fail to give meaningful results, but enter this reaction fairly well in the form of less basic *N*-trimethylsilyl derivatives (Scheme 7) <85CB1632>. Reaction of imines (**69**) with more basic amines (aliphatic, pyrrolidine, piperidine, morpholine) leads to ring opening presumably induced by the nucleophilic attack of amine at C(5) (Scheme 8) <92TL4963>. Yields of (**70**) and (**71**) are fair to high. Aromatic amines being less basic do not react. Ammonia (or aqueous NaOH <85CB1632>) transforms aryl and hetaryl substituted (**69**) into the corresponding cyanothioformamides (**72**) which are useful as herbicides and pharmaceuticals <85EGP212387>. *o*-Aminophenol with (**54**) gives (**73**) which is dehydrochlorinated by sodium hydride affording dithiazolobenzoxazine (**74**) (Scheme 9) <92JHC639>.

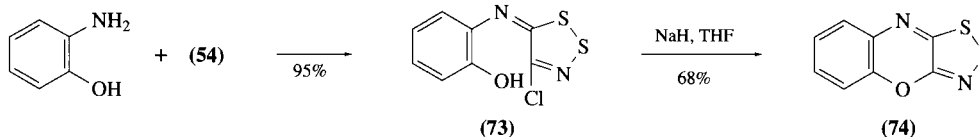
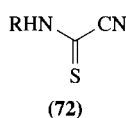
Other phenols attack through a carbon atom of the aromatic ring <85CB1632, 92JHC639>. Phenol itself reacts almost exclusively at its *para* position; yields of the isolated *para* (**75**) and the corresponding *ortho* products were found to be 82% and 8%, respectively <92JHC639>.



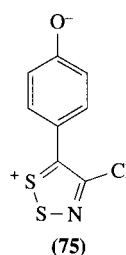
Scheme 7



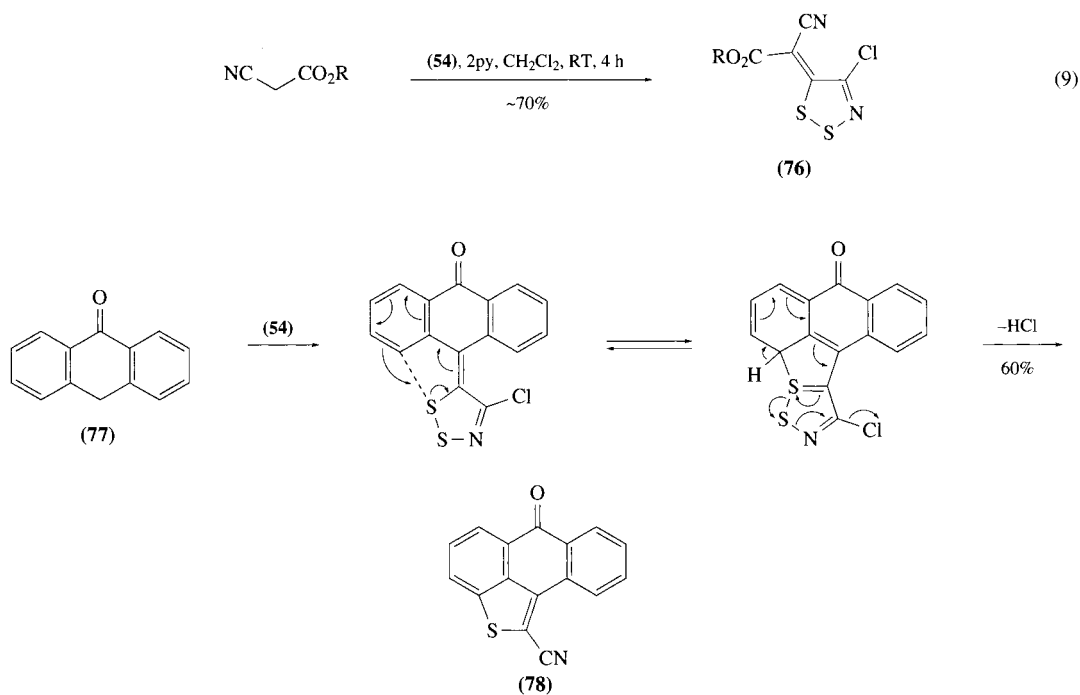
Scheme 8



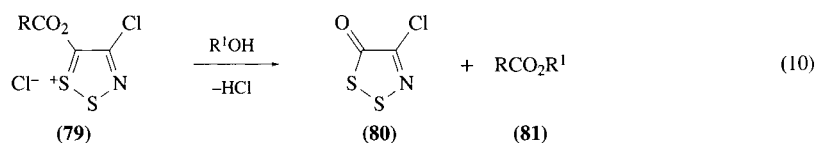
Scheme 9



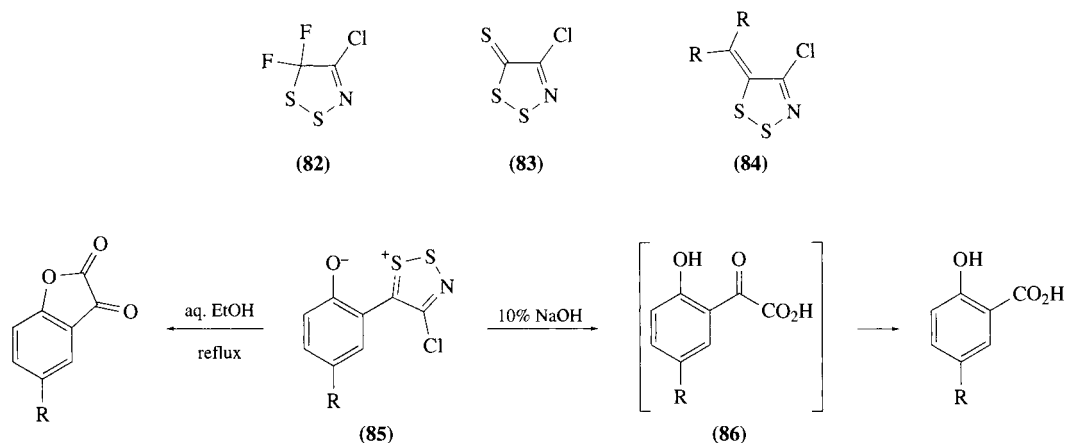
Compounds with an active methylene group displace the 5-Cl atom in (**54**) to give 5-methylene derivatives (**76**) (Equation (9)) <85CB1632>. In the case of anthrone (**77**) the initial product undergoes transformation to the fused thiophene (**78**) (Scheme 10) <92JHC639>. Diphenylmethane does not react with (**54**) <92JHC639>. Carboxylic acids in the presence of a base easily replace the 5-Cl atom in (**54**) and the acyloxy derivative formed (**79**) in turn reacts readily with an alcohol to give 4-chlorodithiazolone (**80**) and ester (**81**) (Equation (10)) <93TL2737>. This reaction sequence constitutes an extremely mild procedure for esterification of carboxylic acids. Amongst several bases tested, 2,6-lutidine gave the best results and yields were usually high with various carboxylic acids and alcohols.



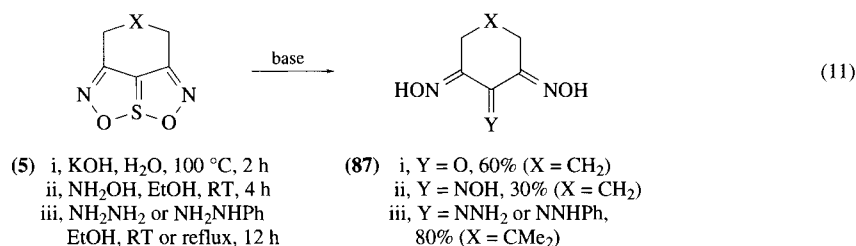
Scheme 10



Potassium fluoride in the presence of a crown ether fluorinates **(54)** exhaustively at the 5-position to give **(82)** leaving the ring intact ^{<85CB1632>}. Thione **(83)** readily reacts with diphenyldiazomethane to give **(84)** which is unstable and undergoes rearrangement (see Section 4.11.5.1); diazoacetate and diazomalonate react similarly at a higher temperature ^{<92JHC639>}. The 1,2,3-dithiazole ring in **(85)** is totally hydrolyzed in 10% aqueous sodium hydroxide or in boiling aqueous ethanol (Scheme 11) ^{<85CB1632>}. The intermediate α -ketocarboxylic acid corresponding to **(86)** was isolated in the hydrolysis of the *para*-bonded isomer **(75)** ^{<85PS(23)277>}. On reaction with base the heteropentalene **(5)** undergoes ring opening to a 1,3-dioxime with concomitant displacement of the sulfur atom by the attacking reagent to give **(87)** (Equation (11)) ^{<79BSF199>}.

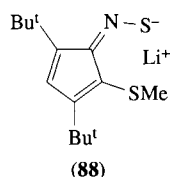


Scheme 11



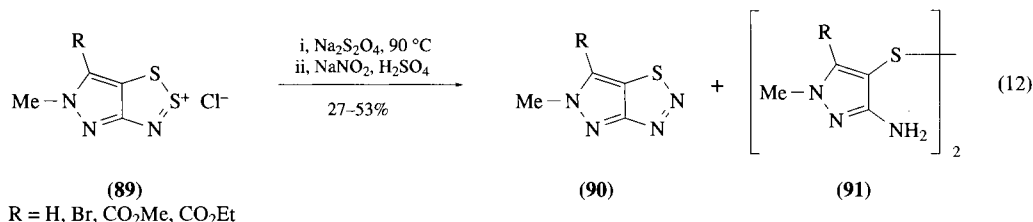
4.11.5.5 Nucleophilic Attack at Ring Sulfur

4,6-Di(*t*-butyl)-cyclopenta-1,2,3-dithiazole (**52**) undergoes cleavage at the SS bond to give (**88**) on reaction with methyl lithium at -80°C ; no nucleophilic addition at the pentafulvene moiety occurs <85TL189>.

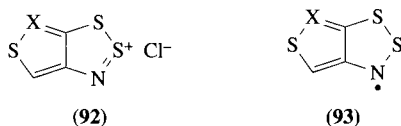


4.11.5.6 Reactions Involving Radicals, Electron-deficient Species, Reducing Agents and at Surfaces

Herz salts (**89**) made from 3-aminopyrazoles (Section 4.11.8.5) give pyrazolo[3,4-*d*]-1,2,3-thiadiazoles (**90**) when subjected to reduction by sodium dithionite followed by nitroization (Equation (12)) <84JOC1224>. If the reduction is carried out in an inert atmosphere the disulfide (**91**) is formed which upon nitroization gives (**90**) in 63% yield. Notably, benzo-fused Herz salts give benzo-1,2,3-thiadiazoles simply on treatment with nitrozing mixture <84CHEC-1(6)916>.

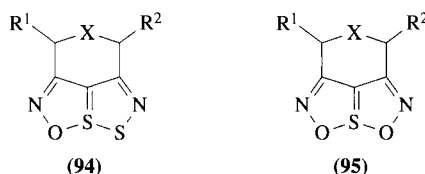


Herz salts of type (**92**; X = C, N) are reduced in high yield by zinc or sodium powder to the corresponding radicals (**93**) which persist in solution <82PS(13)107, 84CCC684, 85PS(23)277>. The radical can be oxidized by halogens back to the Herz salt. Both processes are also brought about electrochemically as exemplified by cyclic voltammetry of naphtho[2,1-*d*]-1,2,3-dithiazolyl <84CCC684, 85PS(23)277>.



The heteropentalenes (**94**) are reduced electrochemically to anion radicals (**94⁻**). The process is reversible as demonstrated by cyclic voltammetry using a carbon paste working electrode <85JCS(P2)1797>. The electrochemical half-peak reduction potential in aqueous methanol $E_p/2$ shows that ring units X = S, SO, SO₂ ($-E_p/2 = 437; 423; 383$ mV) increase the ability of (**94**) ($R^1 = R^2 = \text{H}$) to accept an electron compared with analogues with X = C-centered groups ($-E_p/2 = 513-543$ mV) presumably due to an appreciable negative inductive effect of the above S-centered groups. The same is true for (**95**): $-E_p/2 = 643; 573; 523$ mV when X = S, SO, SO₂ ($R^1 = R^2 = \text{H}$), whereas

$-E_p/2 = 643\text{--}723$ mV when $X = \text{C}$ -centered groups $\langle 85\text{JCS(P2)833} \rangle$. Introduction of phenyl and heteroaromatic substituents into the cyclohexane ring causes the reduction potential in both series to assume less negative values (i.e. facilitate the reduction) evidently owing to a negative inductive effect of the substituents. Again, the more pronounced positive resonance effect of oxygen compared with sulfur could be the reason for destabilization of anion radical $(95^{\cdot-})$ vs. $(94^{\cdot-})$ reflected in the more negative electrochemical potential of (95) , $X = \text{S}$, $R^1 = R^2 = \text{H}$ ($-E_p/2 = 543$ mV) vs. (94) , $X = \text{S}$, $R^1 = R^2 = \text{H}$ ($-E_p/2 = 473$ mV) $\langle 85\text{JCS(P2)1797} \rangle$.



$X = \text{CH}_2, \text{CHMe}, \text{CHPh}, \text{CMe}_2, \text{CHFuryl}, \text{CHThienyl}, \text{S}, \text{SO}, \text{SO}_2$
 $R^1, R^2 = \text{H}, \text{Me}, \text{Ph}, \text{py}$

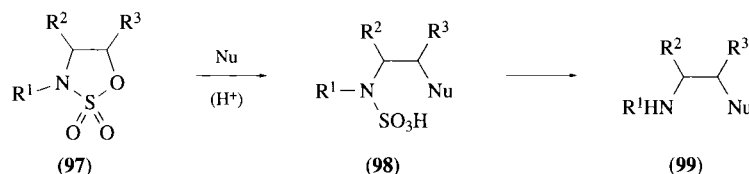
The reversibility of reduction of (94) and (95) combined with the low value of their negative reduction potentials makes these compounds effective in electron transfer to O_2 to give superoxide $\text{O}_2^{\cdot-}$. This is believed to be responsible for the herbicidal activity of bipyridyl herbicides, in particular Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) and Diquat (1,1'-ethylene-2,2'-bipyridinium dichloride). In fact the $-E_p/2$ values of (95) ($X = \text{S}, \text{SO}, \text{SO}_2, R^1 = R^2 = \text{H}$) are lower than or comparable to those of Paraquat and Diquat $\langle 84\text{BBA(765)236} \rangle$ and for the respective (94) are definitely lower $\langle 85\text{BBA(810)385} \rangle$. Owing to the above properties (94) and (95) catalyze effectively the reduction of oxygen by oxydoreductase; thus, the initial rate of O_2 liberation catalyzed by (95) is comparable to that catalyzed by Paraquat and Diquat, whereas (94) is ≈ 10 times more effective $\langle 85\text{BBA(810)385} \rangle$. Further, (94) and (95) effectively quench the emission of excited state chromophores enhancing the photochemical decomposition of water; thus, quenching rate constants for (95) are $\approx 6\text{--}8$ times larger than for Paraquat, being close to a diffusion controlled limit $\langle 85\text{ICA11} \rangle$. Finally, (95) changes photosynthesis in leaves by stimulating CO_2 fixation with the advantage over Paraquat that the active concentration is much lower and $\text{K}^+, \text{Ca}^{2+}, \text{Mg}^{2+}$ cations do not interfere with the effect; the best results were shown by (95) ($X = \text{S}, R^1 = R^2 = \text{H}$) $\langle 87\text{ZN(C)829} \rangle$.

Arylimines (68) in a protonated form are reduced by sodium cyanoborohydride to *N*-arylcyanoforamides $\langle 92\text{MI 411-01} \rangle$.

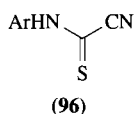
4.11.6 REACTIVITY OF NONCONJUGATED RINGS

4.11.6.1 Reactions of Hydrogenated Derivatives of Fully Conjugated Ring Compounds

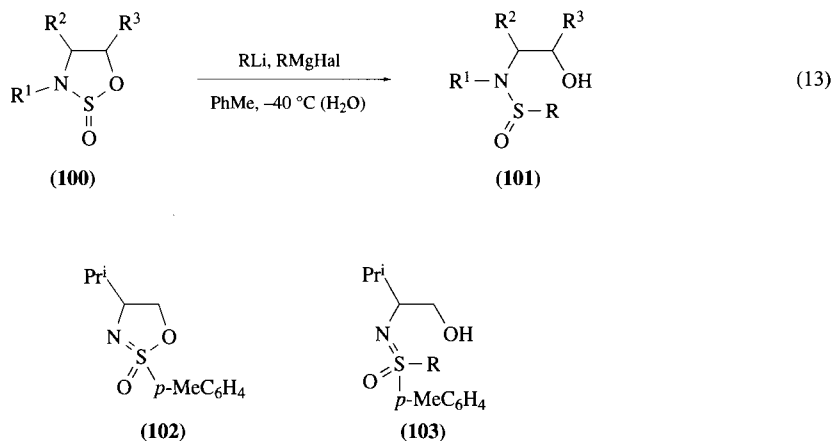
Cyclic sulfonamidates (97) are susceptible to nucleophilic substitution at an O-bonded carbon atom. The reaction may be stopped at (98) or (99) depending on reaction conditions and the nature of the nucleophile (Scheme 12). With amines as nucleophiles ethylenediamines were obtained ($R^1 = \text{Ar}$) $\langle 85\text{EGP219185} \rangle$. 2-Thienyl lithium ($R^1 = o\text{-chlorobenzyl}$) $\langle 92\text{EUP497695} \rangle$, $\text{F}^-, \text{N}_3^-, \text{CN}^-$, ($R^1 = p\text{-methoxybenzyl}, R^2 = \text{Bn}, R^3 = \text{H}$) $\langle 91\text{JOC3177} \rangle$ opened the ring to form correspondingly β -substituted ethylamino derivatives (96) . β -Functionally substituted α -amino acids were synthesized stereoselectively in fair to high yields when $R^2 = \text{CO}_2\text{Bu}^t$ ($R^1 = \text{Bn}, R^3 = \text{H}$), the nucleophiles being $\text{H}_2\text{O}, \text{N}_3^-, \text{CN}^-, \text{SCN}^-$, pyrazole, $^-\text{CH}(\text{CO}_2\text{Et})_2$ $\langle 90\text{TA881} \rangle$.



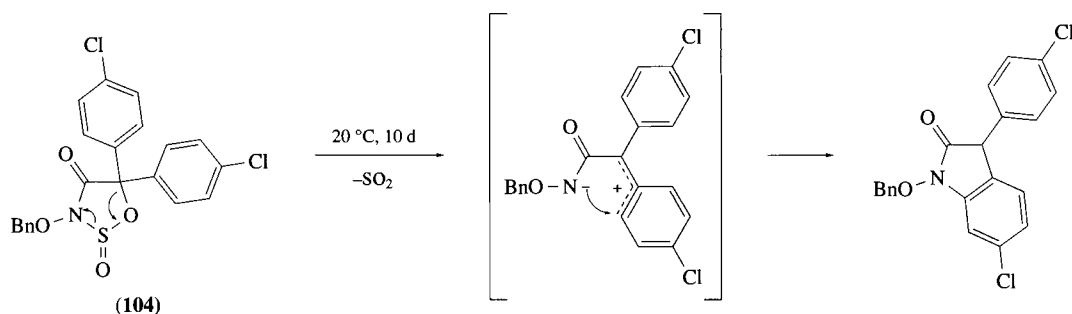
Scheme 12



Cyclic sulfinamidates (**100**) react with a nucleophile at their sulfur atom as demonstrated by formation of open-chain products (**101**) (Equation (13)) with Li- and Mg-organic reagents <91TL5885>. Yields and stereoselectivity at the sulfur atom are high. In the same manner interaction between 4-isopropyl-2-*p*-tolyl-4,5-dihydro-1,2,3-oxathiazole 2-oxide (**102**) and metalloorganic compounds occurs stereoselectively to give (**103**) in excellent yields <92TL6959>.



Appropriately substituted cyclic sulfinamidates (**104**) may undergo a fragmentation/cyclization involving an aryl substituent (Scheme 13) <86AP(319)1084>.



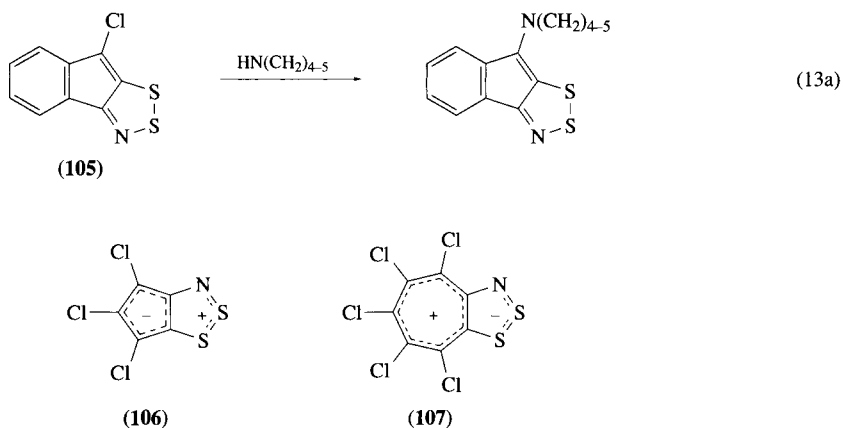
Scheme 13

4.11.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Sulfur atoms extraneous to the heteropentalene system in (**4**; X = S) can be oxidized by MCPBA to SO and SO₂ groups in 64–70% yields <85JCS(P2)833>. Arsenic pentafluoride coordinates to the thiadiazole ring of (**59**; R = Cl) as shown in (**15**) (x-ray analysis) <86ZN(B)162>, whereas (η^2 -ethene)bis(triphenyl-phosphane)platinum(0) inserts into the thiadiazole ring to give a new six-membered metallocycle <86CB366>.

Chlorinated cyclopenta-1,2,3-dithiazoles such as (**105**) and (**125**) (Section 4.11.8.5) are susceptible to nucleophilic substitution (e.g. Equation (13a)) <93JCS(P1)769>, whereas chlorinated cyclohepta-1,2,3-dithiazoles of the type (**127**)–(**129**) (Section 4.11.8.5) do not react with nucleophiles. This difference may be explained by the opposite charge separation between fused cycles in the two

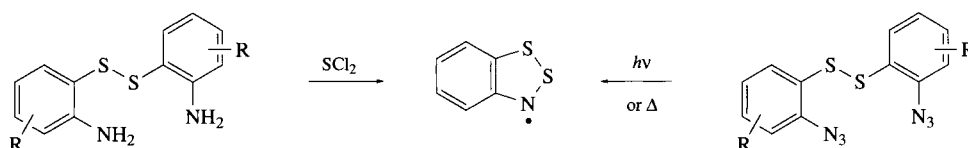
systems as demonstrated by resonance structures **(106)** and **(107)** <93JCS(P1)769>. The chlorine atom in **(131)** is also activated towards nucleophilic substitution <93JCS(P1)769>.



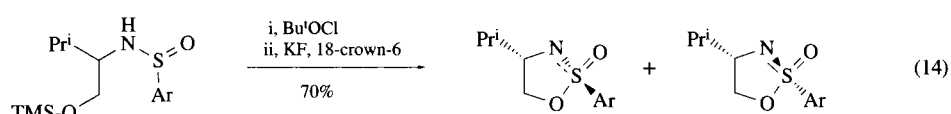
4.11.8 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

4.11.8.1 Formation of One Bond between Two Heteroatoms

Bis(*o*-aminoaryl)disulfides with SCl_2 afford stable 1,2,3-dithiazolyl radicals in good yield <84CCC684>. The same result is obtained by irradiation or thermolysis of bis(*o*-azidoaryl)disulfides (Scheme 14) <84CCC684>. The 1,2,3-oxathiazoline ring is formed effectively from 1-arylsulfonamido-2-trimethylsilyloxyethanes in a one-pot synthesis (Equation (14)) <92TL6959>. The diastereoisomers obtained were separated chromatographically and their structures assigned by x-ray analysis.

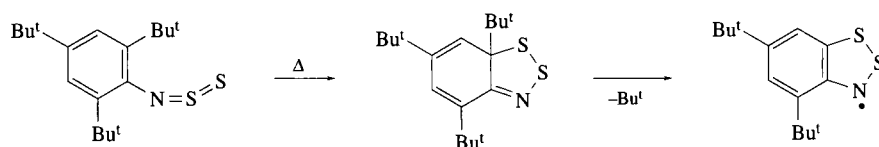


Scheme 14



4.11.8.2 Formation of One Bond Adjacent to a Heteroatom

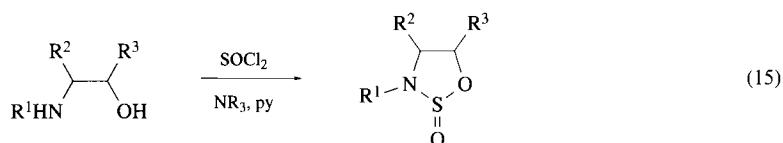
2,4,6-Tris(*t*-butyl)-*N*-thiosulfinylaniline when gently heated is transformed to a stable dithiazolyl radical with ejection of the *ortho-t*-butyl group (Scheme 15) <84CCC684>. The intermediate exists in equilibrium with the starting compound in normal conditions <84CHEC-I(6)909>.



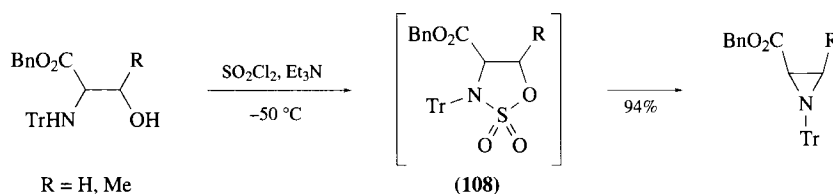
Scheme 15

4.11.8.3 Formation of Two Bonds: 4-Atom Fragments and Sulfur

The main way of achieving this type of cyclization involves the action of SOCl_2 on a vicinal aminohydroxyethane moiety in the presence of an amine as base (Equation (15)). The amino group substituent R^1 can be aryl <90JHC195>, arylmethyl <91JOC3177, 92EUP497695>, alkyl <86BSF397, 90TA881, 90TA885, 91TL5885>, or alkoxyl <86AP(319)1084>. When the ethane entity has one <90TA881, 90TA885, 91JOC3177> or two substituents <86AP(319)1084, 86BSF397, 91TL5885>, the reaction proceeds at 20°C to -30°C in benzene, toluene or CH_2Cl_2 . When $\text{R}^2 = \text{R}^3 = \text{H}$, the reaction mixture requires boiling in ethyl acetate <92EUP497695>. An elevated temperature may be needed also when R^2 represents carbonyl oxygen <84GEP(O)3311636>. Yields are fair. Fused bicycles <86BSF397, 90TA885> were obtained when a cyclic subunit was present in the starting aminoethanol structure. Reaction products were obtained often as a mixture of two stereoisomers at sulfur. 1,1'-Thionylimidazole may be substituted for SOCl_2 in this reaction <86AP(319)1084>.

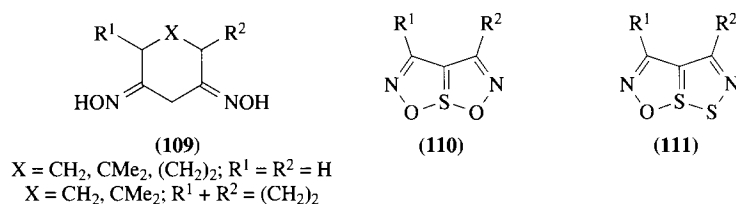


When SO_2Cl_2 was used as a reagent the corresponding five-membered cycle (108) breaks down and so provides a useful route to aziridines (Scheme 16) <92TL3013> see also <91JOC3177>.

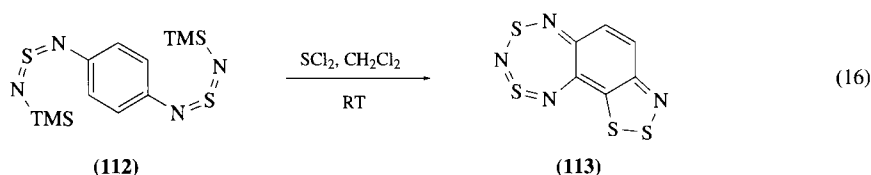


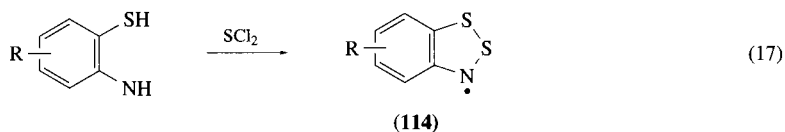
Scheme 16

Heteropentalene systems (94) and (95) are formed from the cyclic 1,3-dioximes (109) and SCl_2 at -60°C in THF <72TL1835, 79BSF199, 83JAP8300987, 85JCS(P2)833, 89JAP8966120>. Acyclic 1,3-dioximes usually give poor yields of (110) and (111) but the parent of the series (110; $\text{R}^1 = \text{R}^2 = \text{H}$) was reported <79BSF199>.



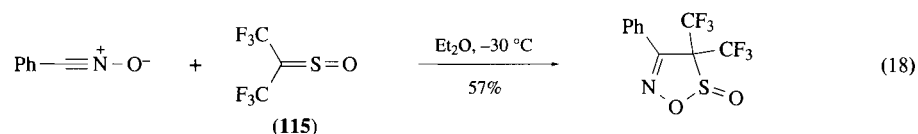
A very unusual reaction which formally belongs to this section occurs with aromatic bis(sulfur-diimines) (112) and SCl_2 (Equation (16)) <83CJC1562>. This gives the dithiazole (113) in 1% yield together with a polymer $(-\text{SNSNC}_6\text{H}_4\text{NSN}-)_n$. *o*-Mercaptophenyl- and -naphthylamines with SCl_2 give stable 1,2,3-dithiazolyl radicals (114) in good yield (Equation (17)) <84CCC684>. Strangely enough the same radicals are obtained when thiobisanilines are gently heated neat or in solution <84CCC684>.





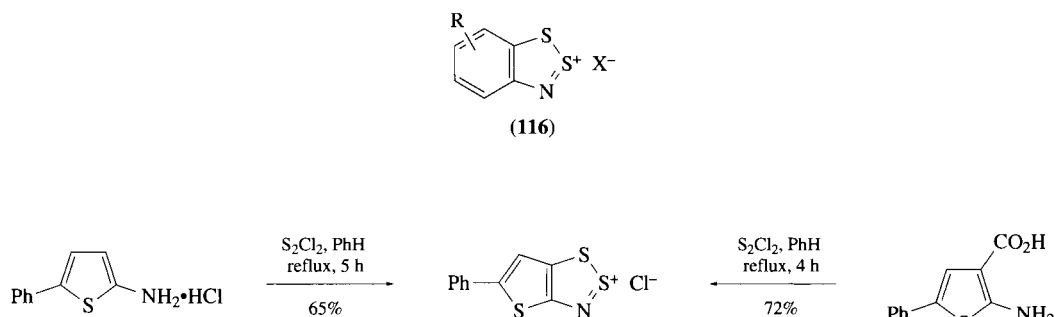
4.11.8.4 Formation of Two Bonds: [3 + 2] Atom Fragments by Cycloaddition

A 1,2,5-oxathiazoline 2-oxide is obtained by 1,3-cycloaddition of benzonitrile oxide to bis(trifluoromethyl)sulfine (115) (Equation (18)) <88CB75> (see Section 4.11.10).



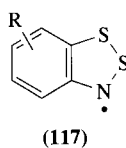
4.11.8.5 Formation of Two Bonds: [3 + 2] Atom Fragments by Other Processes

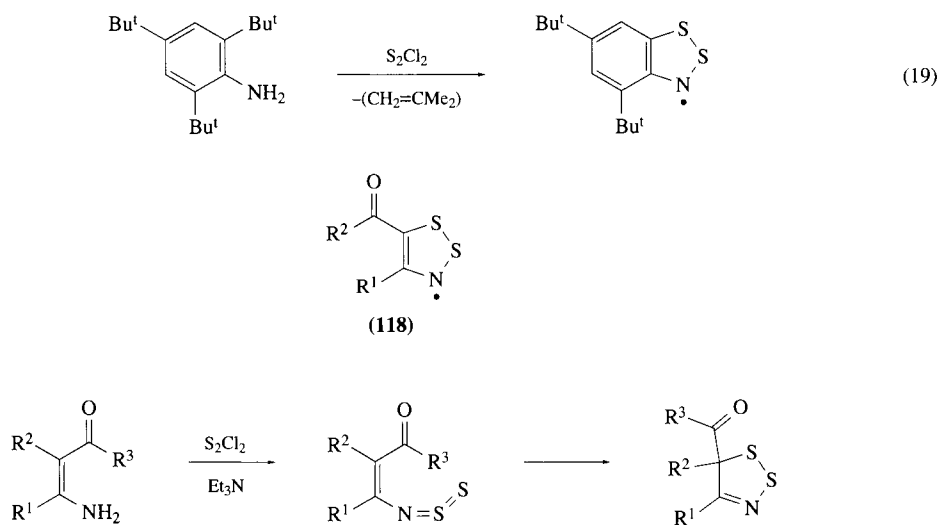
The best known reaction of this type is the synthesis of fused dithiazolylum (Herz) salts with an aromatic or heteroaromatic fused ring (of type (116)) by action of S_2Cl_2 on aryl- and hetaryl amines (CHEC-1, v.6, p.395). A new example is provided by formation of the Herz salt (63) from 7-aminoquinoline <89JMC1566>. A few examples are known where the amino group is in the heterocyclic ring itself, for example Scheme 17, although in several cases such reactions failed <79KGS477, 84JOC1224>. The reactions shown in Scheme 17 were complicated by chlorination when carried out in AcOH.



Scheme 17

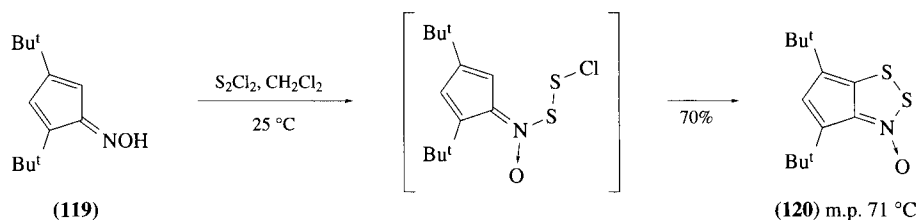
1,2,3-Dithiazolyl radicals of type (117) were shown to be intermediates in the Herz reaction in the course of an extensive investigation by Mayer *et al.* <84CCC684, 85PS(23)277>. The reaction has been modified to provide a route to such dithiazolyls as a new class of stable radicals. Aryl- and hetaryl amines do not react when the ring is π -electron deficient, e.g. nitro substituted. On the other hand the tendency of these radicals to be formed is so high that a *t*-butyl group can be extruded in the process (Equation (19)) <85PS(23)277>. Enaminoketones are transformed into stable radicals of type (118) by this method <84CCC684>. However in the presence of a base (NEt_3), cyclization to dithiazolines occurs through the intermediacy of thiosulfinylamines which could be isolated (Scheme 18) <81BCJ3541, 85PS(23)277>.



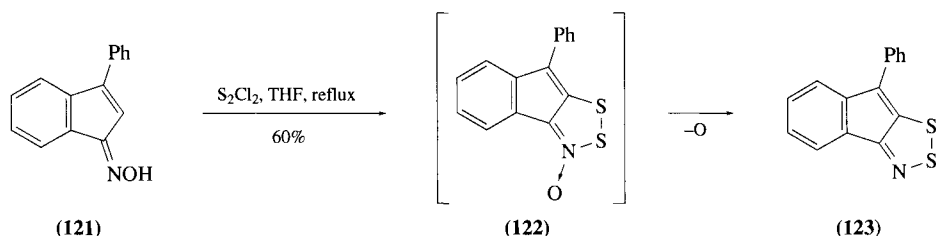


Scheme 18

A stable 10π -electron cyclopenta-1,2,3-dithiazole system (**120**) was prepared from the cyclic oxime (**119**) and S_2Cl_2 (Scheme 19) <85TL189>. In the case of 1-oximino-3-phenylindene (**121**) the corresponding *N*-oxide (**122**) was only an intermediate which underwent deoxygenation (Scheme 20) <92JHC639, 93JCS(P1)769>. This reaction has been improved and extended to other cyclic oximes including saturated ones (**124**) and (**126**) (Scheme 21) <93JCS(P1)769>. The greatest improvement came from the use of a base, especially ethyldiisopropylamine (Hünig's base, HB), which led to the highest yields (e.g. (**123**): 80% at 4°C). Introduction of chlorine atoms into the five-membered carbocycle, e.g. (**125**), demonstrates the chlorinating capacity of S_2Cl_2 and in the case of unsaturated substrates such as (**124**) and (**126**) its role as an oxidant is apparent. The multiple chlorination and oxidation steps involved in the formation of (**125**) suggest a complex multistage mechanism, which makes the reaction especially vulnerable to reaction conditions and could be responsible for the depressed yield. Another cause of the latter is the destructive effect of S_2Cl_2 on (**125**). When the carbon ring is protected with substituents as in (**119**) and (**121**) chlorination is prevented.

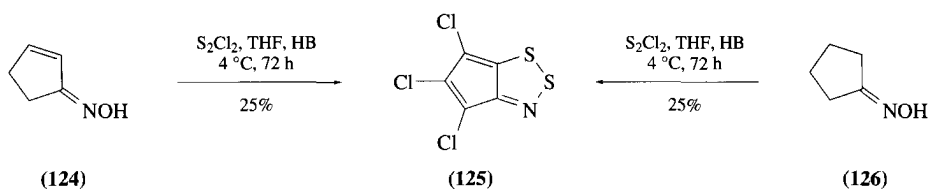


Scheme 19



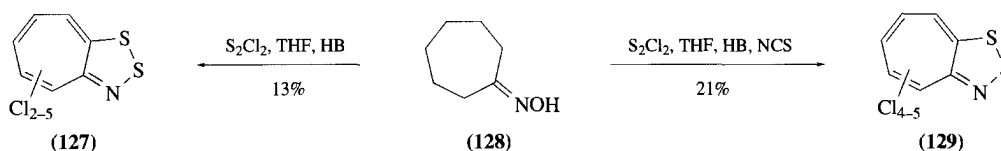
Scheme 20

The reaction proceeds similarly with seven-membered cyclic oximes to give cyclohepta-1,2,3-dithiazoles (**127**) and (**129**) (Scheme 22) <93JCS(P1)769>. To effect chlorination up to 15 equivalents of S_2Cl_2 are needed; polychlorination is assisted by NCS. The noncyclic α,β -unsaturated oxime (**130**)

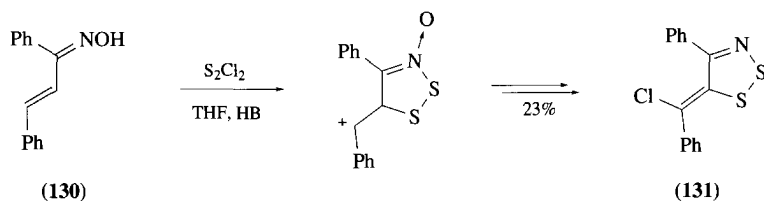


Scheme 21

also enters this reaction to give (131) (Scheme 23) <93JCS(P1)769>. When cyclic 1,3-dioximes (109; X = CH₂) were used, tricyclic fused systems (94) and (95) were obtained in which heterocyclic pentalene systems are incorporated <79BSF199, 83JAP8300987, 84USP4440564, 85JCS(P2)1797, 87JAP8736388>. A great number of these variously substituted compounds and also bicyclic heteropentalenes, (111; R¹ = R² = Ph) were prepared <83JAP8300987>. The reaction is preferably conducted in an inert atmosphere (N₂, Ar).

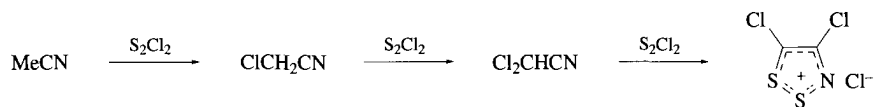


Scheme 22



Scheme 23

The extensively studied Appel's salt can be produced by prolonged chlorination of acetonitrile with S₂Cl₂ (Scheme 24) <85CB1632>. For preparative purposes chloroacetonitrile gives the best yield (85%). Another simple method for synthesis of Appel's salt may be provided by reaction of S₂Cl₂ with ethylamine (yield and conditions of the process not disclosed) <85PS(23)277>.

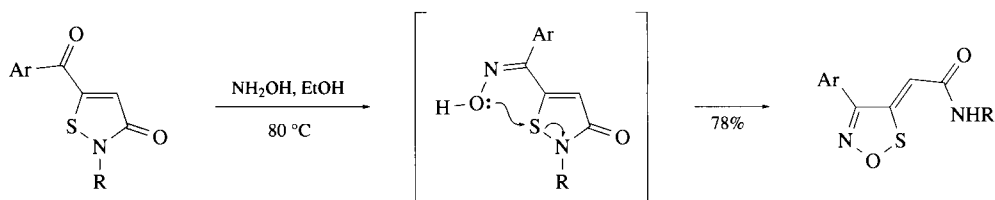


Scheme 24

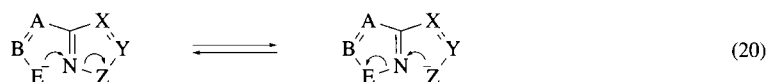
4.11.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Oximation of a carbonyl group adjacent to an isothiazole ring unexpectedly led to a smooth rearrangement to the 1,2,5-oxathiazole ring (Scheme 25) <84JHC1679>. This process closely resembles the generalized Boulton–Katritzky rearrangement of the azole series (Equation (20)) <74JHC45>.

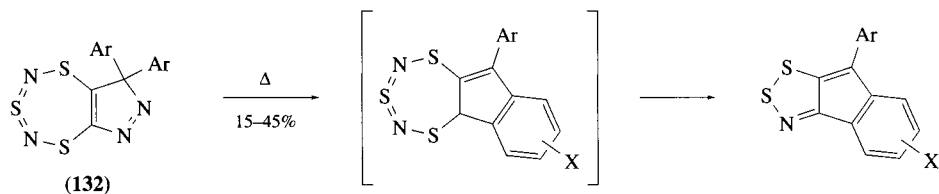
Replacement of the nitrogen atom by sulfur further extends the scope of the generalized Boulton–Katritzky rearrangement.



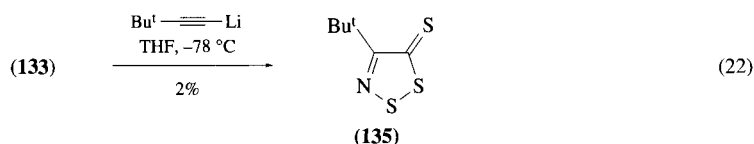
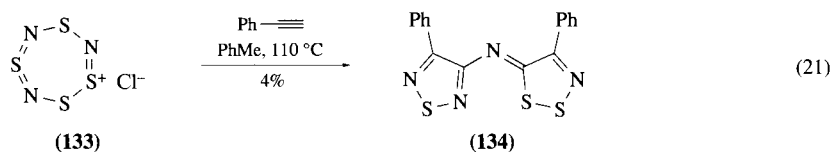
Scheme 25



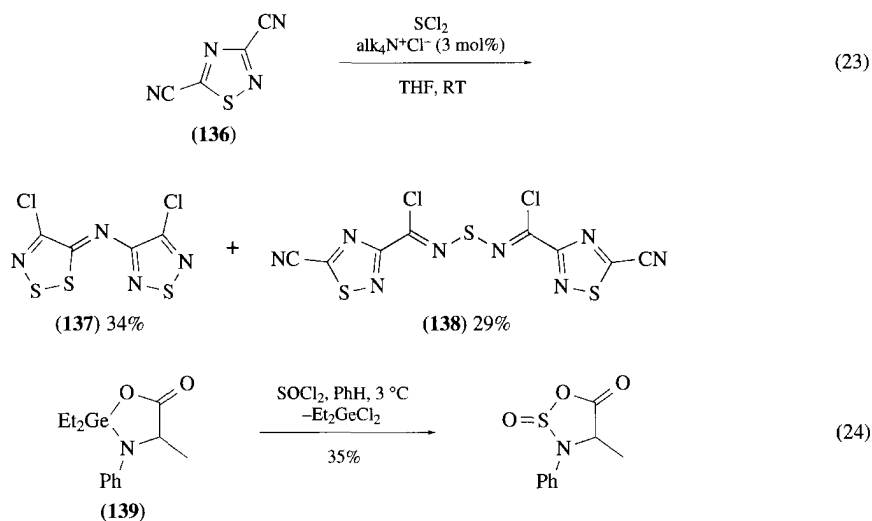
Pyrazolotrithiadiazepines (**132**) are converted to condensed 1,2,3-dithiazoles on heating, either neat (210 °C, 5 s) or in solvents (140–180 °C, 3–20 min) (Scheme 26) <91JCS(P1)311>. A suggested mechanism for this highly involved reaction includes rupture of both heterocycles with extrusion of heteroatomic fragments. When heating in a solvent was interrupted the intermediate shown was isolated and in turn transformed separately into the end product. An analogous nonfused heterocycle (**133**) heated with phenylacetylene in boiling toluene gave a 1,2,3-dithiazole derivative (**134**) (together with derivatives of 1,2,5-thiadiazole and 1,3,2-dithiazole) (Equation (21)) <89JCS(P1)2489>. Li salts of phenyl- and *t*-butyl acetylenes were more reactive, the latter giving at a low temperature the 1,2,3-dithiazole derivative (**135**), again in poor yield (Equation (22)) <89JCS(P1)2489>.



Scheme 26



3,5-Dicyano-1,2,4-thiadiazole (**136**) with SCl_2 gives rise to the 1,2,3-dithiazole (**137**) in an as yet obscure process. A second, more easily explained product (**138**) was also isolated (Equation (23)) <86ZN(B)162>. Germanaioxazolidines (**139**) are transformed into oxadiazolidines on reaction with SOCl_2 , a reaction which formally involves exchange of the Et_2Ge entity by a sulfoxide group (Equation (24)) <90PS(53)411>.



4.11.10 SURVEY OF RING SYNTHESIS

Synthesis of 1,2,3-dithiazoles is the most extensively studied. The widely used and very long-known Herz reaction of arylamines with S_2Cl_2 to give benzo-1,2,3-dithiazolium salts (Section 4.11.8.5) has been extended to hetarylamines (Scheme 17). More importantly, a new impetus for its investigation and development was provided when benzo-1,2,3-dithiazolyl radicals were shown by Mayer and co-workers to be intermediates. The reaction in a modified form was transformed by the above authors to an effective method for synthesis of this new class of stable radicals. When applied to acyclic enaminoketones the thiosulfinylamine precursor of the free radical could be isolated (Scheme 18). It was also extended to cyclic and acyclic oximes to afford fused and monocyclic 1,2,3-dithiazoles of nonradical nature, e.g. (125), (127), (131), etc. Use of cyclic and acyclic 1,3-dioximes in this reaction opened the way to numerous oxadithiadiaz- and (as a by-product) dioxathiadiazapentalenes (94), (95), (110), (111), which had been inaccessible earlier.

The reaction between acetonitrile and S_2Cl_2 to give 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) discovered by Appel and his co-workers in the mid-1980s provided an important new route to this versatile compound (Scheme 24).

Reagents other than S_2Cl_2 may be used to convert *o*-mercaptoaminoarenes to the 1,2,3-dithiazolium system: $SOCl_2$ to give 1,2,3-dithiazolium salts (<84CHEC-I(6)936>) and SCl_2 to produce benzo-1,2,3-dithiazolyl radicals (114). The latter reagent unexpectedly led to a 1,2,3-dithiazole ring in the reaction with 3,5-dicyano-1,2,4-thiadiazole to give (137) and with bis(sulfurdiimino)benzene (112) to give (113).

Novel routes to 1,2,3-dithiazole ring systems from polysulfurdi- and triazepines discovered by Rees and co-workers involve their reactions with acetylenes to give (134) and (135) and the thermolysis of (132).

Examples of the formation of the 1,2,3-oxathiazole ring involve almost exclusively the conversion of *vic* amino hydroxy compounds to the *S*-oxide derivatives. The formal *S*-oxide of the product may be present as a substituent on the nitrogen or oxygen of the hydroxy amine and cyclization effected by dehydration with dcc (<84CHEC-I(6)931>) or Bu^tOCl (Equation (14)). In the 1980s a direct cyclization of the amino hydroxy compounds by $SOCl_2$ was extensively developed by various research groups (Equation (15)). Reaction of 2-(α -hydroxybenzyl)aziridines (<84CHEC-I(6)939>) and O,N-germanium derivatives (<84CHEC-I(6)938>, (139)) with $SOCl_2$ may be assigned to this category. An interesting innovation was the successful use of 1,1'-thionylimidazole instead of $SOCl_2$. Attempts to use SO_2Cl_2 to obtain 1,2,3-oxathiazole *S*-dioxide ended with high yield of an aziridine derivative presumably via the expected *S*-dioxide (Scheme 16).

A different approach to 1,2,3-oxathiazole *S*-oxides involves the reaction of β -bromo-sulfonamides with $KOBu^t$ (<84CHEC-I(6)931>).

1,2,5-Oxathiazoles are produced from sulfines in 1,3-cycloaddition reactions with nitrones (<84CHEC-I(6)934>). With nitrile oxides only those sulfines which have sufficiently strong electron-withdrawing substituents such as CF_3 (115) display the desired regioselectivity; otherwise 1,3-

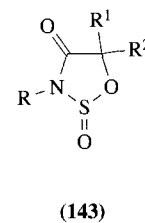
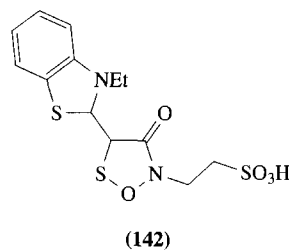
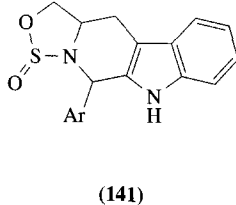
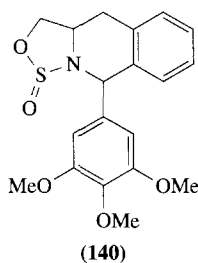
addition proceeds in the opposite direction to give 1,3,5-oxathiazoles <84CHEC-I(6)934>. The isothiazolone ring containing an appropriately located α -oximinoalkyl substituent rearranges smoothly to the 1,2,5-oxathiazole ring (Scheme 25), formally an example of the generalized Boulton–Katritzky rearrangement. The reaction of cyclic and acyclic 1,3-dioximes with SCl_2 to give dioxathiadiazapentalenes and (as a by-product) oxadithiadiazapentalenes (**95**) and (**94**) containing the condensed 1,2,5-oxathiazole ring has been extensively elaborated since 1972. Thus, reactions of 1,3-dioximes with S_2Cl_2 (see above) and SCl_2 complement each other.

4.11.11 IMPORTANT COMPOUNDS AND APPLICATIONS

Dioxathiadiazapentalenes of the general formula (**5**) constitute a new chemical family of herbicides. The principle of their action is that of the known bipyridyl herbicides, especially Paraquat and Diquat, and consists in generating toxic peroxides in plants (Section 4.11.5.6). The ease of transformation into anion radicals responsible for peroxide production is measured by electrochemical half-peak reduction potential which for derivatives (**5**; $\text{X} = \text{CH}_2, \text{S}, \text{SO}, \text{SO}_2$) is comparable with that for Paraquat and Diquat <84BBA(765)236>. The most phytotoxic derivative (**5**; $\text{X} = \text{S}$) <87ZN(C)829> is less toxic than Paraquat to animals: $LD_{50} \approx 250\text{--}1000 \text{ mg kg}^{-1}$ in rats and $LD_{50} 1000 \text{ mg kg}^{-1}$ in mice <84BBA(765)236>. The new herbicides may be used in the preemergency (soil drench) and postemergency (foliar spray) modes <84USP4440564>. Consumption of (**5**; $\text{X} = \text{CH}_2$) is 2 kg acre^{-1} <83JAP8300987>.

These heteropentalenes are also toxic to bacteria cells *Escherichia coli*. Penetrating into the cells they are reduced by an enzyme system and then convert O_2 to toxic O_2^- and H_2O_2 returning themselves to the initial state <89MI 411-01>. Activity as an oxygen promotor with catalase and superoxidase was found for (**5**; $\text{X} = \text{S}$) in concentrations down to 0.005 mM <89JAP8966120>.

Cytostatic <87JAP87283960> and cytotoxic <90EUP357122> properties were registered for (**140**) and (**141**), respectively. 1,2,3-Oxathiazoline-3-oxides (**143**) were claimed to be used as pesticides <84GEP(O)3311636>. An improved preservation of color was secured at high temperature in photographic emulsions by the use of (**142**) <84JAP84166950>.



4.12

1,3-Oxa/thia-2-azoles

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4.12.1 INTRODUCTION

Research into 1,3-oxa/thia-2-azoles has expanded substantially with about 50 references in the literature in the period 1982 to 1994 compared with about 20 between the early 1960s and the early 1980s.

1,3,2-Dithiazoles are by far the best represented of the three types of 1,3-oxa/thia-2-azole systems covered in this chapter. New synthetical possibilities have appeared for 1,3,2-dioxazole types but as before there are few references to the 1,3,2-oxathiazole systems.

One of the major new areas of study concerns the stable radicals and cations of 1,3,2-dithiazoles

and their theoretical investigation, synthesis, reactions, and applications have received wide attention. X-ray and electron diffraction structural analysis has made a substantial contribution to all kinds of 1,3,2-dithiazoles, and electron spin resonance (ESR) spectroscopy to their radical species. Photolysis and thermolysis studies have also provided additional insight into these systems.

The main structural types of the azoles are shown in Figure 1. Most have become experimentally available; those not yet known are indicated in brackets. The basic parent structures shown in rows **A** and **B** are termed azoles and azolidines, respectively. Row **C** indicates the known oxo, thioxo, and imino structures, the first and second in the row being termed azolones, the third structure azolidinedione. Rows **D** and **E** demonstrate the known cations: azolium and azolidinium, respectively. Row **F** shows the known free radicals: azolyls and azolidinyls. The structures in rows **C–F** may be also depicted by alternative canonical forms as in rows **G–I**, or in a generalized form as shown by the right-hand formulae of rows **H** and **I**. Structures which may be presented in several valence forms are printed in various parts of the chapter in different forms depending on the context and taking account of the representation in an original source.

Benzofused structures are known for 1,3,2-dithiazoles **A**, their cations **D** and radicals **F**.

S-Mono- and *S*-dioxides have been reported for **A** and **B** left-hand structure types.

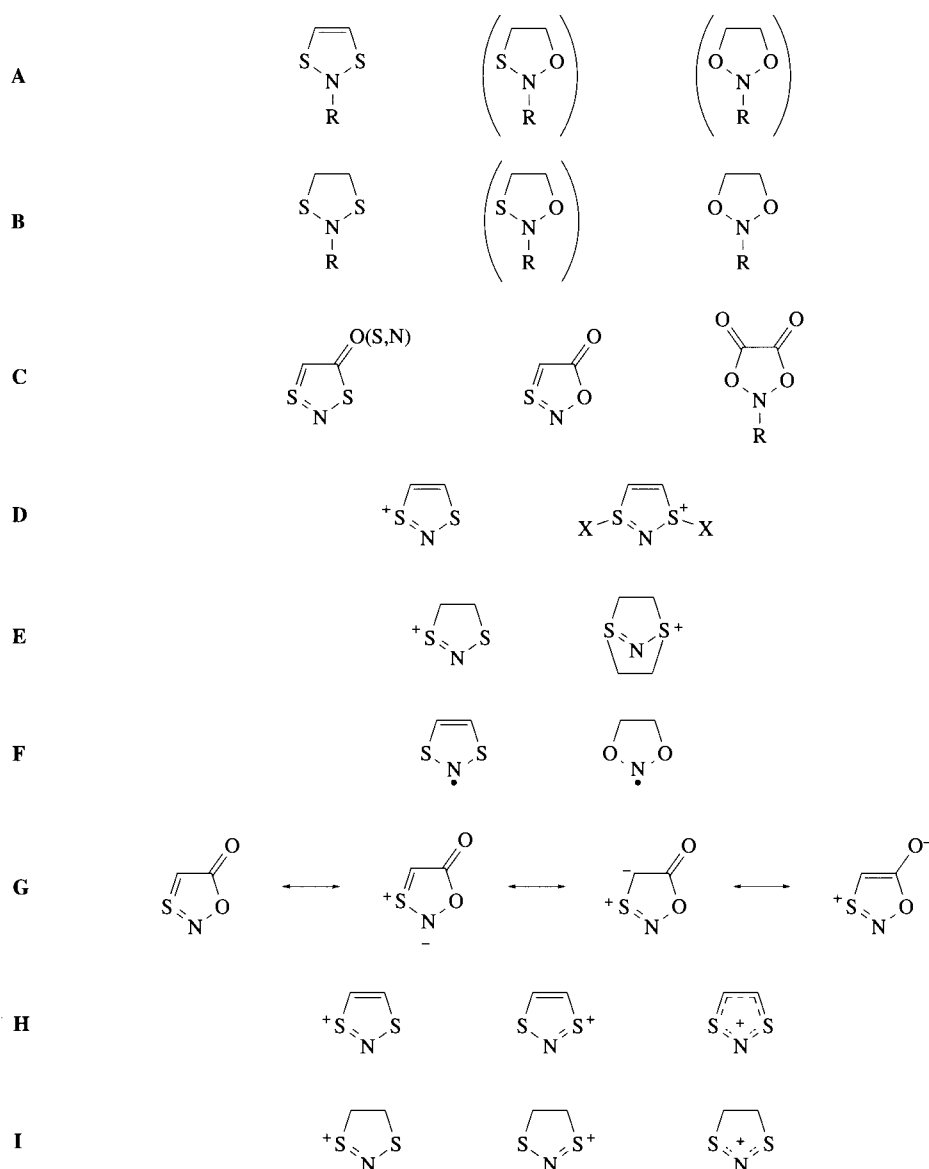


Figure 1 Main structural types of azoles.

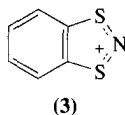
4.12.2 THEORETICAL METHODS

Calculations carried out on basis of INDO and GAUSSIAN 76 programs showed the 1,3,2-dithiazolyl cation (**1**) to have some aromatic character but not sufficient to prevent its easy reduction to the radical (**2**); the calculated bond lengths and angles agreed well with those derived experimentally by x-ray diffraction <83CC807, 85JCS(D)1405>.



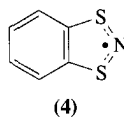
Calculated stabilization energies $E_{\text{radical}} - E_{\text{cation}}$ (here E is the binding energy of a radical and cation) are negative and indicate that the radicals are more stable than the cations in the absence of their counterions <85JCS(D)1405>.

CNDO-2 calculations for (**3**) demonstrated its five occupied orbitals to be lower on the energy scale than those in naphthalene, because of the positive charge. The cation (**3**) may be classified as a 10π -electron system of the heteronaphthalene type. The charges on S (+0.6) and N (−0.3) should be taken to mean that contact with an anion is made by S, not by N atoms <90IC4821>.



The INDO and GAUSSIAN 76 calculations of ESR constants and molecular geometry values in the radical (**2**) showed a fair agreement with experiment. The very low substituent effect on a_{1+N} constants implies that there is no significant delocalization of an unpaired spin density from the heterocycle to substituent <83JCS(F1)925>.

The radical (**4**) appears to be a weakly associated dimer in the solid state according to CNDO-2 calculations. Orbitals of the two molecules interact forming common bonding and antibonding orbitals, hence the dimer is classified as a two-center, two-electron, $\pi^*-\pi^*$ system (**25**). Thermodynamically the dimer (**25**) is more stable than the alternative structures in which the monomers are connected by a S^+-S^+ or $N-N$ bond. The dimerization energy for (**25**) seems to be not more than 5 kcal mol^{−1}. Total energy calculations for the dimer showed the energy minimum to be with the N atoms bent out of the C_2S_2 planes by 8.5° (cf. 11° in x-ray experiment (Section 4.12.3.1)). The same calculations for a monomer produced a shallow curve indicating a highly deformable C_2S_2N ring <90IC4821>. The latter property is in line with a high thermal parameter in the direction perpendicular to the ring as revealed by electron diffraction study <87CC66>.



Ab initio calculations by 4-21G and TZ + P methods helped to rationalize the conformation of 4,4,5,5-tetrafluoro-1,3,2-dithiazolidine (**7**) revealed experimentally in gaseous and solid states. The energy minimum was found for a twist envelope conformation with the S atom bent out of the (nearly) planar arrangement of the other four atoms; with the N atom bent out instead the energy was only 1 kcal mol^{−1} more on account of two eclipsed CF₂ groups repulsion. In fact the former conformation dominated in the gaseous state, while both were equally involved in the crystal, where the small energy barrier may be easily compensated by packing effects <93JPC9625>.

A strong dependence was revealed by MNDO calculations (equivalent in this respect to *ab initio* method) between the dihedral angle of the carbonyl oxygen with respect to the plane of 1,3,2-dithiazolyl radical ring in 1,3,2-thiazolyl esters (**35**) and spin density on ring S atoms as reflected in ESR experiments (Section 4.12.3.6) <88MRC755>.

Radicals (**5**) and (**6**) were shown by GAUSSIAN-82 calculation to be stable. They should be easily (activation energy 1.3–2.0 kcal mol^{−1}) derived from the parent NH compounds by elimination of H atoms and ought to be highly reluctant (activation energy > 33 kcal mol^{−1}) to N—N dimerize <88CCC2128>. These expectations were largely confirmed for the radical (**5**) synthesized at almost the

same time by Kostyanovsky and co-workers (89IZV1819). The cation derived from (5) by removal of the unpaired electron (calculated ionization energy 8.86 eV) should be more stable by ≈ 130 kcal mol $^{-1}$ (88CCC2128). On the energy surface calculated by methods GAUSSIAN-80 and -83 for reaction between ethylene and NO $_2^+$ in gaseous phase the cation in question occupied an energy minimum as a transition state (84JA1074).



4.12.3 EXPERIMENTAL STRUCTURAL METHODS

4.12.3.1 X-ray and Electron Diffraction

4,4,5,5-Tetrafluoro-1,3,2-dithiazolidine (7) has an envelope conformation in the gas phase (electron diffraction study) and in the crystal (x-ray structural analysis) (93JPC9625). The S atom is located in the flap in the first case; S and N play the part alternatively in the second case, both conformational varieties comprising the unit cell while being interconnected by N $\cdots$ H—N bonds. A quantum chemical calculation was made to rationalize these structural features (Section 4.12.2).

All ring bonds in (7) are close to single bond length (see Table 1). When CC is a double bond (8), other ring bonds become shorter. The feature of this molecule is a long bond with Ts group NS 1.733 Å. The dihedral angle between the N flap and the rest of the envelope-like ring is 41.7°.

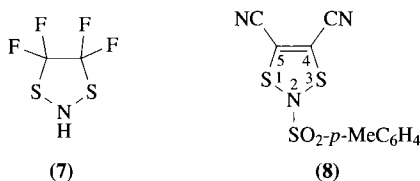


Table 1 X-ray data for 1,3,2-dithiazoles.

Structure	Ring bond lengths (Å)					Ref.
	C—C	C5—S1	C4—S3	S1—N2	S3—N2	
(7) ^a	1.571	1.802	1.802	1.715	1.715	93JPC9625
(8)	1.332	1.754	1.765	1.712	1.704	89CB385
(9) ^b	1.420	1.648	1.717	1.588	1.621	87CSC2468
(10) ^c	1.437	1.673	1.768	1.609	1.568	89CC1134, 84CC57
(11) ^c	1.416	1.663	1.752	1.596	1.629	89CC1134
(12) ^c	1.409	1.691	1.733	1.600	1.625	89CC1134
(13) ^c	1.414	1.680	1.753	1.594	1.618	89CC1134
(15) ^a	1.449	1.722	1.724	1.611	1.610	85CC1654
(16)	1.492	1.808	1.815	1.609	1.595	90CJC852
(17)	1.511	1.804	1.814	—	1.634	86CC966
(18)	1.399	1.670	1.679	1.589	1.612	85JCS(D)1405
(19)	1.356	1.689	1.712	1.617	1.585	91CC369
(20)	1.411	1.708	1.708	1.598	1.598	90IC4821
(21) ^d	1.324	1.749	1.749	1.634	1.634	87CC66
(22) ^a	1.368	1.726	1.730	1.644	1.637	90CB881
(24)	1.394	1.741	1.746	1.644	1.648	90IC4821, 87CC66
(26)	1.428 ^e	1.711 ^f	1.716	1.617 ^f	1.623	88JCR(S)358

^aMean of independent molecules in the unit cell. ^bC=S, 1.668. ^cC(4)=N(6)—C(7): (10) 1.297, 1.410; (11) 1.342, 1.335; (12) 1.351, 1.329; (13) 1.353, 1.316. ^dElectron diffraction in the gas phase. ^eMean of 1.421 and 1.435. ^fMeans of 1.708–1.714 (CS) and 1.616–1.618 (SN) in one ring (means of 1.711–1.720 (CS) and 1.617–1.629 (SN) are for the other ring).

An exocyclic double bond makes the SN bond lengths uneven reflecting different valence states of two ring S atoms, the one on the exocyclic double bond side of the ring having longer bonds (9)–

(9)
(10)

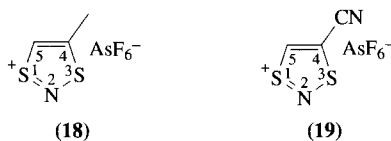
(11) $n = 1$
 (12) $n = 2$

(13)
(14)

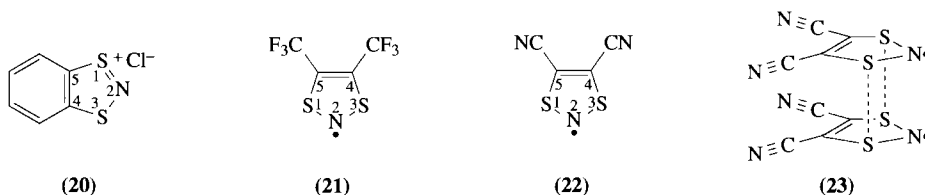
(15)

(16) (16a) (17)

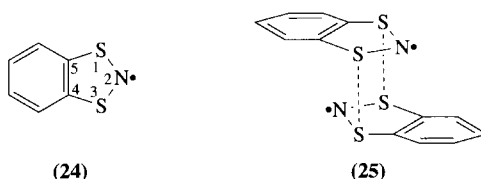
The monocyclic 4,5-bis(trifluoromethyl)-1,3,2-dithiazolyl radical (**21**) in the gas phase (electron diffraction) is planar, completely symmetrical, with CS and SN bonds somewhat longer than in



monocyclic cations (18) and (19), but with the CC bond shorter apparently by reason of π -SOMO nature <87CC66>. The analogous dicyano-substituted radical (22) in the solid state has all ring bonds longer than the monocyano cation (19). A more important feature, however, is a distinct dimeric association by $S \cdots S$ (3.14 Å) intermolecular bonding (23), the contacts being shorter than van der Waals radii sum (3.48 Å) and longer than a single SS bond (1.89–2.16 Å). The two molecules are practically parallel to each other, the N atom is slightly (by 4.4°) bent out of ring plane <90CB881>.

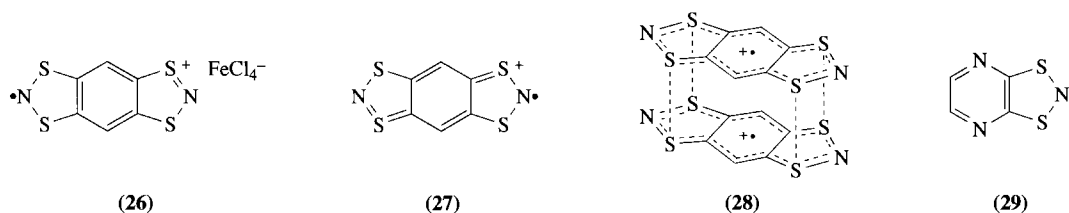


The benzo-1,3,2-dithiazolyl radical (24) again has CS and SN bonds longer and CC bond shorter than its cation counterpart (20). The molecules are also linked by $S \cdots S$ contacts (3.175 Å) in dimers of the same type except for the opposite orientation (25) of the partners. Here the nitrogen atom is forced out of the plane of the rings by 11° (0.186 Å) as a consequence of a greater localization of the unpaired electron on the atom. These intermolecular bonds provide an explanation for the diamagnetic behavior of the radical in the solid state <87CC66, 90IC4821>.



The tricyclic benzo-bis-1,3,2-dithiazolyl radical cation (26) is completely planar and symmetrical about the benzene ring, hence the positive charge and unpaired electron should be delocalized over the both heterocyclic rings. The benzene ring CC bonds common with the heterocycles are slightly longer than the other (equal) four (1.428 vs. 1.390 Å) which implies a quinonoid resonance structure (27). The bond lengths in the heterocyclic part are again slightly longer than in the related cation (20), in which the positive charge reduces the repulsion between non-bonding electrons. Like the 1,3,2-dithiazolyl radicals, the radical cations are associated as dimers in which the two molecules lie almost superimposed in parallel planes 3.35 Å apart (28). The dimer units are separated by anions and are ordered in a staggered fashion. The Fe–Cl distances (2.18 Å) in the tetrahedral anion are consistent with $FeCl_4^-$ (2.18 Å), rather than with $FeCl_4^{2-}$ (2.3 Å), which means that the radical cation has one positive charge. The nature of the anion was also confirmed by ^{57}Fe Mössbauer measurements <88JCR(S)358>.

Interestingly, the pyrazino-1,3,2-dithiazolyl radicals (29) which are also arranged strictly one over the other and oriented identically, in the crystal form long continuous stacks, in a type of polymeric extension of dimerization <91SM3287>.



4.12.3.2 NMR Spectroscopy

Selective data on ^1H NMR spectra are presented in Table 2.

A twisted envelope conformation with N as flap was deduced for 1,3,2-dioxazolidine (**30**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$) from the AA'BB' spectrum of the ring protons combined with an isochronism of the ring C atoms. Axial NH proton orientation was inferred from a J coupling constants analysis and comparison with analogous known systems. The form of the spectrum did not change up to 170°C indicating configurational stability of the ring nitrogen, the activation free energy of the N inversion being assessed to be as high as $\approx 28 \text{ kcal mol}^{-1}$ compared with $\approx 20 \text{ kcal mol}^{-1}$ for acyclic N,N -dialkoxyamines. The spectrum gave no evidence of a fast NH proton exchange for deuterium in D_2O or CD_3OD prior to addition of KOH [88KGS396].

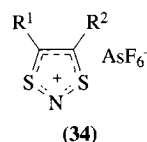
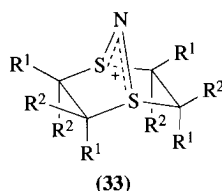
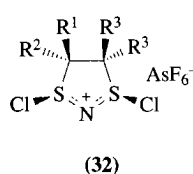
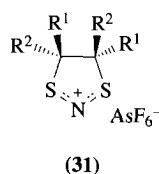
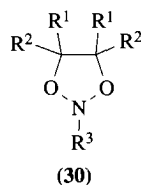


Table 2 ^1H NMR data for 1,3,2-dioxazoles and -dithiazoles.

Structure	Chemical shifts (δ , ppm)			Solvent	Ref.
	R^1	R^2	R^3		
(30)					
$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$	3.91	(3.01)	axial	CDCl_3 (C_6D_6)	88KGS396
	4.21	(3.52)	equat.		
$\text{R}^1 = \text{R}^2 = \text{H}; \text{R}^3 = \text{CONMe}_2$		3.55	axial	C_6D_6	88KGS396
		4.04	equat.		
(31)					
$\text{R}^1 = \text{H}; \text{R}^2 = \text{Me}$	6.37	2.87		SO_2	86CC966
(32)					
$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$	5.3	5.3	5.3	SO_2	90CJC852
$\text{R}^1 = \text{R}^3 = \text{H}; \text{R}^2 = \text{Me}$	5.0	2.3	4.7	SO_2	90CJC852
$\text{R}^1 = \text{Me}; \text{R}^2 = \text{R}^3 = \text{H}$	2.0	5.9	5.3	SO_2	90CJC852
(33)					
$\text{R}^1 = \text{R}^2 = \text{H}$	3.33	2.82		SO_2	86CC966
$\text{R}^1 = \text{H}; \text{R}^2 = \text{Me}$	3.20 exo	1.53 exo		SO_2	86CC966
	3.54 endo	1.77 endo			
(34)					
$\text{R}^1 = \text{R}^2 = \text{H}$	11.0	11.0		SO_2	90CJC852
$\text{R}^1 = \text{H}; \text{R}^2 = \text{Me}$	10.7	3.4		SO_2	90CJC852
$\text{R}^1 = \text{H}; \text{R}^2 = \text{CF}_3$	11.1	—		SO_2	91IC3342
$\text{R}^1 = \text{H}; \text{R}^2 = \text{CN}$	10.8	—		SO_2	91IC3342

4.12.3.3 ^{13}C , ^{14}N , and ^{19}F NMR Spectroscopy

Some representative ^{13}C and ^{14}N chemical shifts for ring carbon and nitrogen atoms are collected in Table 3. The ^{14}N chemical shift in (**32**) suggests a strongly shielded N atom and implies a

considerable negative charge associated with it <90CJC852>. Separation of the ^{19}F NMR signals of 2-R-4,4,5,5-tetrafluoro-1,3,2-dithiazolidine into an AA'BB' spin system at low temperature ($< -60^\circ\text{C}$) is due to the N inversion with a free-energy barrier $\Delta G^* = 38.7$ (R = Bn) <89CB1071>, 39.7 kJ mol^{-1} (R = Ph) <85CB2811>.

Table 3 ^{13}C and ^{14}N NMR data for 1,3,2-dioxazoles and -dithiazoles.

Structure	Chemical shifts (δ , ppm)				Solvent	Ref.
	Ring C		Ring N (from MeNO ₂)			
	C-R ¹	C-R ²	ppm	$\Delta\nu_{1/2}$ (Hz)		
(30)						
R ¹ = R ² = R ³ = H	68.95	68.95			CDCl ₃	87IZV1556, 88KGS396
R ¹ = R ² = H; R ³ = CONMe ₂	68.32	68.32			C ₆ D ₆ , C ₆ D ₅ CD ₃	87IZV1556, 88KGS396
(31)						
R ¹ = R ² = H			134	680	SO ₂	88IC2749
(32)						
R ¹ = R ² = R ³ = H	62.5	62.5	−243	415	SO ₂	90CJC852
(33)						
R ¹ = R ² = H			−298	600	SO ₂	88IC2749
(34)						
R ¹ = R ² = H	170	170	−5	350	SO ₂	88IC2749, 91IC3342
R ¹ = H; R ² = Me	167	187	−14	350	SO ₂	91IC3342
R ¹ = H; R ² = CF ₃	175	170	0	300	SO ₂	91IC3342
R ¹ = H; R ² = CN	175	154	2	500	SO ₂	91IC3342, 91CC369
R ¹ = R ² = Me	185	185	−31	400	SO ₂	91IC3342
R ¹ = R ² = CF ₃	176	176	3	400	SO ₂	91IC3342
R ¹ = R ² = CO ₂ Me	175	175	16	1600	SO ₂	91IC3342
R ¹ = R ² = SiMe ₃	194	194	−2	400	SO ₂	91IC3342
R ¹ = R ² = Ph	184.1	184.1			SO ₂	92CJC2972
(15)		161.8			SO ₂	85CC1654

4.12.3.4 UV Spectroscopy

Tetrathiatetraazulene (**15**) has long wavelength maxima at 322 (log $\epsilon = 3.35$) and 492 nm (log $\epsilon = 3.31$). This pattern together with simple IR and ^{13}C NMR spectra is indicative of a highly symmetrical and delocalized structure <85CC1654>. 5-Phenyl-1,3,2-dithiazole-4-thione exhibits absorption at 550 nm <89JCS(P1)2489>.

Dicyano <90CB881> and bis(trifluoromethyl)- <87CC66> substituted 1,3,2-dithiazolyl radicals (**21**) and (**22**) have two major absorption regions in common: 227–235 and 265–287 nm (an intensive extra one at 300 nm appears for the dicyanoderivative). Quinoxalino-1,3,2-dithiazolyl radical shows seven intensive absorption maxima: 717, 684, 650, 359, 351, 253, and 235 nm <90CB881>.

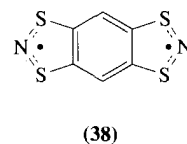
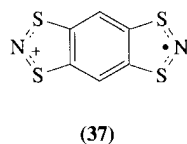
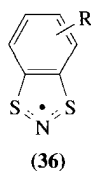
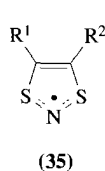
A hypsochromic shift was observed for the benzo-bis-1,3,2-dithiazole system (Section 4.12.4.6) with increasing oxidation state from diradical (**62**) through radical cation (**61**) to dication (**60**): 560, 504, and 450 nm <86SM239>.

4.12.3.5 IR Spectroscopy

Tetrathiatetraazulene (**15**) gives only four IR bands: 1488, 895, 885, and 625 cm^{-1} (cf. Section 4.12.3.4) <85CC1654>. In 5-substituted 1,3,2-dithiazole-4-one, -thione, and -phenylimine the exocyclic double bonds were assigned 1639 (C=O), 1290 and 1190 (C=S), and 1552 cm^{-1} (C=N) <89JCS(P1)2489>. Detailed assignments were made for 1,3,2-dithiazolyl radicals <85JCS(D)1405>.

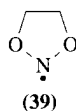
4.12.3.6 ESR Spectroscopy

1,3,2-Dithiazolyl radicals of the type (35), (36), and (37) give ESR spectra with g -factors from 1.990 to 2.0071 and a_{14N} from 1.0714 to 1.150 mT, a_{33S} from 0.370 to 0.423 mT at room temperature to -108°C in different solvents $\langle 83JCS(F1)925, 84CC573, 85JCS(D)1405, 86SM239, 88MRC755, 88JCR(S)358 \rangle$, $a_{15N} = 1.5360$ in (35; $R^1 = R^2 = \text{CO}_2\text{Me}$) $\langle 88MRC755 \rangle$. No or only very weak spin coupling of the heterocyclic N atom to the CN group in (35; $R^1 = R^2 = \text{CN}$) $\langle 90CB881 \rangle$ or to aromatic protons in (36; $R = \text{H}$ or Me) $\langle 84CC573 \rangle$ or in (37) or (38) $\langle 86SM233 \rangle$ was detected indicating that most of the spin density is localized on the heterocyclic ring. Large g -factors show that a partial spin delocalization over the SNS entity of the heterocycle to occurs; the main site of the spin density is, however, N atom ($\rho_N = 0.56$, $\rho_S = 0.10$, $\rho_C = 0.18$) $\langle 83JCS(F1)925 \rangle$. The unpaired spin population was estimated to be 45% on N atom and 25.5% on each S atom $\langle 88MRC755; 90CB881 \rangle$. The low degree of spin delocalization is considered to be indicative of the low aromaticity of the 1,3,2-dithiazolyl ring. Additional evidence is that similar a_N values are found in non-aromatic 1,3,2-dithiazolidinyl and even open-chain $(\text{PhS})_2\text{N} \cdot$ radicals $\langle 83JCS(F1)925 \rangle$. Accordingly, an analysis of the temperature dependence of ESR spectra has led to the conclusion that N atom out-of-plane bending about the SS axis occurs $\langle 83JCS(F1)925, 85JCS(D)1405 \rangle$. (Cf. N atom bent out of plane in (36) revealed by x-ray structural analysis in Section 4.12.3.1.)



For (35; $R^1 = R^2 = \text{CO}_2\text{Me}$) the ESR powder spectra turned out to be very sensitive to the dihedral angle of the carbonyl oxygen with respect to the ring plane (cf. quantum chemical calculations; Section 4.12.2). A very small discrepancy between the angles for both $\text{C}=\text{O}$ groups caused spin densities on both S atoms to diverge strongly and hence S lines in the spectrum to be considerably different $\langle 88MRC755 \rangle$.

The 1,3,2-dioxazolidinyl radical (39) gives an ESR spectrum with a g -factor = 2.0046, $a_N = 1.600$ mT, $a_H = 0.250$ mT. The aminyl structure of the radical is confirmed by g -factor and hyperfine coupling constant a_N which are similar to those for other known aminyl radicals and considerably different from those for isomeric nitroxyl radicals $\text{RO(R)NO} \cdot$ $\langle 89IZV1819 \rangle$.



4.12.3.7 Mass Spectrometry

1,3,2-Dioxazolidines bearing carbon-attached substituents on the ring nitrogen gave mass spectra $\langle 84OMS(19)113, 87IZV1556 \rangle$ in which fragmentation of the substituents but not that of the ring was observed $\langle 84OMS(19)113 \rangle$.

1,3,2-Dithiazoles and -dithiazolidines variously substituted as neutral molecules $\langle 85CB2811, 89JCS(P1)2489, 89CB385 \rangle$, cations $\langle 86CC966 \rangle$, or radicals $\langle 87CC66, 90CB881 \rangle$ usually give a molecular ion peak. More details of fragmentation is presented for N-substituted 4,4,5,5-tetrafluoro-1,3,2-dithiazolidine $\langle 85CB2811 \rangle$, 5-substituted 1,3,2-dithiazole-4-thione, -one and -phenylimine $\langle 89JCS(P1)2489 \rangle$, 1,3,2-dithiazolyl cations $\langle 85JCS(D)1405 \rangle$, 4,5-dicyano- and quinoxalino-1,3,2-dithiazolyl radicals $\langle 90CB881 \rangle$. Fragments SN , S_2N , and S_2NR have often been observed.

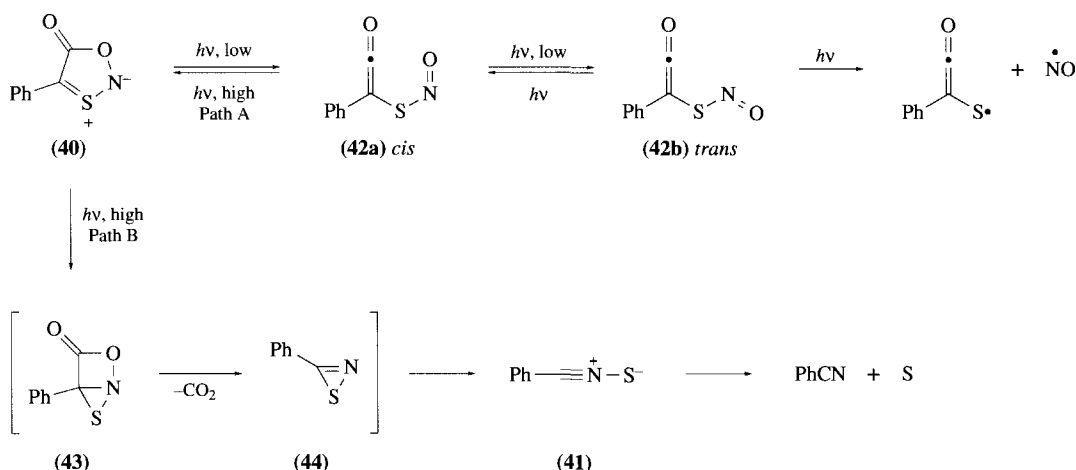
4.12.4 REACTIVITY OF FULLY CONJUGATED RINGS

A large part of this section is devoted to the reactions of 1,3,2-dithiazole type cations and radicals, and covers transformations of the cations to the radicals and vice versa, formation of charge transfer complexes, etc. all of which is largely new since the publication of the first edition of *Comprehensive*

Heterocyclic Chemistry (CHEC-I). Reactivity of 1,3,2-dithiazole-5-ones, -thiones, -imines, and 1,3,2-oxathiazole-5-ones is also much more widely covered than in CHEC-I, their thermolysis, photolysis, oxidation, methylation, amination, hydrolysis, 1,3-cycloaddition, etc. are discussed.

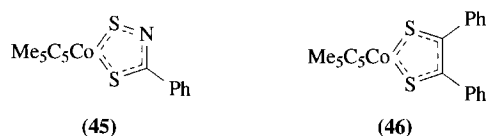
4.12.4.1 Thermal and Photochemical Formally Unimolecular Reactions

The extensively investigated $\langle 84\text{CHEC-I}(6)914 \rangle$ low temperature (10–85K) photolysis of the mesoionic 4-phenyl-1,3,2-oxathiazolone (**40**) (Scheme 1) has been shown to depend strongly on the local viscosity $\langle 87\text{JCS(P2)}1227 \rangle$. In media of high viscosity (neat crystalline state or in rigid matrices of organic solvents and polymers) path B leading to benzonitrile sulfide (**41**) is favored. In media of low viscosity (in soft N_2 matrices) the ring-opening path A leading to phenyl(nitrosothio)ketene (**42**) predominates. (The terms “high” and “low” on arrows indicate those viscosities which favor the direction shown.) A rigid, highly viscous medium is supposed to restrict all those atom movements which would cause a molecule to expand in volume, consequently it should oppose the ring opening to (**42**). The singlet excited molecule (**40**) is thus forced to emit a photon, lose CO_2 or pass over to a triplet state. The transient structures (**43**) and (**44**) depicted in square brackets have long been generally accepted since they were first suggested in 1966 $\langle 66\text{TL4043} \rangle$, but so far they have escaped direct experimental detection. However, the structures should not be associated with extreme thermal instability and they ought to be observable spectroscopically, therefore the question arises as to their role in this photochemistry $\langle 87\text{JCS(P2)}1227 \rangle$.

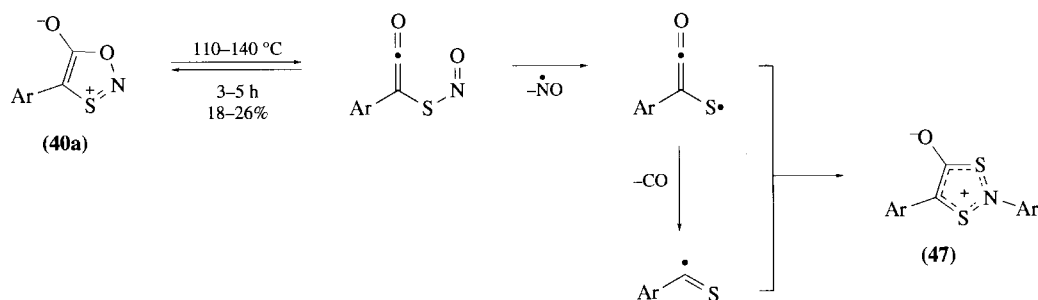


Scheme 1

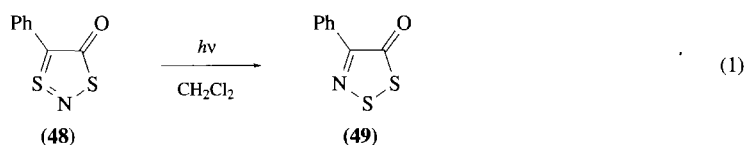
When (**40**) is irradiated by Hg lamp at room temperature in the presence of pentamethylcyclopentadienyl dicarbonyl cobalt(III), Co(III) dithiolato complexes (**45**) and (**46**) are formed implying involvement of benzonitrile sulfide as an intermediate $\langle 92\text{CL243} \rangle$. Thermolysis of (**40**) (and its phenyl ring substituted derivatives (**40a**)) at 110–140 °C in aromatic solvents results in formation of another heterocyclic mesoionic structure (**47**) and appears to proceed as a radical process (Scheme 2) $\langle 91\text{TL4023} \rangle$. The reaction is inhibited by radical scavengers.



4-Phenyl-1,3,2-dithiazolone (**48**) on exposure to a normal laboratory daylight is converted into the isomeric 1,2,3-dithiazole (**49**) in 43% yield within a week (Equation (1)) $\langle 89\text{JCS(P1)}2489 \rangle$. In contrast, the thione analogue (**50**) decomposes completely within 24 hours in the same conditions, though it is quite stable in the absence of light and oxygen $\langle 89\text{JCS(P1)}2489 \rangle$.



Scheme 2



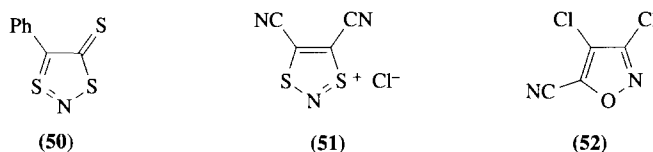
4,5-Dicyano-2-arylsulfonyl-1,3,2-dithiazoles, for example (8) resist irradiation with a Hg lamp, but undergo thermolysis in the vapor phase at 200 °C in high vacuum to give stable 4,5-dicyano-1,3,2-dithiazolyl free radicals (22) <90CB881>. 2-Arylsulfonylsubstituted 1,3,2-dithiazolo[4,5-*b*]quinoxaline (54) could not be sublimed efficiently within a temperature range preceding extensive decomposition. The corresponding free radical (56) can be obtained in other way (see Section 4.12.4.5).

4.12.4.2 Electrophilic Attack at Ring Nitrogen and Carbon

4-Phenyl-1,3,2-dithiazolethione (50) is very rapidly converted by lead tetraacetate into the “-one” analog (48) <89JCS(P1)2489>.

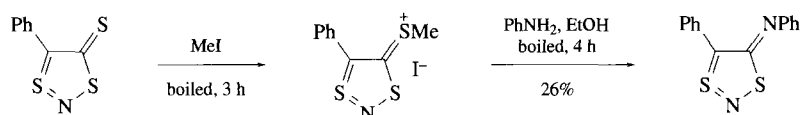
4.12.4.3 Electrophilic Attack at Ring Sulfur

N-Tosyl-4,5-dicyano-1,3,2-dithiazole (8) when treated with Cl_2 or SOCl_2 undergoes a decomposition to 4,5-dicyano-1,3,2-dithiazolium chloride (51), but not with extrusion of tosyl chloride; 3,4-dichloro-5-cyanoisothiazole (52) as a product of oxidative ring cleavage was discovered in the reaction mixture <90CB881>.



4.12.4.4 Nucleophilic Attack at Ring Carbon

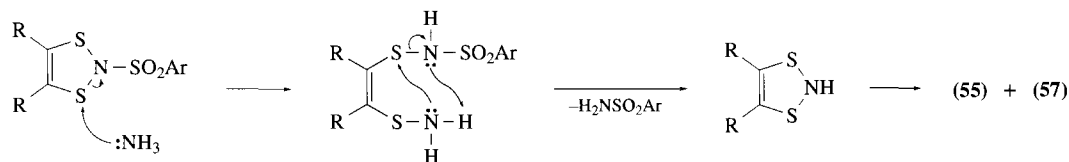
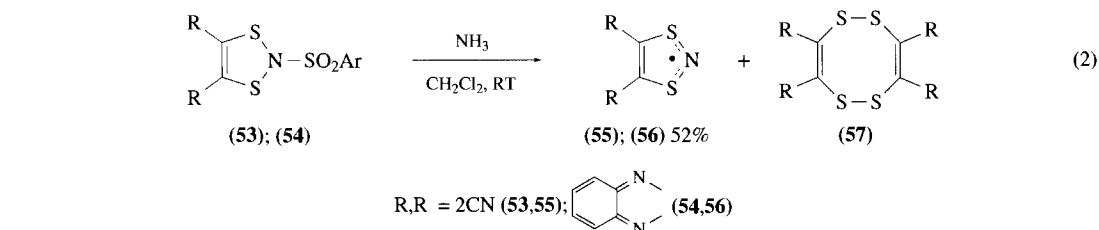
The exocyclic-sulfur in 4-phenyl-1,3,2-dithiazolethione can be displaced by aniline after prior methylation (Scheme 3) <89JCS(P1)2489>. Direct heating of the thione with aniline results in decomposition only.



Scheme 3

4.12.4.5 Nucleophilic Attack at Ring Sulfur

N-Arylsulfonyl-substituted 1,3,2-dithiazoles (**53**) and (**54**), react (Equation (2)) with ammonia, to give stable 1,3,2-dithiazolyl radicals (**55**) and (**56**) accompanied by tetrathiocins (**57**) <90CB881>. ¹⁵N Labelling reveals that ammonia attacks not the sulfonyl group, but rather the cyclic sulfur atom. This implies two successive attacks on the two sulfur atoms of the ring with expulsion of the sulfonamide (Scheme 4) <90CB881>. Other bases such as alkylamines, NaN(SiMe₃)₂, PhONa, and MeONa cause only decomposition. Radical (**55**) decomposes slowly in an inert atmosphere and quickly in air. Radical (**56**) is more stable; it can be stored in AcOH solutions, but instantly decomposes with bases <90CB881>.

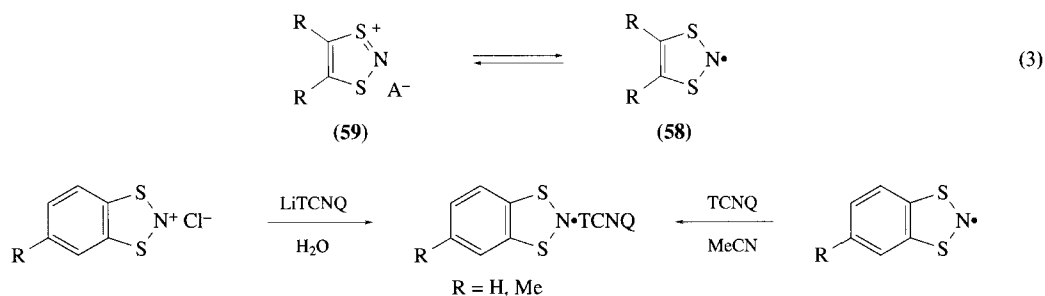


Scheme 4

4.12.4.6 Reactions Involving Radicals, Electron-deficient Species, Reducing Agents and at Surfaces

1,3,2-Dithiazolium cations are easily reduced to the corresponding stable radicals which in turn can be smoothly oxidized back to the cation (Equation (3)) <84CC573, 85JCS(D)1405, 87CC66, 90CB881, 92CJC2972>. The cations may also be reduced electrochemically; cyclic voltametry showing it to be a reversible process. The half-peak reduction potentials (Ag electrode in MeCN) are +0.02 V (**58**; R = H) and -0.63 V (**58**; R, R = H, Me) <83CC807>.

Both cations and radicals may be transformed into stable transfer complexes with tetracyanoquinodimethane (TCNQ) as an electron acceptor (Scheme 5) <84CC573>.

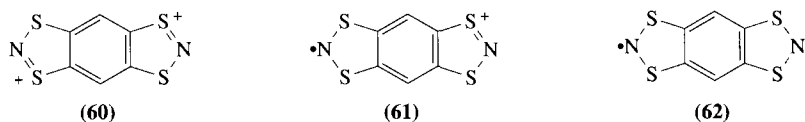


Scheme 5

1,3,2-Dithiazolyl radicals (**58**) do not dimerize at low temperatures in diluted solutions, do not react with O₂, are stable to photolysis (at 350 nm), heat and in aqueous solutions at or above pH8 <83JCS(F1)925>. This makes them different from 1,3,2-dithiazolidinyl radicals. In 1987 <87CC66> solutions of (**58**; R = CF₃) have been shown to contain 65% of the free radical and 35% of the diamagnetic dimer; the concentration of the radical in concentrated solutions does not change with temperature indicating an almost zero enthalpy of dimerization. The latter in neat liquid is -3.5

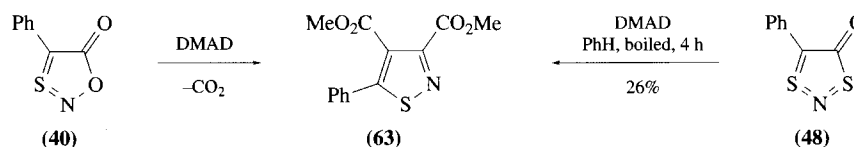
kcal mol⁻¹, hence the paramagnetism of the liquid. In the solid state (0–9) (**58**; R = CF₃) is diamagnetic.

All these transformations except for reversion of radical to cation have been accomplished with the benzobisdithiazolium cation (**60**) which has given rise to radical cation (**61**) and diradical (**62**) <86SM233, 86SM239, 88JCR(S)358>. The diradical (**62**) is a dimer in solution (cryoscopic measurements in hexane) <86SM233>; the radical cation (**61**) is loosely dimeric in the crystal (Section 4.12.3.1).

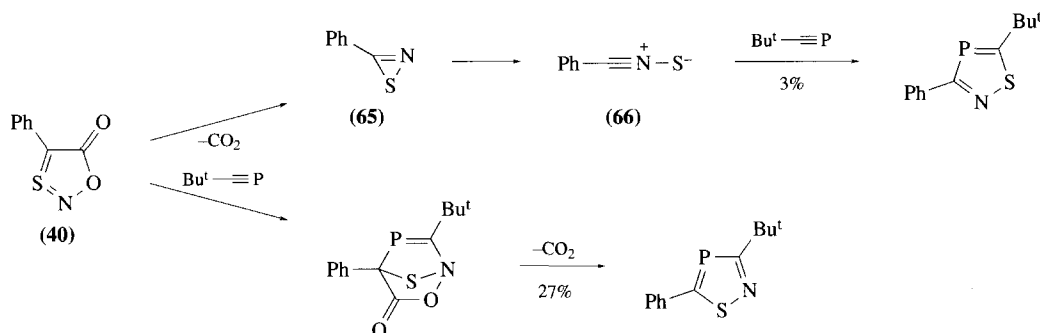
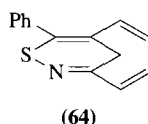


4.12.4.7 Cyclic Transition State Reactions with a Second Molecule

4-Phenyl-1,3,2-oxathiazolone (**40**) readily reacts with DMAD obviously via 1,3-cycloaddition at CSN site of the ring to give isothiazole derivative (**63**) with extrusion of CO₂. The 1,3,2-dithiazole analog (**48**) of (**40**) reacts with DMAD similarly, but much less readily (Scheme 6) <89JCS(P1)2489>. When benzocyclopropene is used as a dipolarophile the cycloaddition–extrusion–ring expansion reaction occurs with (**40**) to give an unstable bridged heteroannulene (**64**) <82CC510, 90JCS(P1)2035>. Phosphalkynes add to (**40**) affording two isomeric thiaphospholes one of which is supposed to be formed via intermediate thiazirine (**65**) and nitrile sulfide (**66**) (Scheme 7) <87CB1809>.

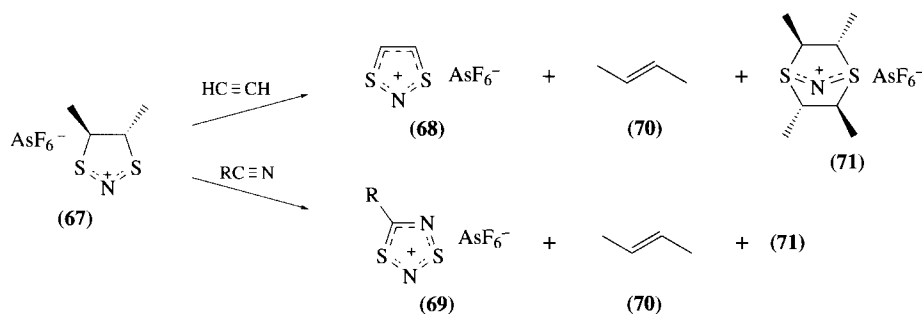


Scheme 6



Scheme 7

The 1,3,2-dithiazolinium cation (**67**) reacts as a dithionitronium cation with ethyne and nitriles to give more stable fully aromatic cations (**68**) and (**69**). The displaced alkene (**70**) combines with the initial cation (**67**) to give heteranorbonylium cation (**71**) (Scheme 8) <86CC966>.

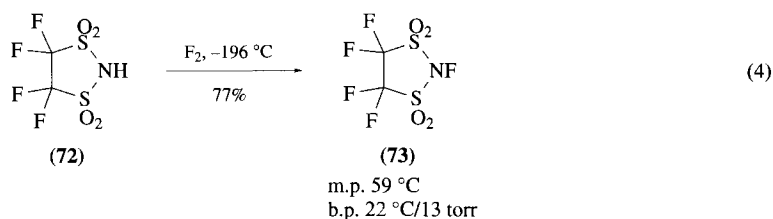


Scheme 8

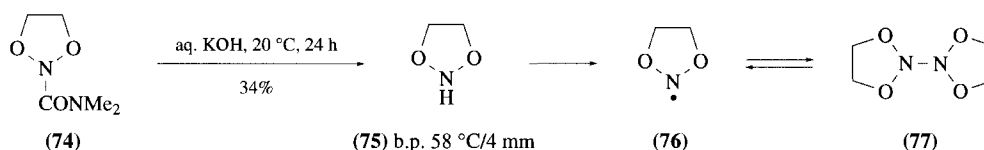
4.12.5 REACTIVITY OF NONCONJUGATED RINGS

4.12.5.1 Reactions of Hydrogenated Derivatives of Fully Conjugated Ring Compounds

The C-perfluorodisulfonimide (**72**) is readily N-fluorinated (Equation (4)) by liquid fluorine <87JA7194, 87JAP8726264>. The N-fluoro derivative (**73**) is a powerful fluorinating agent of high stability and suitable physical properties. It can be converted back to the imide (**72**) by ammonia <82EUP57327>.



N-(Dimethylcarbamoyl)-1,3,2-dioxazolidine (**74**) is hydrolyzed by alkali to the unsubstituted parent (**75**) (Scheme 9) $\langle 87\text{IZV1556} \rangle$; 4,4-dimethyl analogue gives only decomposition products under these conditions $\langle 89\text{KGS393} \rangle$. 1,3,2-Dioxazolidine (**75**) is converted into a free radical (**76**) under the action of various agents: UV irradiation, lead dioxide, sterically hindered quinones, nitroxyl or aroxyl radicals, and slowly just during storage. The radical appears to dimerize reversibly to a hydrazine (**77**) as judged from monitoring by ESR spectroscopy; in solution (**76**) is stable for about 6 months at room temperature $\langle 89\text{IZV1819} \rangle$. A rapid exchange of the NH proton in (**75**) for deuterium in D_2O or CD_3OD ensues only upon addition of KOH $\langle 88\text{KGS396} \rangle$.

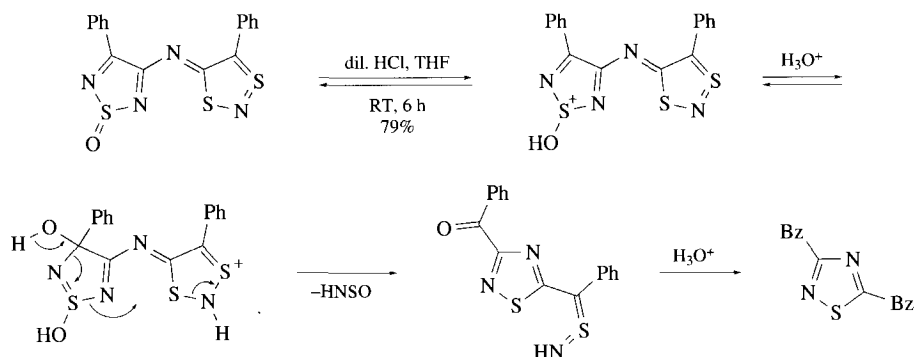


Scheme 9

4.12.5.2 Reactivity of Substituents Attached to Ring Carbon Atoms

The bicyclic imine (**10**) undergoes oxidation at the 1,2,5-thiadiazole ring to S mono- and dioxides ((**11**), (**12**)) the 1,3,2-dithiazole ring remaining intact (<89JCS(P1)2485, 89CC1134>). The susceptibility of the former ring to electrophilic attack is enhanced by the latter ring-donating electrons, which is reflected in structure (**14**). This electron delocalization has been taken as a possible reason for high stability of the imine (**10**) towards UV irradiation, heat, bases, acids and electron-deficient alkynes (in attempted cycloaddition). The exocyclic imine bond is only hydrolyzed on prolonged refluxing with potassium hydroxide in aqueous ethanol.

The oxidized thiadiazole ring in (**11**) renders the bicyclic structure susceptible to acid hydrolysis (Scheme 10). The unexpected new ring formation may be regarded as a consequence of interannular N $\cdots$ S proximity (Section 4.12.3.1).

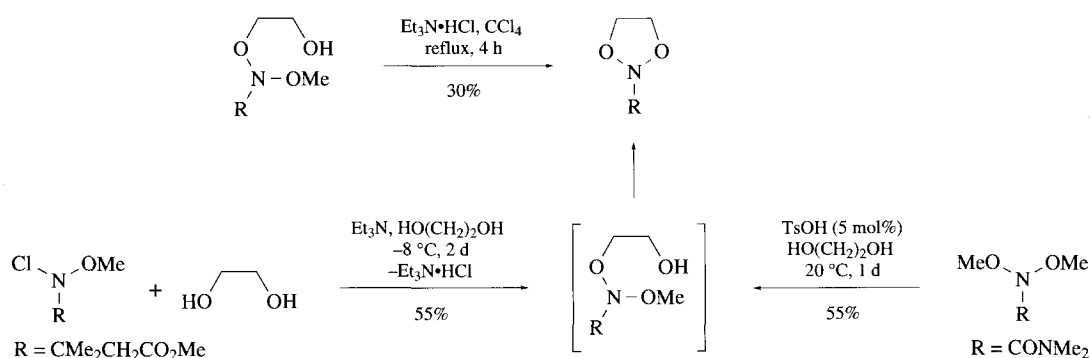


Scheme 10

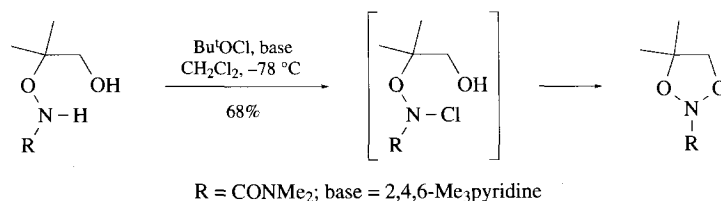
4.12.6 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

4.12.6.1 Formation of One Bond between Two Heteroatoms

1,3,2-Dioxazolidines are obtained by the intramolecular acid-catalyzed cyclization of *N,N*-di-alkoxyamines (preformed or produced *in situ*) or by cyclization of *N*-chloro-*N*-alkoxyamines (Scheme 11 <81IZV2539, 87IZV1556> and Scheme 12 <89KGS393>).



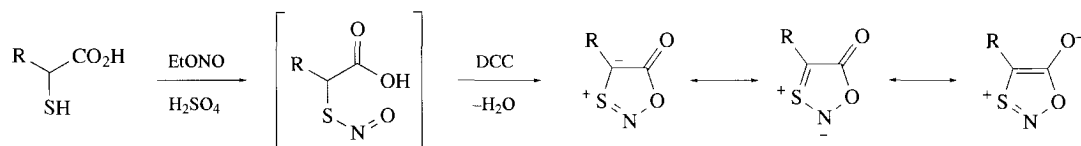
Scheme 11



Scheme 12

4.12.6.2 Formation of One Bond Adjacent to a Heteroatom

Thiomandelic and thiolactic acids are nitrosated to give S-nitroso derivatives which are dehydrated *in situ* by dicyclohexylcarbodiimide to form 1,3,2-oxathiazoline rings (Scheme 13) <72CB188, 81LA1025, 92USP5087631>. Structurally, the products obtained may be regarded as S-analogues of sydnone.

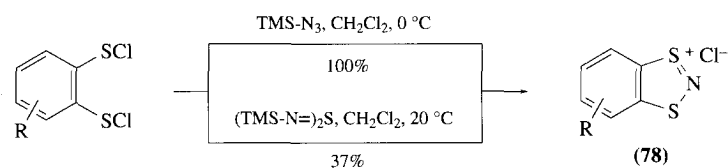


R = Me, Ph, *p*-NO₂C₆H₄, *o,p*-Me₂C₆H₃, *p*-MeOC₆H₄, *o,m,p*-Me₃C₆H₂, *o,m,p*-Me₃C₆H₂, (*o,o',p*-Me₃C₆H₂: not cyclised)

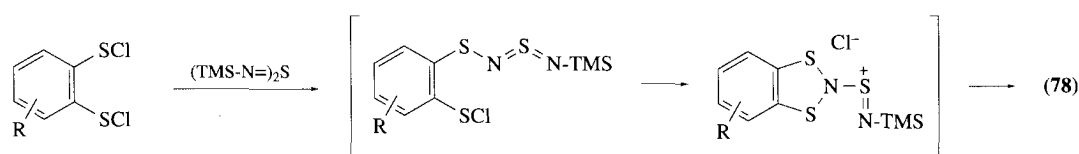
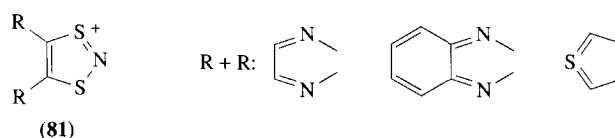
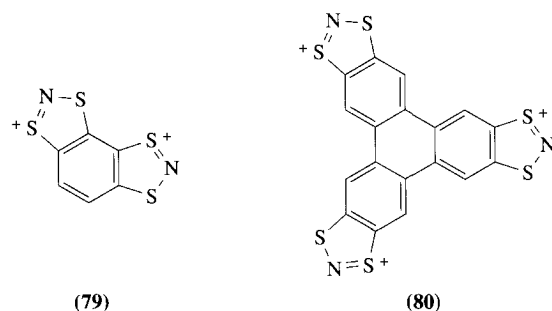
Scheme 13

4.12.6.3 Formation of Two Bonds: Four-atom Fragments and Nitrogen

o-Bis(sulphenylchloride)arenes react with trimethylsilyl azide <84CC573> or bis(trimethylsilyl)-sulfurdiimide <87JCS(P1)211> to give 1,3,2-benzodithiazolium salts (78) (Scheme 14). The former reaction has successfully produced a range of other condensed 1,3,2-dithiazolyl cations: (60) 98% yield <86SM233, 86SM239>, (79)–(81) <91SM3287>. The latter reaction is thought to result from cyclization of the initial intermediate by attack of the remaining chlorosulphenyl group at the N atom which had attacked the first SCl group (Scheme 15). The major product, however, results from attack at the other N atom.

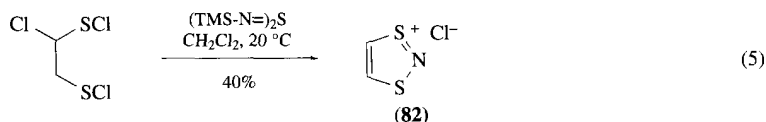


Scheme 14

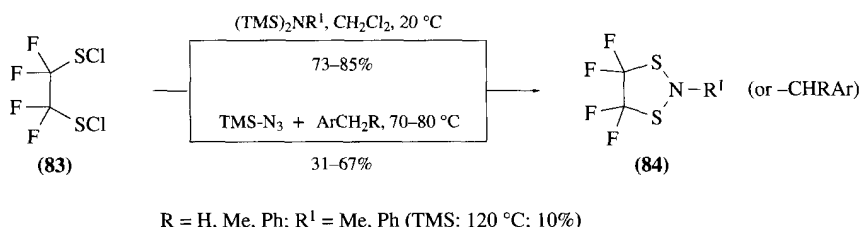


Scheme 15

1-Chloroethane-1,2-disulphenyl dichloride subjected to the action of bis(trimethylsilyl)-sulfurdiimide is transformed into 1,3,2-dithiazolium chloride (**82**), elimination of HCl occurring (Equation (5)) <91JCS(P1)2945>. The remarkable azulene-like bicycle (**15**) is formed (0.5%) as a by-product from 1,2-dichloroethane-1,2-disulphenyl dichloride, present as an impurity in the starting monochloride.

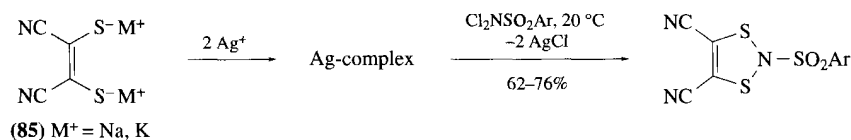


Tetrafluoroethane-1,2-disulphenyl dichloride (**83**) reacts readily with *N,N*-bis(trimethylsilyl)amines to give *N*-substituted tetrafluoro-1,3,2-dithiazolidines (**84**) (Scheme 16) <85CB2811>. The same type of products are obtained by reaction with a combination of trimethylsilyl azide and alkylarenes <89CB1071>. At a low temperature (**83**) was reported to be cyclized by NH_3 to 4,4,5,5-tetrafluoro-1,3,2-dithiazolidine <93JPC9625>.

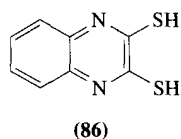


Scheme 16

Cyclization of the salts of vicinal dithiols to 1,3,2-dithiazolines with *N,N*-dichlorosulfonamides may be effected via their silver complexes (Scheme 17) <89CB385>. Dithiol (**86**) also reacts directly with dichlorosulfonamides but the disalts (**85**) could not be transformed into the corresponding dithiol.



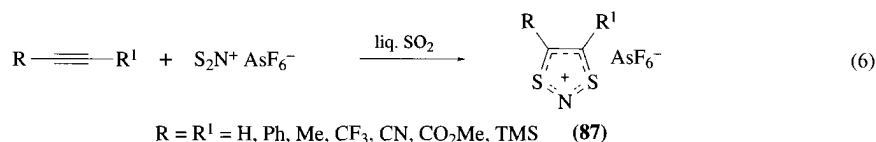
Scheme 17



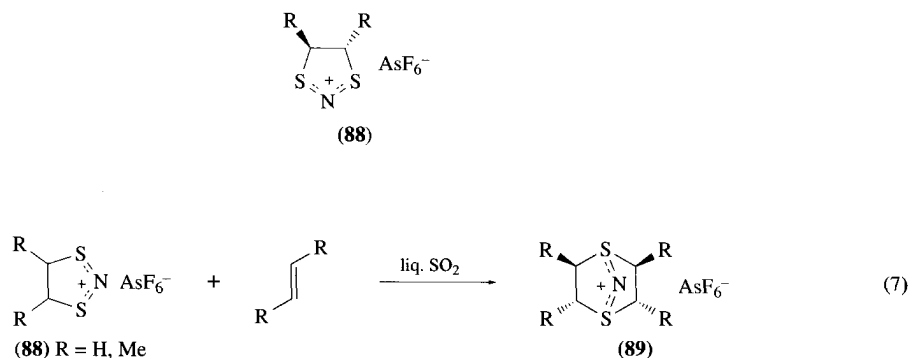
4.12.6.4 Formation of Two Bonds: [3 + 2] Atom Fragments by Cycloaddition

Passmore and co-workers accomplished and elaborated 1,3-dipolar cycloaddition of the dithionitronium cation to a multiple bond, specifically to the triple CC bond with formation of the 1,3,2-dithiazolium cation (**87**) in 95–100% yield (Equation (6)) <83CC807, 85JCS(D)1405, 87CC66, 91CC369, 91IC3342, 92CJC2972>. This is a reverse electron demand process: donation from the HOMO of the dipolarophile into the LUMO of the dithionitronium species <86CC966>. The rate of the process is determined by the energy gap between the HOMO and LUMO and is accelerated by diminishing gap <91IC3342>. The π molecular orbitals of S_2N^+ are of such low energy that interaction is effective even with the most electrophilic alkynes such as hexafluoro-2-butyne <91IC3342>. So too is the interaction with all alkenes, nitriles, and alkynes and therefore the 1,3-cycloaddition of S_2N^+ is of a very general scope <86CC966, 91IC3342>. The kinetics of 1,3-cycloaddition to alkynes is second order

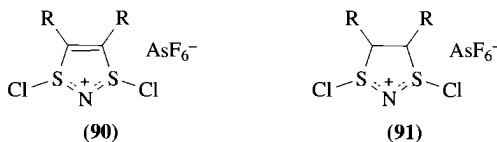
overall, being first order for each of the reagents in accord with the concept of the 1,3-cycloaddition reactions; $\log k$ is inversely proportional to the ionization potential E_i of the triple bond in different alkynes which confirms the reverse electron demand type of the reaction <91CC369>. This is why S_2N^+ interacting with cyano ethyne adds first to the $C\equiv C$ ($E_i = 11.60$ eV) rather than to the $C\equiv N$ bond ($E_i = 14.03$ eV), which reacts very slowly <91CC369>.



1,3-Cycloaddition of S_2N^+ to ethylenic bonds afforded new heterocyclic 5-membered cations (**88**) in very high yield <86CC966>. In contrast to the fully aromatic cation (**87**) the positive charge distribution in cation (**88**) is limited to the S—N—S moiety, which therefore is also capable of 1,3-cycloaddition, though to a lesser extent than S_2N^+ . The second addition leads to a bicyclic structure (**89**) of norbornene type in 90–100% yield (Equation (7)) <86CC966>. Thus, ethylene with equimolar quantity of $S_2N^+ AsF_6^-$ gives (**88**; $R = H$) along with (**89**; $R = H$). Excess of ethylene (4.7 : 1 mol) affords 100% (**89**; $R = H$) <86CC966>.

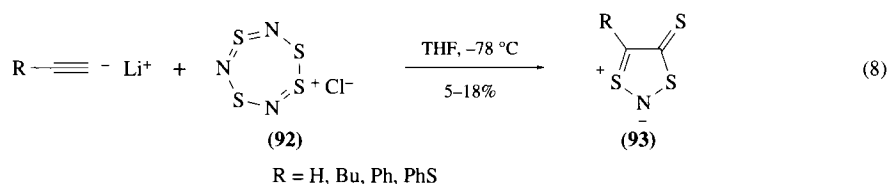


Dichlorodithionitronium cation, Cl_2NSCl^+ , adds to alkynes forming cations (**87**) in 97% yield probably via the intermediate 1,3-dichloro-1,3,2-dithiazolinium cations (**90**) <90CJC852>. Cation $Cl_2S_2N^+$ is less reactive than S_2N^+ ; it does not add to hexafluoro-2-butyne or MeCN. However, it is more accessible and preferable for preparative purposes. It adds also to alkenes quantitatively giving stable 1,3-dichloro-1,3,2-dithiazolinium cations (**91**) which in turn can add to excess of alkene with loss of chlorine affording bicyclic cations (**89**) <90CJC852>. Tetrafluoroethene does not react evidently on electronic grounds, tetramethylethene fails to form expected adducts presumably for steric reasons.

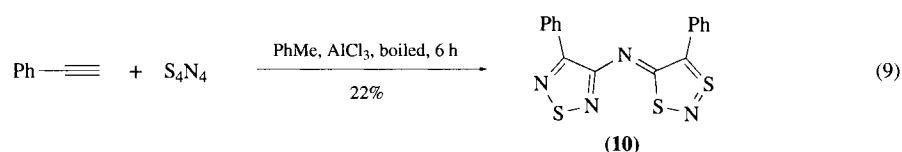


4.12.6.5 Formation of Two Bonds: [3 + 2] Atom Fragments by Other Processes

Lithium salts of ethynes give 1,3,2-dithiazolethiones (**93**) on reaction with tetrathiatriazepinium chloride (**92**) (Equation (8)) <89JCS(P1)2489>. The suggested mechanism involves coupling of the organic anion and the inorganic heterocyclic cation, followed by a regrouping of the heterocyclic part with involvement of the triple bond.



Phenylethyne with tetrasulfur tetranitride and AlCl_3 in boiling toluene affords the bicyclic imine (**10**) which contains the first example of an unsaturated neutral 1,3,2-dithiazole ring <84CC57>. Earlier, this product had been obtained without AlCl_3 in 8% yield but was assigned the wrong structure <76H(4)1243>. A key step in the proposed mechanism is the addition of two phenylethyne molecules to NSN units in S_4N_4 ; this is followed by rearrangement of the rest of the adduct (Equation (9)) <87JCS(P1)207>.



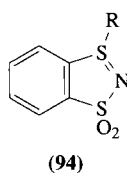
Phenyl vinyl sulfoxide, an effective “ethyne equivalent” in some addition reactions, with S_4N_4 in boiling toluene gives the tetrathiatetraaza azulene (**15**) in which 1,3,2-dithiazole and dithiatriazepine rings are fused <85CC1654>. Only one vinyl group adds to an NSN unit of S_4N_4 according to the postulated mechanism; with the elimination of PhSOH alkenic unsaturation reappears allowing further intramolecular addition accompanied by a rearrangement. The driving force for this process is the conversion of the non-aromatic 12π cage structure of S_4N_4 to the planar 14π aromatic system (**15**) through incorporation of a C—C π -bond. The same product (**15**) is obtained (in 4% yield) when phenyl vinyl sulfoxide is replaced by phenyl vinyl sulfone <85CC1654>.

Tetrasulfur dinitride S_4N_2 readily reacts with ethynes in various organic solvents to give 1,3,2-dithiazolyl stable radicals (**58**) <87CC66, 83JCS(F1)925>.

4.12.7 SURVEY OF RING SYNTHESIS

Synthesis of 1,3,2-dithiazoles has received the most attention.

The first examples were benzene disulfonimide derivatives prepared from *o*-benzenebis(sulfonyl chloride) or -disulfonic acid with amines or HNO_2 respectively <84CHEC-I(6)914>, or benzothiazole derivatives (**94**) obtained from benzenesulfonamides or azides containing ortho SR or SOR groups <84CHEC-I(6)914>.



In the 1980s, new approaches were found and other structural types were synthesized. Wolmershaeuser and co-workers used aromatic or alkenic *vic* dithiols or their silver complexes in reaction with dichlorosulfonamides to obtain fused or monocyclic *N*-sulfonyl 1,3,2-dithiazoles in good yield (Scheme 17). Roesky and co-workers introduced the reaction of aliphatic *vic* bis(sulfonylchlorides) into reaction with bis(TMS)amines or TMS azide (mixed with alkylarenes) to prepare 1,3,2-dithiazolidines (**84**) in good yield. A very interesting heterazulene with a fused 1,3,2-dithiazole ring (**15**) (Section 4.12.6.3) was synthesized by Rees and co-workers from a *vic* bis(sulfonylchloride) treated with bis(TMS)sulfurdiimide, and also from a vinylsulfoxide or -sulfone treated with S_4N_4 (Section 4.12.7.5). This research group showed that alkynic compounds react with S_4N_4 and tetrathiatriazepinium cation to give imino- and thiono-1,3,2-dithiazoles (**10**), (**93**) (Section 4.12.6.5).

Passmore and Sutcliffe with co-workers obtained stable 1,3,2-dithiazolyl radicals (**58**) from ethynes and S_4N_2 (Section 4.12.6.5).

The Passmore group developed methods to prepare quantitatively various kinds of 1,3,2-dithia-

zolum cations (**87**)–(**91**) from ethynes and alkenes using dithionitronium and dichlorodithionitronium cations as reagents in liquid SO₂. A variety of benzo and heterocyclic fused 1,3,2-dithiazolum cations (**59**), (**78**)–(**81**) were synthesized in high yields from *o*-bis(sulfenylchloride)arenes and -hetarenes and TMS azide (Wolmershaeuser) or in lower yields, with bis(TMS)sulfurdiimide (Rees) (Section 4.12.6.3).

1,3,2-Oxathiazoles are known solely in the form of mesoionic 1,3,2-oxathiazol-5-ones prepared first by Gotthardt by nitrosation of α -thiolcarboxylic acids (Scheme 13) <84CHEC-1(6)914>, the only reported method up to now.

1,3,2-Dioxazolidines are produced by cyclization of *N,N*-dialkoxy- or *N*-alkoxy-*N*-chloroamines (Scheme 11) <93CRV725>. The synthetic potential of this method far surpasses that of the photochemical addition of nitrobenzene to alkenes <84CHEC-1(6)-914>.

4.12.8 IMPORTANT COMPOUNDS AND APPLICATIONS

1,3,2-Dithiazole derivatives have attracted considerable attention as a possible source of conducting charge-transfer complexes and ferromagnetic materials due to the ability of these heterocycles to give stable cations and radicals <91SM3287>. The radicals are good donors in charge-transfer complexes, especially high efficacy was demonstrated by 1,3,2-dithiazole compounds with anellated isocyclic and heterocyclic rings. Complexes of benzo-1,3,2-dithiazolyl radicals with tetracyanoquinodimethane (TCNQ) possess conductivity as high as 3 S cm⁻¹ <84CC573, 86SM239>.

A new wave of interest and productive research was aroused by synthesis of tricyclic condensed derivative benzobis(1,3,2-dithiazole) (BBDTA) which was shown experimentally to afford at least three distinct oxidation states: dication, radical cation, and diradical <86SM233, 86SM239>. This has been helpful for developing an approach to ferromagnetic organic metals in which homomolecular stacks are formed from donor–acceptor complexes in which the donor is a triplet and the acceptor a radical ion derived from the donor <86SM233>. Initial experiments showed conductivities 10⁻⁴–10⁻³ S for complexes of BBDTA radicals with TCNQ <86SM239>.

Perfluoro-1,3,2-dithiazolidine 1,1,3,3-tetraoxide (**73**) is a useful fluorinating agent <87JAP8726264>. Compound (**72**) (free or in salt form) is proposed for use as a polymerization catalyst <82EUP57327>, the salts are suggested as ingredients in battery electrolytes <88FRP2606217>. *N*-*sec*-Alkyl substituted 1,3,2-dioxazolidines may be used for photofading prevention of organic dyes <88JAP88267942>. *N*-Chloroalkyl-1,3,2-dioxazolidine-4,5-diones represent a new class of chemiluminescence energy transfer agents <B-87MI 412-01>. *N*-Aroylsubstituted 1,3,2-oxathiazolines have been claimed to have use in photography as print stabilizers at storage <88JAP88271339>, dye-releasing compounds in photothermographical processes <87JAP87245256, 87JAP87244044> and reagent-releasing compounds <87JAP87293243>. 4-Methyl- or aryl-substituted 1,3,2-oxathiazole-5-ones have been proposed as cardiovascular agents <92USP5087631>.

4.13

1,2-Oxa/thia-4-azoles

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Russian Academy of Sciences, Moscow, Russia

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4.13.1 INTRODUCTION

1,2,4-Dithiazoles are the most common and thoroughly researched of the three azoles presented in this chapter. On the whole, the research on all three heterocyclic types has expanded appreciably since the publication of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I): about 170 references for the 12 years since 1980 compared to about 110 references for the 20 years prior to 1980.

Much work has been devoted to [2 + 3] cycloadditions both in the synthesis of and in reactions of this kind of heterocycle. Dimroth rearrangement is another feature which has been explored widely. X-ray structural analysis was extensively used alongside physico-chemical methods to elucidate the structure of novel compounds.

Cyclically conjugated rings (i.e. not containing sp^3 -hybridized carbon and nitrogen ring atoms), represented by the formulae in rows **A** and **B** of Figure 1, occur in neutral (-azoles) and cationic (-azolium) systems, respectively. Formulae of nonconjugated rings are collected in rows **C** and **D** (-azolines) and rows **E–G** (-azolidines). Structures not yet found in practice are enclosed in brackets. The dithiazolium formula in row **B** represents only one of the three canonical forms for this system (row **H**).

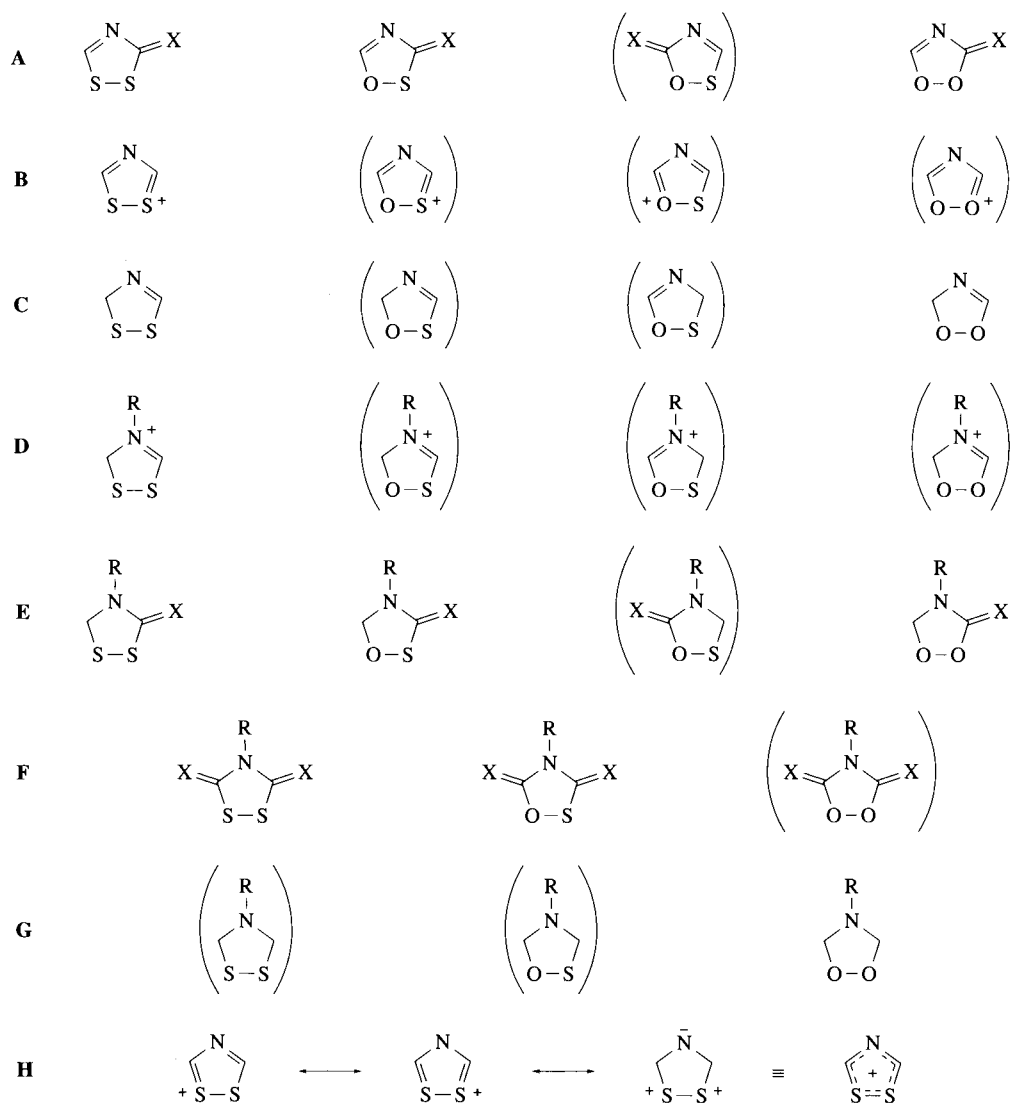
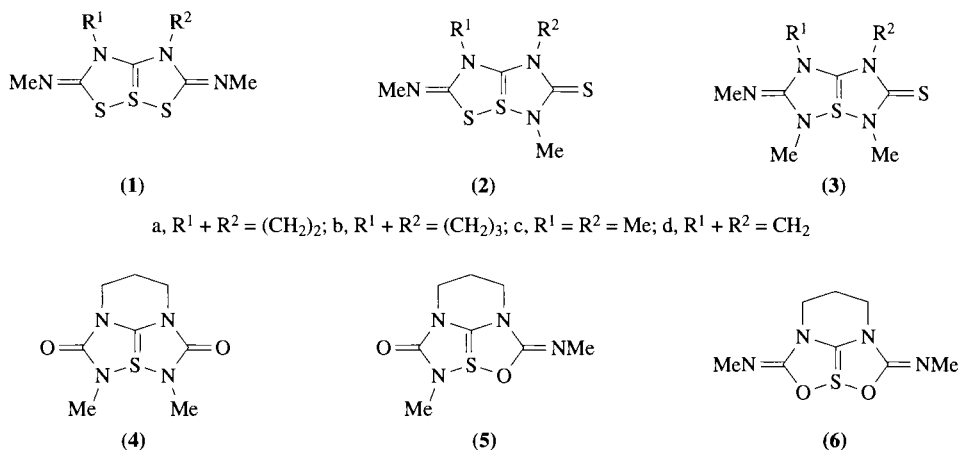


Figure 1 Possible structures for 1,2,5-(oxa/thia)-4-azoles.

Enthalpies of formation ΔH_f^0 and bond lengths (SS, SN) were calculated by the MNDO method for 1,6-dihetera-6 $\alpha\lambda^4$ -thia-3,4-diazapentalenes (**1**), (**2**), and (**3**) as the most probable pentalene structures formed in the reaction of 3-imino-1,2,4-dithiazolidine-5-ones with isothiocyanates (see Section 4.13.6.1.4 and Tables 1 and 2) <83JCR(S)128>. The ΔH_f^0 data show the ring strain to be maximal for a system with an N-S-N chain (**3**), the most favorable being the system (**1**). The effect of substituents R¹ and R² can be seen in both Tables 1 and 2. The same authors calculated ΔH_f^0 for (**4**), (**5**), and (**6**) to obtain values -57.4, 30.5, and 127.8 kJ mol⁻¹ respectively.



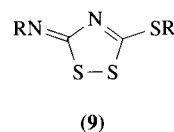
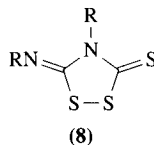
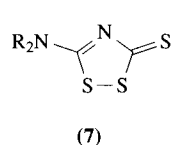
<i>Compd.</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>
(1)	287.9	265.4	319.8	511.2
(2)	356.0	310.2	360.6	^a
(3)	428.1	353.9	394.7	719.3

^a Ring opens to form a zwitterionic species.

<i>Compd.</i>	<i>Bond</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>
(1)	S-S	2.103	2.055	2.055	2.168
(2)	S-S	2.144	2.094	2.079	^a
	S-N	1.804	1.771	1.761	^a
(3)	S-N	1.850	1.806	1.779	1.911

^a Ring opens to form a zwitterionic species.

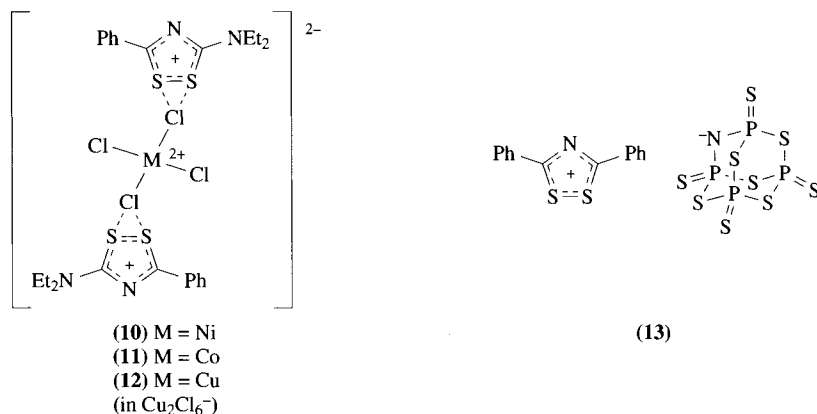
MNDO calculation of ΔH_f^0 for 3-amino-1,2,4-dithiazole-5-thione indicated that, of its possible isomeric forms (7), (8), and (9) (R = H), (7) is the most favorable. This structure had been found experimentally in the crystal and in solution but the differences are small and structures (8) and (9) may also take part in reactions. In fact, methylation of (7; R = H) gives (9; R = Me) shown by MNDO calculation to possess the lowest ΔH_f^0 $\langle 82JCR(S)65 \rangle$. The MNDO method was used to calculate the structure and energy of 3-amino-1,2,4-dithiazole-5-one, its molecular cation and also its fragmentation ions $\langle 82MI 413-01 \rangle$.



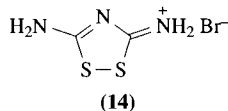
4.13.3 EXPERIMENTAL STRUCTURAL METHODS

4.13.3.1 X-ray Diffraction

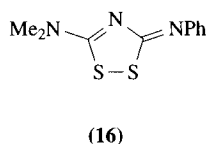
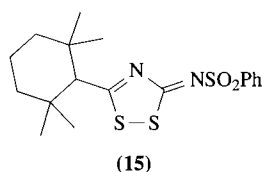
The dithiazolium cation moiety in structures (10) <89ZAAC(576)203>, (11) <90ZAAC(586)79>, (12) <91ZN(B)1113>, and (13) <86ZAAC(542)123> has been shown to possess a fully delocalized π -electron system. This is evidenced by planarity of the ring, shortening of the ring bonds relative to unconjugated bonds and also to those in an uncharged 1,2,4-dithiazole cycle. Substituents [Ph, -N(CH₂CH₃)₂] assume a nearly coplanar disposition with respect to the ring and the substituent-to-ring bonds are shortened implying conjugation. Tetrahedrally shaped metal centred anions in (10) and (11) make close contacts (3.26–3.32 Å, shorter than of Van der Waals radii 3.65 Å) by their negatively charged chlorine atoms with ring sulfur atoms of the dithiazolium cation.



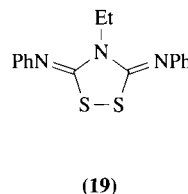
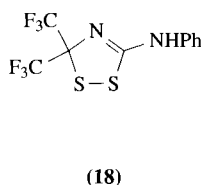
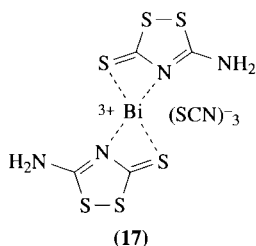
A new, more accurate x-ray analysis of 3,5-diaminodithiazolium bromide (14), <82MI 413-02, 82SA(A)971> has confirmed the earlier findings that SS and CS bonds are essentially of single bond length, while bonds in the NCNCN chain contract and even out suggesting that conjugation is localized mainly in the above chain; thus the whole perfectly planar ring cannot be considered aromatic. Secondly, the proton is located on an amino group, not on the ring nitrogen atom, which thus retains its lone electron pair (not involved in the conjugation) ready for bonding and imparts to the positively charged ring a paradoxical ability to donate electrons, for example for a coordination bond with Cu⁺ <75CC550>.



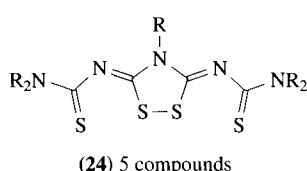
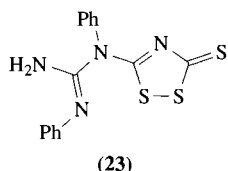
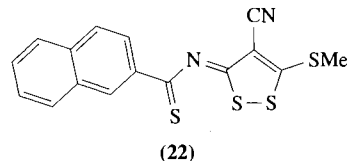
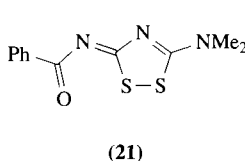
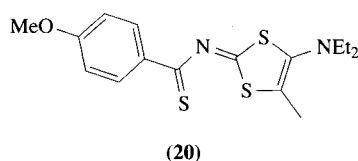
The neutral 3-imino-3*H*-1,2,4-dithiazole (15) <88CB689>, corresponding in geometry to an earlier studied analogous compound (16) <77PS(3)185>, is planar together with the attached atoms of substituents, but though the bond lengths in the shorter CNCN chain show more pronounced alternation the whole pattern of bond lengths in the heterocycle could be understood in terms of quasiaromatic electron delocalization <79COC(4)839>.



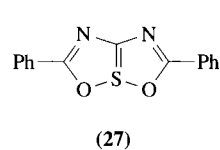
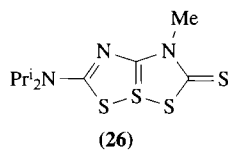
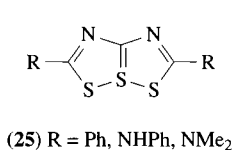
3-Amino-1,2,4-dithiazole-5-thione in the bismuth complex (17) appears as a bidentate ligand <89MI 413-01> in contrast to its previously observed monodentate character. The Bi—S distance (mean 2.873 Å) corresponds to a normal covalent bond, whereas the Bi—N distance (mean 2.678 Å) lies between the sum of covalent radii (2.20–2.25 Å) and the sum of ionic and van der Waals radii (≈ 2.74 Å). An obviously nonaromatic 1,2,4-dithiazoline ring in (18) deviates only slightly from planarity, the hydrogen being located on the exocyclic nitrogen <90CB691>. The 1,2,4-dithiazolidine ring in (19) is completely planar <86BCJ987> and the whole geometry is very close to that of the 4-benzyl analogue studied earlier <84CHEC-I(6)897>.



The structures (20) <85ACS(B)103>, (21) <90JPR208>, (22) <85CC1704>, and the earlier analyzed (23) <78AX(B)2570> and (24) <84CHEC-I(6)897> allow a comparison of the interaction of the ring sulfur atom with the coplanar exocyclic double bonded sulfur, oxygen, or nitrogen atoms. All the found distances have a value between the van der Waals radii sum and standard single bond lengths. The least deviation from a standard single bond length is observed for (22). The N···S interaction in (23) was regarded as essentially insignificant <78AX(B)2570>. The O···S interaction in (21) was assessed as sufficiently strong to imply a thiapentalene structure; the electron lone pair of oxygen was thought to interact with the *d*-orbital of sulfur <90JPR208>. The S···S interaction was estimated by the authors as strong <84CHEC-I(6)897>. The extent of engagement of both atoms depends considerably on the structure of the heterocycle involved.



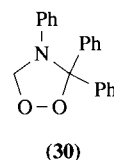
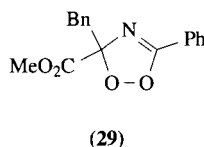
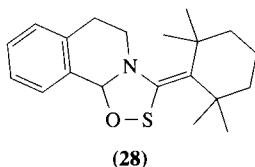
In trithiadiazapentalenes (25; R = Ph) <73ACS(A)510>, (25; R = NHPH) <81ACS(A)663>, (25; R = NMe2) <77BSB291>, and (26) <82ACS(A)445> SS bonds are somewhat longer than a standard SS single bond and consequently somewhat weaker. The bicyclic nucleus is planar, except for (26), where two halves of it are inclined to each other at an angle of 9.9°. In (25; R = NPh) the two SS bonds are unequal in length (2.227 and 2.477 Å) apparently because of distortion imposed by intermolecular hydrogen bonds. The similar inequality between two SO bonds (1.852 and 1.917 Å) in (27) is less explicable <81ACS(A)645>. They are also longer than a standard single SO bond.



The 1,2,4-oxathiazolidine ring in (28) has an envelope conformation, the OCN flap being bent at $\approx 5^\circ$ relative to the OSCN plane. The ring bonds are actually single: SO 1.661 Å, OC 1.482 Å, CN 1.443 Å, Csp²N 1.437 Å, Csp²S 1.823 Å <78AG480>. The OC bond (1.352 Å) adjacent to the N = C

bond in 3*H*-1,2,4-dioxazole ring (**29**) is intermediate in length between single and double apparently because of O=C=N conjugation. The OO bond length (1.464 Å) almost coincides with that in H₂O₂, the rest of ring bonds also being single. The ring is nonplanar: O-2 is moved out of plane of the other four atoms by 13.7° <92CSC2172>. The 1,2,4-dioxazolidine ring (**30**) deviates even more from planarity; all ring bonds have single bond lengths <88CC1550>.

Molecular structure was also determined by x-ray analysis for (**241**; A—B: CH=CH) <83CC199> (**236**; R = Bn) and (**238**; R = Bn) <86JOC407>, but no bond lengths and angles were given.



4.13.3.2 Proton NMR Spectroscopy

Table 3 contains chemical shifts data for a series of representative structures.

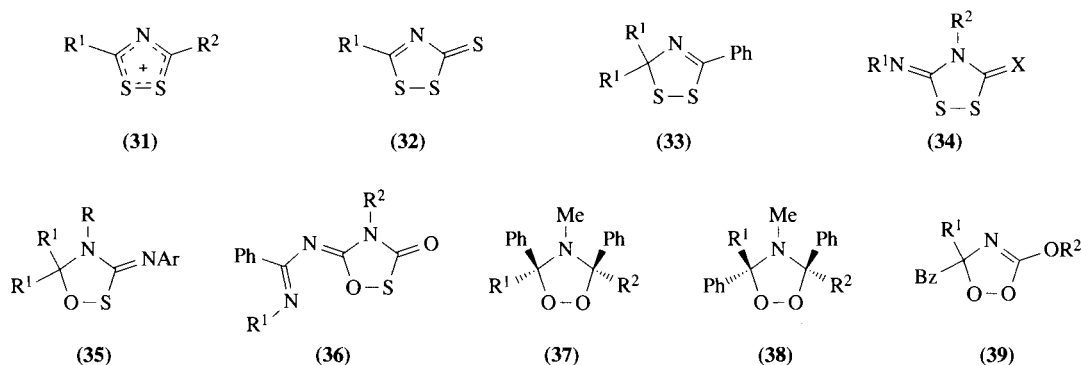
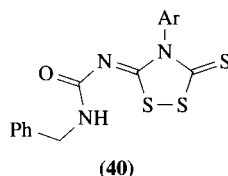


Table 3 Proton NMR data for 1,2,4-dithiazoles, -oxathiazoles, and -dioxazoles.

Structure	Chem. shifts δ , ppm		Solvent	Ref.
	R^1	R^2		
(31) $R^1 = H$; $R^2 = Ph$	10.96		TFA	74AP(307)828
$R^1 = R^2 = NMe_2$	3.281		(CD ₃) ₂ SO	87BCJ2686
	3.395			
(32) $R^1 = H$	9.49		CDCl ₃	85ZAAC(525)112
(33) $R^1 = H$	5.70		CCl ₄	74AP(307)828
$R^2 = Me$	1.83		CDCl ₃	82HCA1825
(34) $X = O$; $R^1 = Me$; $R^2 = Ph$	3.06		CDCl ₃	90JPR181
$R^1 = R^2 = Me$	3.14	3.26	not indicated	87JOC2783
$R^1 = R^2 = CH_2Me$	3.35	3.89	not indicated	87JOC2783
$X = S$; $R^1 = R^2 = Me$	3.10		CD ₃ C ₆ D ₅	91JOC3268
(35) $R^1 = R^2 = Me$	1.55	3.0	CDCl ₃	90JHC1993
(36) $R^1 = R^2 = Me$	3.66	3.54		86CB3737
(37) $R^1 = R^2 = H$	5.379	5.379	CDCl ₃	84TL3035
(38) $R^1 = R^2 = H$	5.808	5.808	CDCl ₃	84TL3035
(39) $R^1 = R^2 = Me$	1.88	4.04	CDCl ₃	90JCS(P1)1011

Proton NMR spectroscopy was used to follow successive transformations of iminothiatriazoline (**159**) in its reaction with pyridylisothiocyanate (see Section 4.13.8.4.) <88JHC1459>. Two singlets from NMe₂ in (**31**; $R^1 = R^2 = NMe_2$) were considered to be a sign of a restricted rotation of the NMe₂ groups <87BCJ2686>. A doublet at δ 4.35–4.4 in compounds (**40**) was quoted as evidence of hydrogen location on the benzyl bearing a nitrogen atom, rather than on the imino group <92JHC451>.

Two singlets δ 4.67 and 5.03 in the reaction mixture were assigned to CH_2 groups of benzyl substituents as evidence for the heterapentalene intermediate (**106**; $\text{R} = \text{Ts}$) in Scheme 19 <90JHC1629>. The characteristic downfield shift of the R^1 alkyl signals during the transformation of thione (**34**) to dithione (**51**) can be used to follow the course of this type of Dimroth rearrangement <91JPR107>. A high field shift of CH_2 protons by ≈ 1 p.p.m. in (**237**; $\text{R} = \text{Et}$) relative to (**236**; $\text{R} = \text{Et}$) was used to assign both structures <86JOC407>.



4.13.3.3 Carbon-13 NMR Spectroscopy

Some representative ^{13}C NMR data are given in Table 4. Dimroth rearrangement can be followed by the change of the ^{13}C signal corresponding to the $\text{C}=\text{S}$ group in the initial dithione (**230**; $\text{X} = \text{S}$) or oxothione (**230**; $\text{X} = \text{O}$) into a signal corresponding to the $\text{C}=\text{N}$ bond in the iminothione or oxoimino product from δ 187–190 to 176–178 ppm <91JPR107> and from $\delta \approx 175$ to 144–150 ppm <90JPR181> respectively. The signal of the $\text{C}=\text{O}$ group in compound (**21**) δ 177.3 is strongly shifted downfield from the usual amide region ($\approx \delta$ 165); this was interpreted as an indication of an appreciable contribution of pentalene character (**41**) to the real structure of the substance, as was also confirmed by x-ray analysis <90JPR208>.

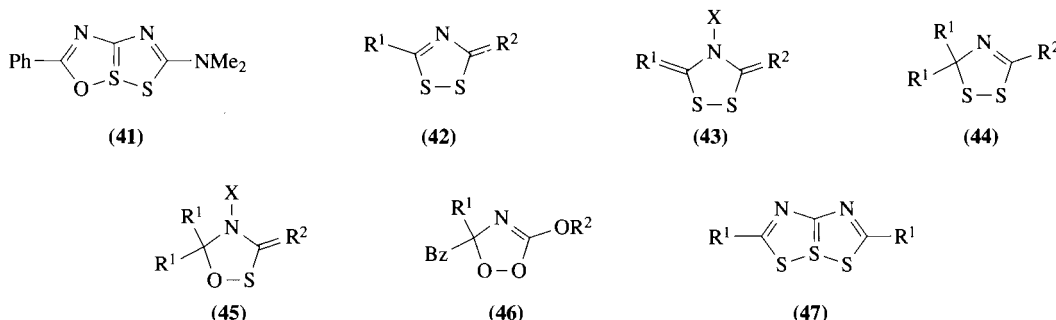


Table 4 Carbon-13 NMR data for 1,2,4-dithiazoles, -oxathiazoles, and dioxazoles.

Structure	Chem. shifts δ , ppm of ring carbon		Solvent	Ref.
	$\text{C}-\text{R}^1$	$\text{C}-\text{R}^2$		
(42) $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{S}$	190.8	214.8	CDCl_3	85ZAAC(525)112
$\text{R}^1 = \text{PhNH}$; $\text{R}^2 = \text{S}$	179.1	209.3	$(\text{CD}_3)_2\text{SO}$	80JCR(S)266
(43) $\text{R}^1 = \text{MeN}$; $\text{R}^2 = \text{O}$; $\text{X} = \text{Ph}$	149.4	168.4	CDCl_3	90JPR181
$\text{R}^1 = \text{PhN}$; $\text{R}^2 = \text{O}$; $\text{X} = \text{Ph}$	150.0	168.7	CDCl_3	90JPR181
$\text{R}^1 = \text{PhCH} = \text{NN}$; $\text{R}^2 = \text{O}$; $\text{X} = \text{Ph}$	162.0		CDCl_3	91JHC1957
$\text{R}^1 = \text{BnN}$; $\text{R}^2 = \text{O}$; $\text{X} = \text{Bn}$	148.5	169.2	CDCl_3	75JOC1728
(45) $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{NAr}$; $\text{X} = \text{Me}$	100.4	159.8	CDCl_3	90JHC1993
$\text{R}^1 = \text{CD}_3$; $\text{R}^2 = \text{NCOCCl}_3$; $\text{X} = \text{Bn}$	100.5	179.7	CDCl_3	92JHC17
$\text{R}^1, \text{R}^2 = \text{CCl}_3$, NCS ; $\text{R}^2 = \text{NCOCCl}_3$, $\text{X} = \text{Bn}$	107.1	182.6	CDCl_3	92JHC17
(47) $\text{R}^1 = \text{PhNH}$	181.2	185.9 ^a	$(\text{CD}_3)_2\text{SO}$	89JPR115
$\text{R}^1 = \text{PhO}$	195.0	190.0 ^a	$(\text{CD}_3)_2\text{SO}$	90JPR208, 89M(120)997
(44) $\text{R}^1 = \text{CF}_3$; $\text{R}^2 = \text{NHPh}$	97.5	167.5	CDCl_3	90CB691
(42) $\text{R}^1 = \text{PhNH}$; $\text{R}^2 = \text{NCOPh}$	178.9	185.6	$(\text{CD}_3)_2\text{SO}$	90JPR208
$\text{R}^1 = p\text{-ClC}_6\text{H}_4\text{O}$; $\text{R}^2 = \text{NCOPh}$	191.0	186.5	$(\text{CD}_3)_2\text{SO}$	90JPR208
(43) $\text{R}^1 = \text{PhN}$; $\text{R}^2 = \text{EtN}$; $\text{X} = \text{Ph}$	153.9	150.3	CDCl_3	86JOC407
(46) $\text{R}^1 = \text{R}^2 = \text{Me}$	110.1	160.2	CDCl_3	90JCS(P1)1011

^aFor C3a

4.13.3.4 UV Spectroscopy

UV Absorptions of (32; $R^1 = H$) in ether (Table 5) <85ZAAC(525)112> bear little resemblance to UV spectra of amino analogues (32; $R^1 = NH_2, NMe_2, NHCO_2Et$) either in acid or in basic solutions. Absorption bands for the dithiazole cation (31; $R^1 = R^2 = NMe_2$) <87BCJ2686> are markedly shifted relative to bands of the unsubstituted diamino cation in ethanol (31; $R^1 = R^2 = NH_2$) <84CHEC-I(6)897>. UV spectral comparison of (34; $X = O, R^1 = N=CHPh, R^2 = Ph$) with the other two derivatives (34; $X = O$) in Table 5 was used in structural assignment <91JHC1957>.

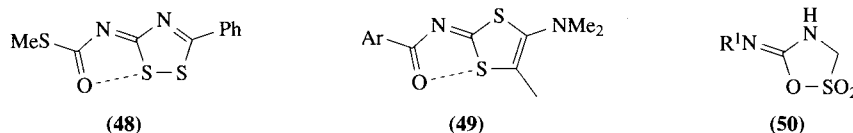
Table 5 UV Absorption maxima for 1,2,4-dithiazoles.

Structure	λ_{max} (nm)(log ϵ)	Solvent	Ref.
(32) $R^1 = H$	228(4.09), 227(3.67), 320(3.66), 404(3.80)	Et ₂ O	85ZAAC(525)112
(31) $R^1 = R^2 = NMe_2$	266(4.40)	EtOH	87BCJ2686
(34) $X = O; R^1 = R^2 = Ph$	204(4.48)	^a	91JHC1957
$X = O; R^1 = N=CHPh; R^2 = Ph$	202(4.32), 261(4.17), 314(4.14)	^a	91JHC1957
$X = O; R^1 = N=CHPh; R^2 = CHPh$	204(4.53), 260(4.49), 316(4.37)	^a	91JHC1957
(42) $R^1 = -CH(CMe_2CH_2)_2CH_2,$ $R^2 = NSO_2Ph$	236(4.0) 342(3.7)	isooctane	88CB689

^a Not indicated.

4.13.3.5 IR Spectroscopy

Some IR ring-stretching frequencies of non-complexed 1,2,4-dithiazoles and oxathiazoles are shown in Table 6. A very low frequency of carbonyl stretching band (1560 cm^{-1}) for (48) <85LA1874> as well as for (49) <85ACS(B)103> indicates a considerable interaction of the carbonyl oxygen with ring sulfur atom. IR spectra of 3,5-diamino-1,2,4-dithiazolium halides and its metal halide complexes have been studied in some detail <82SA(A)971, 90ZAAC(586)79>.

Table 6 IR Stretching vibrations (cm^{-1}) for 1,2,4-dithiazoles and -oxathiazoles.

Structure	IR Absorptions (cm^{-1})			Ref.
	$\nu(C=O)$	$\nu(C=S)$	$\nu(C=N)$	
(44) $R^1 = Me; R^2 = Ph$			1640	82HCA1825
(34) $R^1 = R^2 = Me; X = O$	1705		1640	87JOC2783
$R^1 = R^2 = Et; X = O$	1695		1620	87JOC2783
$R^1 = R^2 = Pr^a; X = O$	1690		1630	87JOC2783
$R^1 = R^2 = Bu^a; X = O$	1670		1630	87JOC2783
(32) $R^1 = H$		975	1443	85ZAAC(525)112
(50) $R^1 = Ph$			1630	91PS(57)203

4.13.3.6 Mass Spectrometry

Fragmentation routes of 1,2,4-dithiazole derivatives have been suggested and discussed for (42; $R^1 = H, R^2 = S$ <85ZAAC(525)112>, $R^1 = NPr^i_2, N(c-C_6H_{11})_2, R^2 = S$ <82ZC377>) and (44; $R^1 = H, R^2 = N(CH_2CH_2)_2O$ <82ZC377>, $R^1 = Me; R^2 = Ph$ <82HCA1825>). As a rule the fragmentation begins with loss of one or two ring sulfur atoms. In the case of (44; $R^1 = Me, R^2 = Ph$) benzonitrile is lost as an entity strongly stabilized by conjugation. The mode of further fragmentation depends on substituents and other structural features. Molecular ion peaks appear in the above examples and

in (**43**; $R^1 = \text{NAlk}$, $R^2 = \text{O}$, $X = \text{Alk}$ <87JOC2783>), (**42**; $R^1 = \text{OAr}$, NR_2 , $R^2 = \text{NCOAr}^1$ <90JPR208>, $R^1 = \text{CH}(\text{CMe}_2\text{CH}_2)_2\text{CH}_2$, $R^2 = \text{NSO}_2\text{Ph}$ <88CB689>) except for (**42**; $R^1 = \text{CH}(\text{CBu}^t_2\text{CH}_2)_2\text{CH}_2$, $\text{CH}(\text{CBu}^t_2\text{CH}_2)_2\text{CHBu}^t$, $R^2 = \text{NSO}_2\text{OPh}$ <88CB689>). The main peak for heterathiopentalenes (**168**) is $[\text{M}^+ - \text{ArNH}]$, rather than $[\text{M}^+ - \text{ArNCS}]$, indicating a high stability for the heterapentalene nucleus <89JPR115>.

4.13.4 THERMODYNAMIC ASPECTS

4.13.4.1 Stability and Stabilization

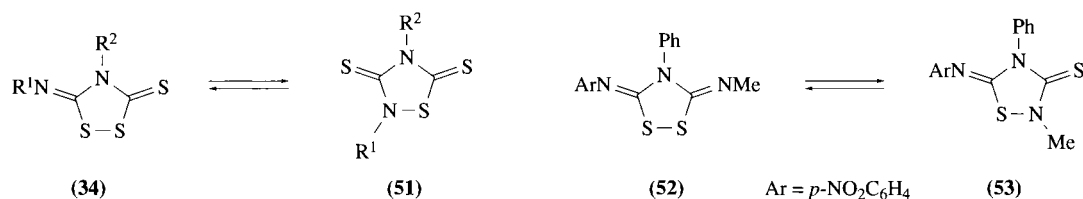
3-Diethylamino-5-phenyl-1,2,4-dithiazolium tetrachloro-(or bromo)nickelate²⁺ (**10**) decomposes in protic (H_2O , EtOH) and strongly coordinating solvents (DMF, DMSO, MeCN, pyridine) in which it is soluble. It can be stored in a dessicator or a sealed tube from a month to a year <89ZAAC(576)203>.

3,5-Diamino-1,2,4-dithiazolium (DADT) complex salts with metal halides are interesting in that coordination with the metal occurs through the electron lone pair of the ring nitrogen as shown by x-ray analysis of $\text{DADT} \cdot \text{CuCl}_2$ <75CC550> and $\text{DADT} \cdot \text{CuBr}_2$ complexes (see Section 4.13.3.1) <82SA(A)971>. The complexes of this positively charged but electron donor ligand are highly soluble in DMF suggesting that dissociation occurs in the solution <82SA(A)1069>. The molar conductivities of all $\text{DADT} \cdot \text{MX}_2$ complexes in DMF ($\Lambda = 59\text{--}90 \text{ } \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$) fit in the region characteristic of 1:1 electrolytes ($\Lambda = 65\text{--}90$) to imply complete dissociation to DADT^+ and $\text{MX}_2 \cdot (\text{DMF})_n^-$ ions. The values for $\text{DADT} \cdot \text{CuI}_3$ ($\Lambda = 109$) and $2\text{DADT} \cdot \text{HgX}_4$ ($\Lambda = 77\text{--}104$) are lower than those for 1:2 electrolytes and suggest a partial coordination of the cation with metal ion in the solution <82SA(A)1069>. Conductivity of the salt (**11**) in MeCN ($\Lambda = 269$) corresponds to a 2:1 electrolyte, i.e. no coordination between the cation and metal ion in solution <90ZAAC(586)79>. Attempts to isolate the free base from DADT complex salts (e.g. by alkali) showed it to be completely unstable decomposing with liberation of sulfur <82SA(A)971>.

Compounds (**75**) with a weak but not completely broken SS bond sharply differ in stability depending on the nature of X <85ACS(B)103>. Those where $X = \text{S}$ are perfectly stable, whereas derivatives where $X = \text{O}$ undergo dissociation even at 20°C furnishing within weeks an orange-red mixture containing the precursor from which the specimens had been originally prepared by adding ynamines (see Section 4.13.5.4). For related examples involving (**77**), (**80**), (**82**), (**83**), see Section 4.13.5.4.

4.13.4.2 Isomerization Equilibrium

Isomerization of 5-imino-1,2,4-dithiazolidine-3-thiones (**34**) into 1,2,4-thiadiazolidine-3,5-dithiones (**51**) by a Dimroth rearrangement (see Section 4.13.6.1.1) is a reversible process <91JPR107>. The equilibrium position strongly depends on the nature of substituents. When $R^1 = R^2 = \text{Me}$ or Pr^i the equilibrium position is (**34**):(**51**) = 1:2, with $R^1 = R^2 = \text{Et}$ the ratio is 1:9. When $R^1 = \text{Ar}$, $R^2 = \text{Alk}$, the equilibrium is almost wholly shifted to the right. The forward process is usually accelerated by bases, the reverse by acids. When both substituents are Ar no isomerization occurs <91JPR107>. Isomerization of the 3,5-diimino analogue (**52**) to a monothione isomer (**53**), accelerated by pyridine, reaches an equilibrium ratio of (**52**):(**53**) = 1:9 <89BSB879>.



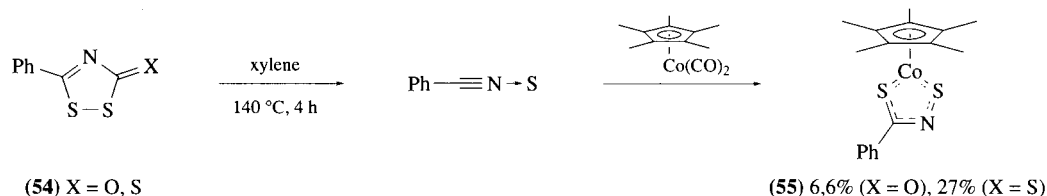
4.13.5 REACTIVITY OF FULLY CONJUGATED RINGS

The overwhelming majority of reactivity studies concern 1,2,4-dithiazoles. One of the most characteristic reactions is 1,3-cycloaddition of compounds with various double and triple bonds across the $\text{N}=\text{C}-\text{S}$, $\text{O}=\text{C}-\text{S}$, and $\text{S}=\text{C}-\text{S}$ moieties of 3-imino-, -oxo-, and -thio-1,2,4-dithiazoles formed by the 3-substituent and neighboring sulfur ring atom (see Section 4.13.5.4), <84CHEC-I(6)897>. A new five-membered heterocycle is formed which is accompanied by the SS bond breaking in the dithiazole ring. Nucleophilic attack at the ring carbon atom is very common. Usually this leads to ring opening followed by an alternative ring closure to afford a great variety of five- or six-membered heterocycles (see Section 4.13.5.2), <84CHEC-I(6)897>. 1,2,4-Dithiazole cations are especially active in this reaction. Typical nucleophiles are those with an activated CH_2 group, nitrogen-containing bases and thiols. A good leaving group (e.g. RO in (62), (63) or RS) can also be displaced by the nucleophile <84CHEC-I(6)897>. Chemical and electrochemical reduction of aminoderivatives breaks the SS bond to give thioureas or dithiobiurets <84CHEC-I(6)897>. Thermolysis or photolysis causes rupture of the ring in various patterns depending on the nature of the substituents (see Section 4.13.5.1), <84CHEC-I(6)897>.

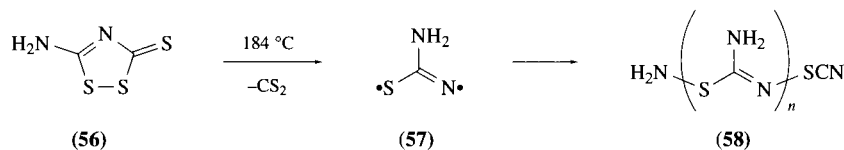
Imino 1,2,4-oxathiazoles (81) (see Section 4.13.5.4) are reported to undergo the type of 1,3-cycloaddition-ring cleavage found with the dithiazoles. 1,2,4-Dioxazoles are deoxygenated by Ph_3P with opening the ring <84CHEC-I(6)897>.

4.13.5.1 Thermal and Photochemical Formally Unimolecular Reactions

On thermolysis 1,2,4-dithiazoles (54) generate benzonitrile sulfide which can be trapped by pentamethylcyclopentadienyl cobalt(III) dicarbonyl to produce cobaltadithiazol (55) (Scheme 1) <92CL243>. 5-Amino-1,2,4-dithiazole-3-thione (56) at 184°C loses 1 mol CS_2 to give the oligomer (58) presumably via the biradical (57) (Scheme 2) <84MI 413-01>. Derivatographic study of thermolysis of 1,2,4-dithiazolium iodides showed them to decompose in two or four overlapping steps depending on substituents <86MI 413-01>.



Scheme 1

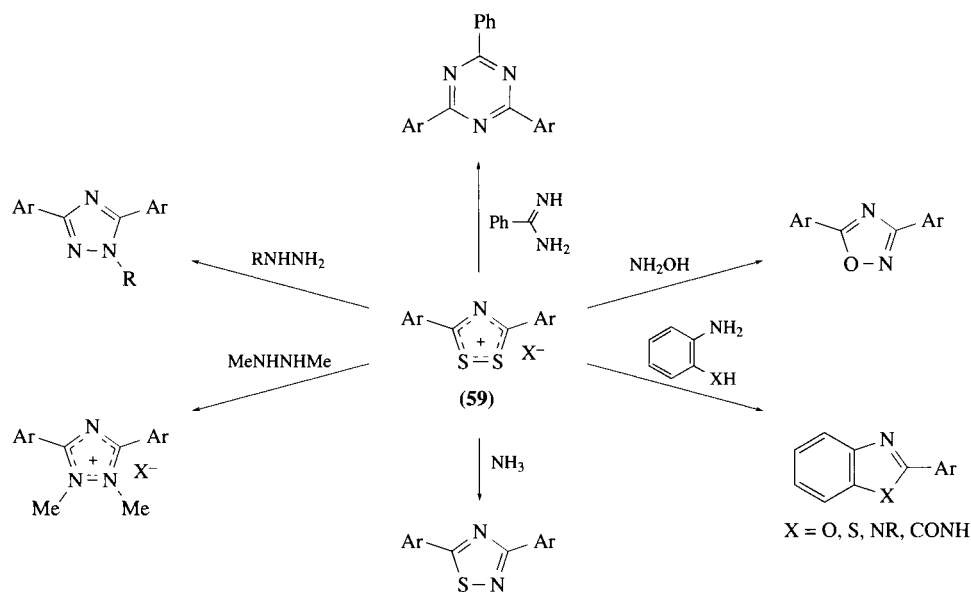


Scheme 2

4.13.5.2 Nucleophilic Attack at Ring Carbon

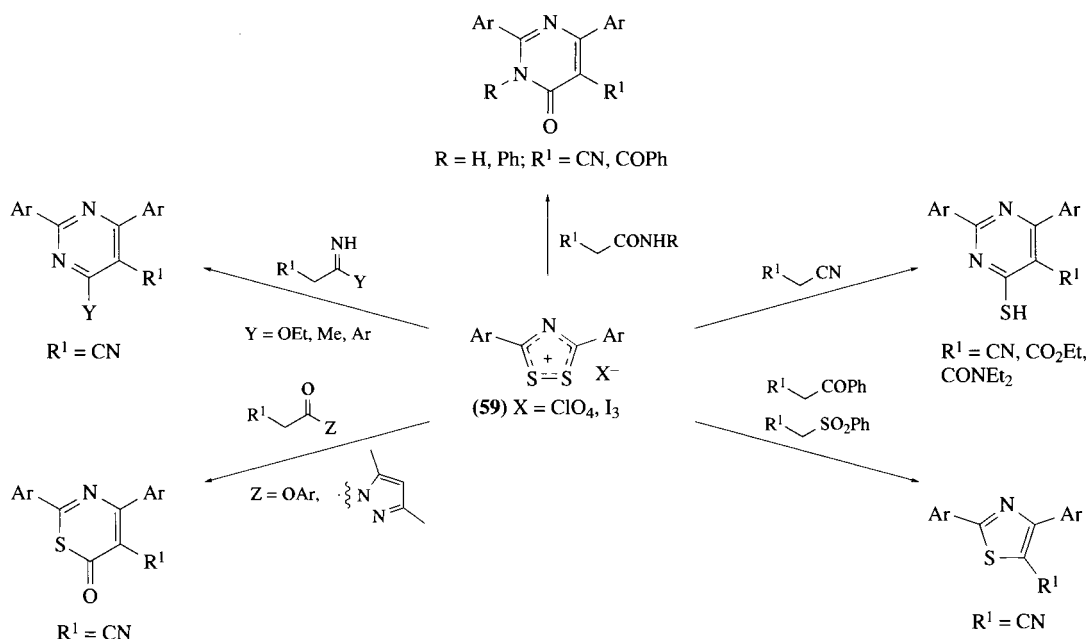
3,5-Diaryl-1,2,4-dithiazolium salts (59) are highly reactive 3,5-dielectrophiles and readily interact with nucleophiles, to give a broad variety of heterocyclic compounds (Scheme 3) <82MI 413-03, 82NKK1518, 85H(23)997>.

Much attention was given to nucleophiles containing an activated methylene group which also afforded a number of heterocyclic products, especially pyrimidines and thiazines variously substituted (Scheme 4). The reaction proceeds in boiling MeOH or THF <84BCJ605> or even at room temperature in MeCN <85ZC327> or DMF <85ZC141, 86EGP240887>. A base (AcONa , MeONa , NaH) is usually required. Yields are 30–90%. Nucleophilic attack is thought to result in formation of ring



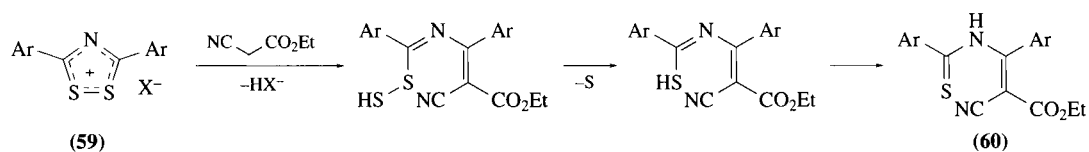
Scheme 3

and open chain intermediates (Scheme 5) $\langle 84BCJ605, 85H(23)997, 85ZC141, 85ZC327 \rangle$, for example the open chain (**60**) was isolated and studied $\langle 85ZC364, 91LA345 \rangle$. It cyclized to pyrimidine derivatives when treated with AcOH or primary and secondary amines and ammonia in AcOH medium by short boiling (Scheme 6) $\langle 91LA345 \rangle$. Mechanisms to explain these complicated transformations have been suggested $\langle 85ZC327, 84BCJ605, 85ZC364, 91LA345, 85H(23)997 \rangle$.

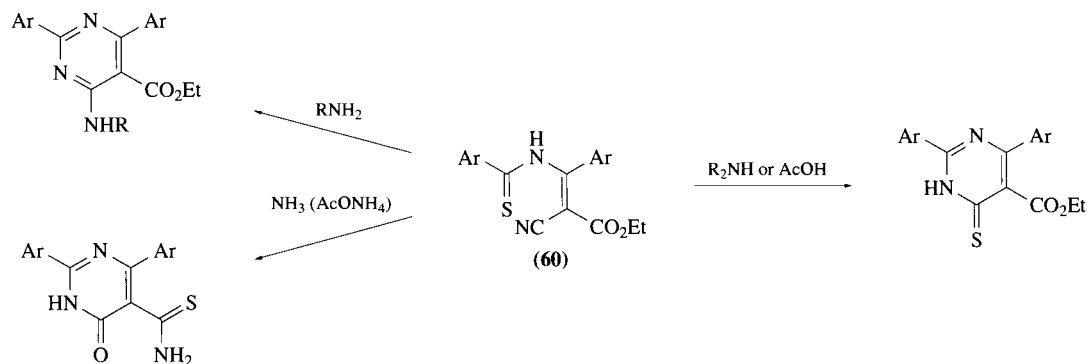


Scheme 4

The dithiazolium salts (**59**) may also be converted into various open chain products by action of alkali, amines, and thiols (Scheme 7) $\langle 85H(23)997 \rangle$. Dithiazolium salts containing a substituent susceptible to displacement by a nucleophile readily give products in which the ring remains intact, for example (**31**; $R^1 = \text{Ph}$, $R^2 = \text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$) gives the hydrazone (**61**) with *p*-nitrophenylhydrazine $\langle 85T5371 \rangle$. The uncharged 1,2,4-dithiazole ring is also prone to nucleophilic attack at carbon atom. For example, 2,5-diaryloxy-1,6,6 α λ^4 -trithia-3,4-diazapentalenes (**62**) smoothly undergo nucleophilic substitution, the second aryloxy group being replaced less easily than the first

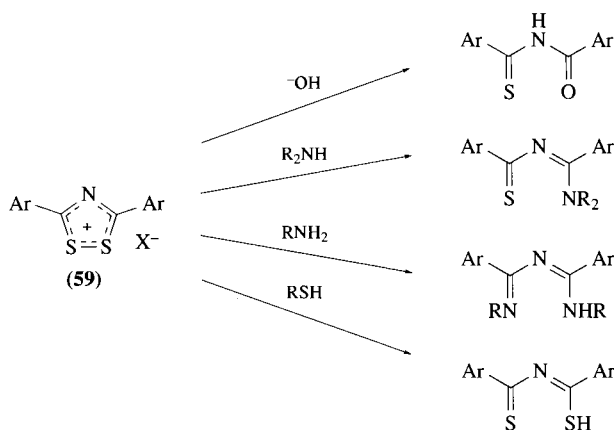


Scheme 5

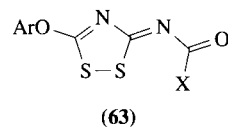
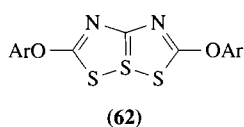
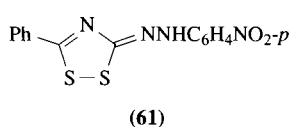


Scheme 6

one by amines <89M(120)997>. The aryloxy group in the monocyclic analogues (63) is similarly displaced with amines <90JPR208>.

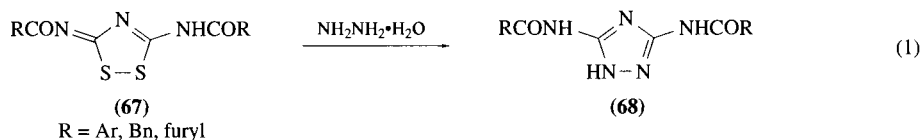


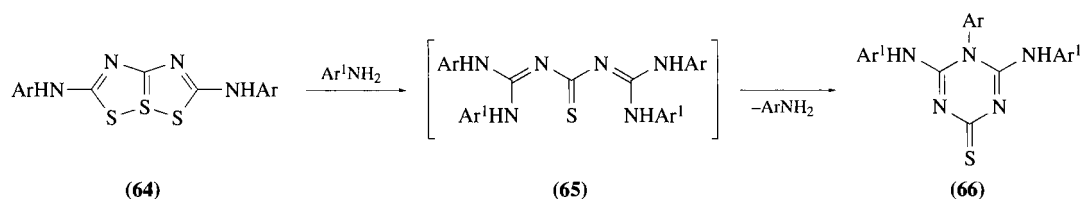
Scheme 7



2,5-Diarylaminotrithiadiazapentalenes (64) react with arylamines with ring opening to give 1,3,5-triazine derivatives (66) via (65) (Scheme 8) <93IJC(B)879>.

3-Acylamino-5-acylimino-1,2,4-dithiazoles (67) are transformed into the corresponding 1,2,4-triazoles (68) when treated with hydrazine hydrate which apparently displaces the SS unit by attack at ring carbon (Equation (1)) <85MI 413-01>.



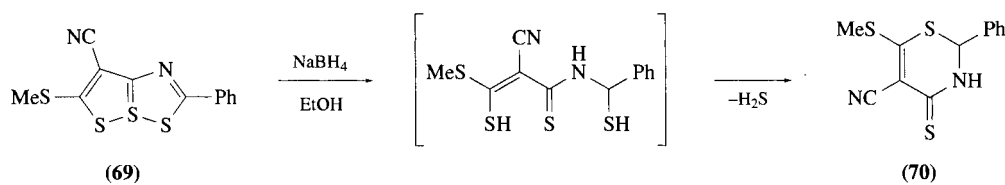


Scheme 8

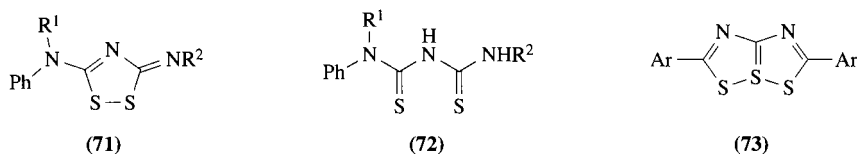
4.13.5.3 Reactions Involving Radicals, Electron-deficient Species, Reducing Agents and at Surfaces

When the known conversion of 1,2,4-dithiazole-3-thiones (**54**; $\text{X} = \text{S}$) into thioacylthiocyanates by the action of Ph_3P [84CHEC-I(6)897] is carried out in the presence of amines, thioacylthioureas are produced [84EGP214377]. An analogous reaction was observed for 1,2,4-dithiazole-3-ones [87JAP87195365]. Sodium borohydride breaks both SS bonds in trithiaazapentalene (**69**) to give thiazine (**70**) (Scheme 9) [85CC1704]. Aminoimino-1,2,4-dithiazoles (**71**) are ring opened to dithiobiurets (**72**) by hydrogen sulfide [82JIC1165, 90JIC(B)937].

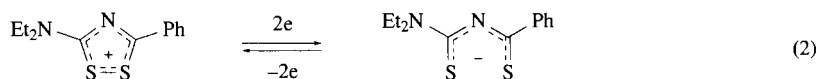
2,5-Diaryl-1,6,6 λ^4 -trithia-3,4-diazapentalene (**73**) is reduced electrochemically under aerobic conditions to a radical anion which is capable of transferring one electron to O_2 to produce the superoxide $\text{O}_2^{\cdot -}$ with regeneration of (**73**) [91CPB1914].



Scheme 9

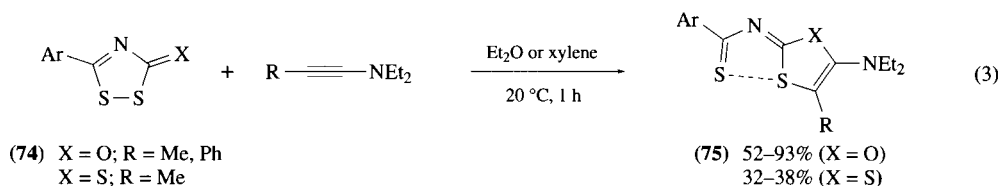


The reversible electrochemical interconversion of 1,2,4-dithiazolium cation and thioacylthiourea anion was demonstrated by cyclic voltammetry (Equation (2)) [91JPR537]. In the presence of chelate-forming metals in the form of anions CuCl_4^{2-} , CuBr_4^{2-} , CoCl_4^{2-} , NiCl_4^{2-} , etc. the thioacylthiourea anion produced is chelated and the reversibility of the reduction is diminished or entirely blocked depending on the metal.

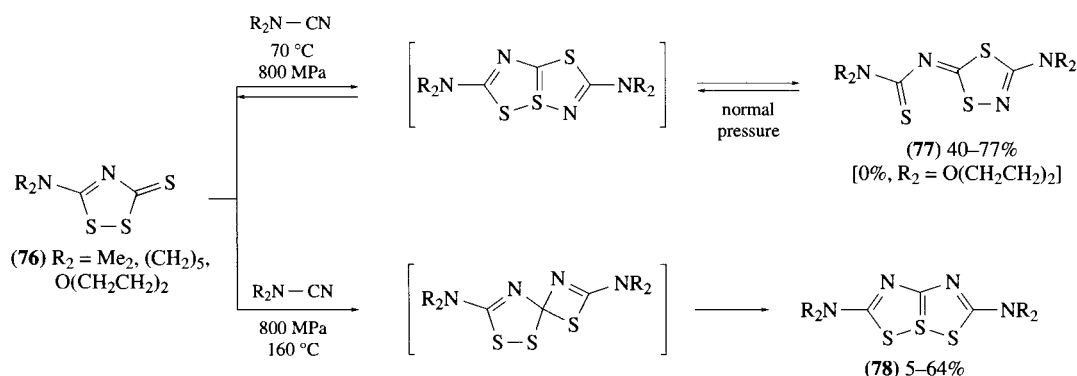


4.13.5.4 Cyclic Transition State Reactions with a Second Molecule

Ynamines add across the $\text{S}-\text{C}-\text{O}$ (or $\text{S}-\text{C}-\text{S}$) grouping of 5-aryl-1,2,4-dithiazole-3-ones (or -thiones) (**74**) with concomitant loosening of the SS bond [85ACS(B)103] to produce (**75**). This is stable when $\text{X} = \text{S}$, but when $\text{X} = \text{O}$ it reverts at 20°C within weeks to a mixture containing the precursor (**74**) (Equation (3)).

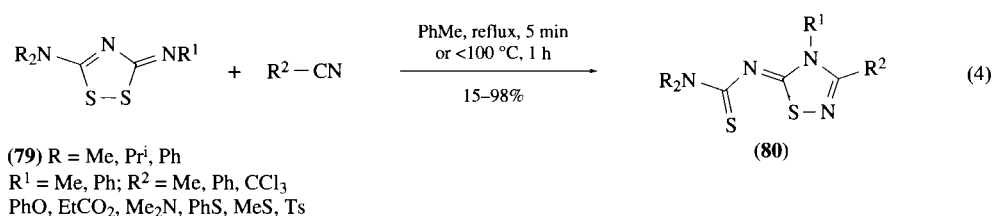


5-Dialkylamino-1,2,4-dithiazole-3-ones (76) add dialkylcyanamides across the S=C—S grouping under high pressure <89CL1357>. At 70 °C 1,3-cycloaddition occurs to give unstable 1,3,5-dithiazole derivatives (77), which break down completely at a normal pressure to the initial components on heating above their m.p. (> 140 °C) or on standing in CHCl₃ solution for one week at 20 °C. At 160 °C [2 + 2] cycloaddition takes place irreversibly to yield stable trithiadiazapentalenes (78) (Scheme 10).

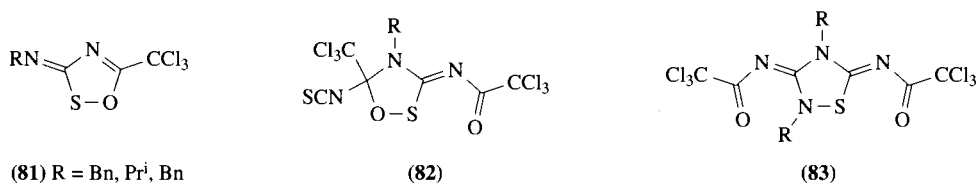


Scheme 10

Nitriles undergo 1,3-cycloaddition to 5-amino-1,2,4-dithiazoline-5-imines (79) across N=C—S grouping with rupture of the SS bond to give 1,2,4-thiadiazoles (80) regioselectively. Electron-accepting substituents in (79) decrease the reactivity (Equation (4)) <85CB3241>.



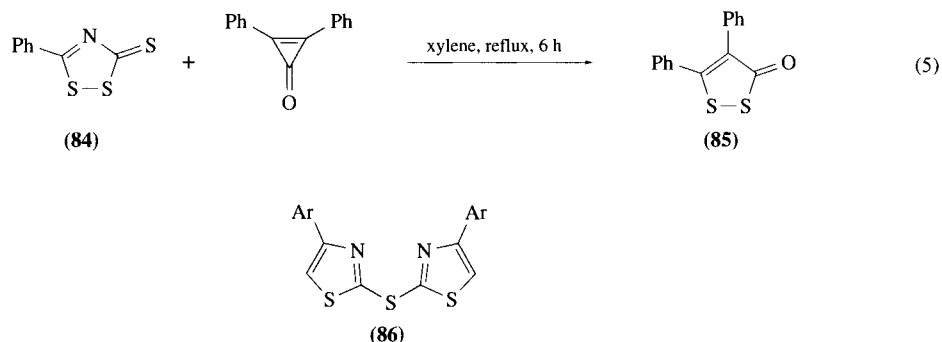
Similar 1,3-cycloadditions of 3-imino-5-trichloromethyl-1,2,4-oxathiazoles (81) (known only in solution) across the C=O bond of trichloroacetylisothiocyanate and the imino C=N bond of trichloroacetylcarbodiimide gives the unstable heterocyclic compounds (82) and (83) respectively <92JHC17>.



4.13.5.5 Other Reactions

Reaction of 5-phenyl-3*H*-1,2,4-dithiazole-3-thione (84) with 1,2-diphenylcyclopropenone leads to the SS bridged ring-opened cyclopropenone product (85) (70%) and the trithiaheterapentalene bicycle (25; R = Ph)(7%) which is believed to result from thermal decomposition of (84) (Equation

(5)) <82LA315>. Heating of 5-amino-1,2,4-dithiazoline-3-thione (**32**; $R^1 = \text{NH}_2$) with aroylmethylthiocyanates ($\text{ArCOCH}_2\text{SCN}$) in hydrochloric acid gives bis(4-arylthiazolyl)sulfides (**86**) <87EGP243027>.



Two types of 1,2,4-dithiazolium cation complexes have been synthesized: metal coordinated (see Section 4.13.4.1) and charge-transfer complexes. The former have been made from 3,5-diamino-1,2,4-dithiazolium halides <84CHEC-I(6)897> and metal halides in DMF and precipitated by CHCl_3 <82SA(A)1069>. The latter have been prepared from 3-phenyl-5-Y-1,2,4-dithiazolium iodide or perchlorate ($Y = \text{Ph}, \text{NEt}_2, \text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$) and chelated transition metals bis(dithiolates), the planarity of the dithiazolium cation and chelated anion being favorable for complexation <90JPR821>.

4.13.6 REACTIVITY OF NONCONJUGATED RINGS

Most reactivity studies have been devoted to 1,2,4-dithiazolidines. Dimroth rearrangement is typical in this series and extensively investigated. It is described in Section 4.13.6.1 and <84CHEC-I(6)897>, but is recurrently referred to in other sections. 1,3-Cycloaddition of double and triple bond-containing compounds across the $\text{N}=\text{C}-\text{S}$ grouping of 3-imino-1,2,4-dithiazolidines is quite common and is often followed by elimination of the opposite unit of the heterocycle to produce various S-containing azoles (see Section 4.13.6.1.4). Nucleophilic attack is common not only at carbon, but also at the nitrogen ring atom leading to considerable variety of chemical transformations (see Section 4.13.6.1.2), <84CHEC-I(6)897>, and at the sulfur ring atom (see Section 4.13.6.1.3), <84CHEC-I(6)897>. Thiolysis of the dithiasuccinoyl protecting group in amino acids is worth mentioning. Reactions at substituents afford trithiadiazapentalenes, quinomethide structures with a great synthetic utility (see Section 4.13.7).

1,2,4-Oxathiazolidin-3-ones lose CO_2 and S at room temperature to give open chain products (see Section 4.13.6.1.1). Fused structures can undergo recyclization <84CHEC-I(6)897>.

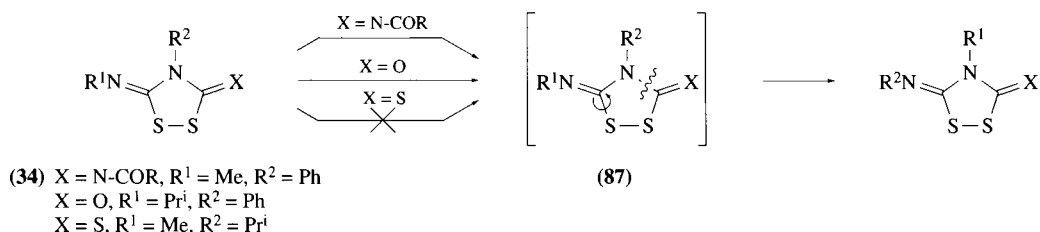
Thermolysis or photolysis of 1,2,4-dioxazolidines leads to rupture of the OO bond to give acyclic molecules <84CHEC-I(6)897>. Thermal decomposition of 3-acyl-1,2,4-dioxazolines at room temperature gives diacylamines (see Section 4.13.6.2.2) and 1,2,4-dioxazolin-3-ones give isocyanates <84CHEC-I(6)897>.

4.13.6.1 Reactions of Isomers of Fully Conjugated Ring Compounds

4.13.6.1.1 Thermal formally unimolecular reactions

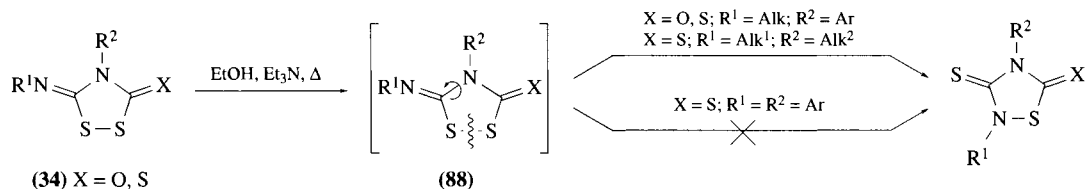
Dimroth rearrangement of 1,2,4-dithiazolidine derivatives can occur with retention or cleavage of the SS bond depending on the nature of substituents. The former pathway is readily realized with monoacylated 3,5-diimino derivatives (**34**; $\text{X} = \text{NCOR}$) <78JOC4951> and takes place for 5-imino-3-one derivatives at 150°C <92JPR685> but 5-imino-3-thione derivatives (**34**; $\text{X} = \text{S}$) <91JPR107> resisted all attempts at isomerization using Et_3N , H_2SO_4 or other conditions. Formally, the process involves rupture of one CN bond, rotation of the NCN entity around the SC bond and formation of a new CN bond as in (**87**) (Scheme 11). It may be assisted by some additives, for example PhNCS

which presumably promote the rearrangement by an addition–elimination sequence, (see Section 4.13.6.1.4).



Scheme 11

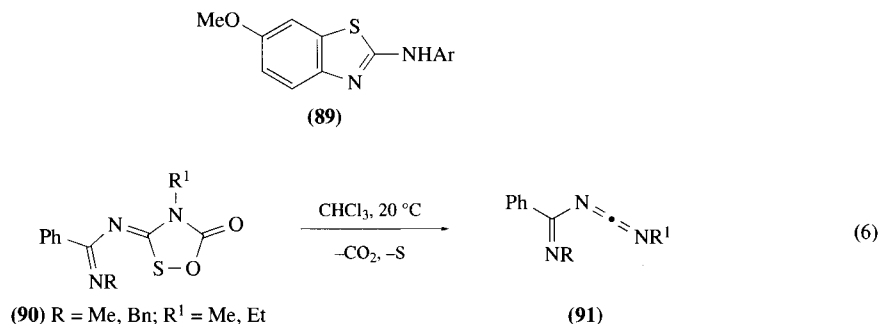
The second pathway leads to 1,2,4-thiadiazolidines and has received more attention. It involves rupture of the SS bond, rotation of the NCS entity around the NC bond and formation of an NS bond as in (88) (Scheme 12). Tittelbach and co-workers exploring thoroughly this kind of transformation have shown that the Dimroth rearrangement for (34; $X = \text{S}$) occurs when both or at least one substituent on the nitrogen atoms are alkyl groups (Scheme 12) <91JPR107>; derivatives (34; $X = \text{O}$) appear to display a similar tendency <90JPR181>. The rearrangement takes place merely on heating (e.g. in a GC column, by melting, or during recrystallization), but is accelerated substantially by a base (usually Et_3N) to afford high yields of the respective 1,2,4-thiadiazolidines. The thermal reaction is reversible for (34; $X = \text{S}$) (see Section 4.13.4.2) <91JPR107>, but is irreversible for (34; $X = \text{O}$) <88JOC1744>. The structure of alkyl substituents in (34; $X = \text{O}$) also affect the purely thermal reaction (150–200°C in GC column): with $\text{Alk} = \text{Me}, \text{Et}$ only rearrangement occurs, with $\text{Alk} = \text{Pr}^n, \text{Bu}^n$ the major rearrangement process is accompanied by a partial decomposition to DCC and with $\text{Alk} = c\text{-C}_6\text{H}_{11}$ this decomposition becomes exclusive <88JOC1744>. Rate measurements for (34; $X = \text{O}$, $R^1 = R^2 = \text{Et}$) showed the rearrangement to have kinetic parameters in CHBr_3 as follows: $k = 10^{-4} \text{ s}^{-1}$ (100°C); $E^a = \Delta H^\ddagger = 36$, $\Delta G^\ddagger = 28 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger = 20 \text{ cal mol}^{-1} \text{ deg}^{-1}$ <88JOC1744>.



Scheme 12

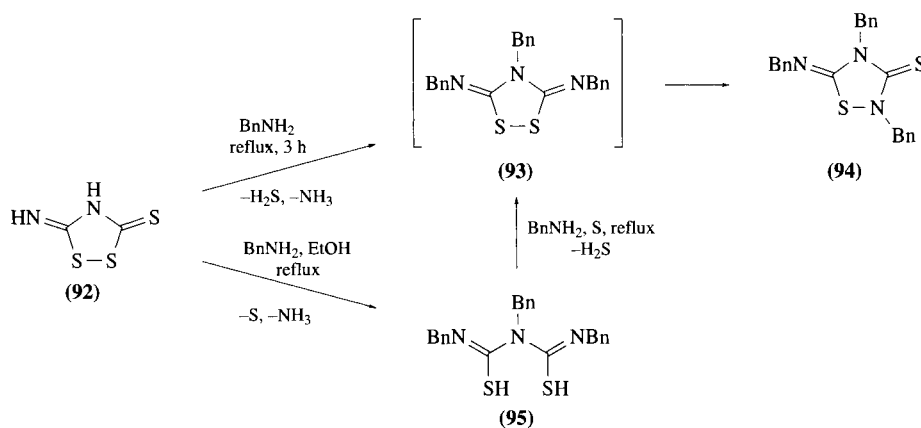
3,5-Diimino derivatives (34; $X = \text{NR}^3$) readily undergo this mode of Dimroth rearrangement and show no sign of the rearrangement in which the SS bond is retained ($R^3 = \text{Py}$) <88JHC1459>, ($R^3 = \text{Ph}$) <90BSB391, 91BSB185>, ($R^3 + R^2 = \text{O-C}_6\text{H}_4$) <83T2311>. Pyridine accelerates the reaction <88JHC1459, 89BSB879>.

When strongly heated, diaryl-5-imino-1,2,4-dithiazole-3-one (34; $X = \text{O}$, $R^1 = R^2 = 4\text{-MeOC}_6\text{H}_4$) loses COS to give a benzothiazole derivative (89) <91JPR579>. 3-Imino-1,2,4-oxathiazolidine-3-one (90) decomposes in solution at room temperature to give a carbodiimide (91) (Equation (6)) <86CB3737>.



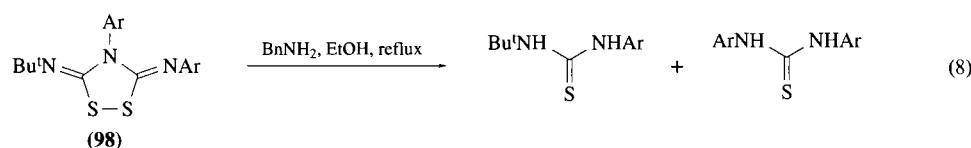
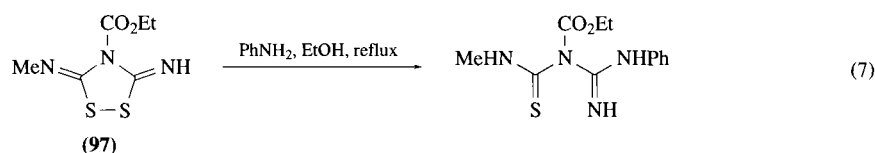
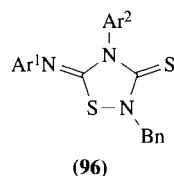
4.13.6.1.2 Nucleophilic attack at ring carbon and nitrogen

5-Imino-1,2,4-dithiazolidine-3-thione (**92**) reacts with an excess of boiling benzylamine to give tribenzyl substituted 5-imino-1,2,4-thiadiazolidine-3-thione (**94**); when the reaction is carried out in boiling ethanol, sulfur is liberated and tribenzyl-substituted 2,4-dithiobiuret (**95**) is produced. The latter in the presence of sulfur transforms into the same (**94**) in boiling neat benzylamine supposedly through oxidative cyclization by sulfur to give the 1,2,4-dithiazole intermediate (**93**) which undergoes a Dimroth rearrangement to (**94**). The intermediate (**93**) is regarded as common to both routes (Scheme 13) <82JIC71>.

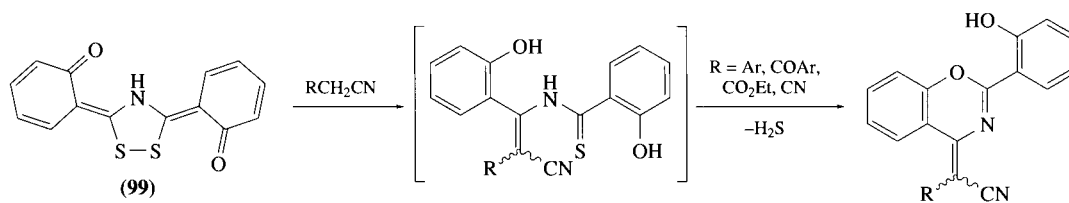


Scheme 13

The analogous diaryl-substituted derivative (**34**; X = S, R¹ = R² = Ar) in boiling BnNH₂ similarly affords (**96**), but fails to produce a 2,4-dithiobiuret derivative in boiling ethanol. 3-Oxo analogues (**34**; X = O, R¹ = R² = Ar) undergo similar transformations with BnNH₂ <82JIC71>. The 3-imino analogue (**97**) gives a thiobiuret derivative with aniline in boiling ethanol <90JIC849> but at a higher temperature further aminolysis appears to take place as can be seen from the behavior of other imino and thione analogues <85JCS(P1)1007>. Some 3,5-diimino derivatives (**98**), however, merely dissociate into two possible thioureas when boiled in ethanol with BnNH₂ <87JIC321>.



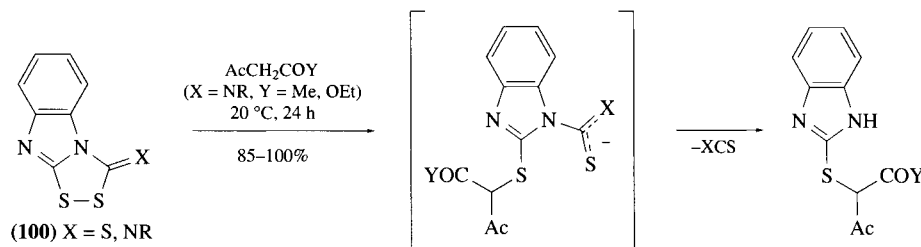
1,2,4-Dithiazolidines containing *o*-quinonemethide structural units in the 3,5-positions (e.g. (**99**)) are converted by reagents with an activated CH₂ group into a range of condensed heterocyclic compounds not easily accessible otherwise (Scheme 14) <85S535, 86PHA283>.



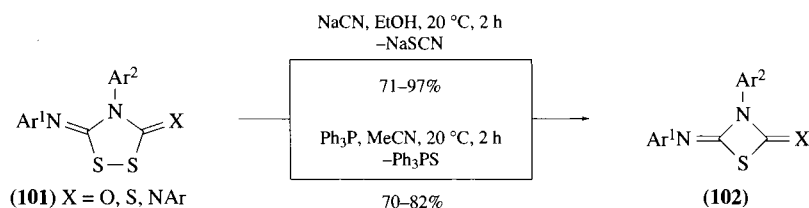
Scheme 14

4.13.6.1.3 Nucleophilic attack at ring sulfur

Fused 5-imino-1,2,4-dithiazolidine-3-thiones and 3-imines (**100**) take up nucleophiles on one sulfur atom, releasing the XCS structural unit of the heterocycle (Scheme 15) <85JCS(P1)1007>. Nonfused analogues (**101**) give up one sulfur atom to the nucleophile, the rest of heterocycle closing to form a 1,3-thiazetidine ring (**102**) (Scheme 16) <87ZC142>.

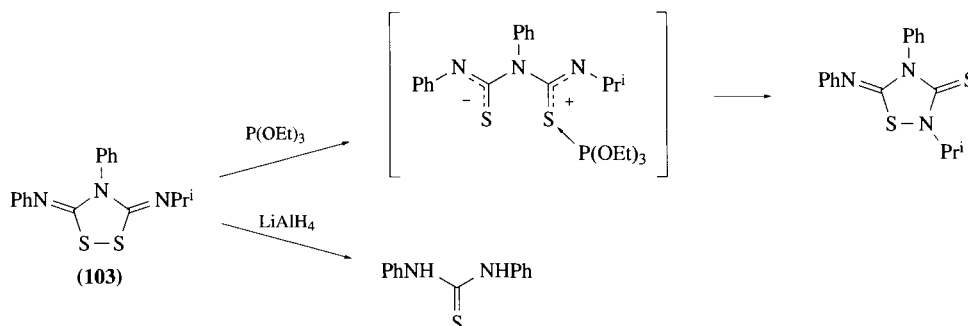


Scheme 15



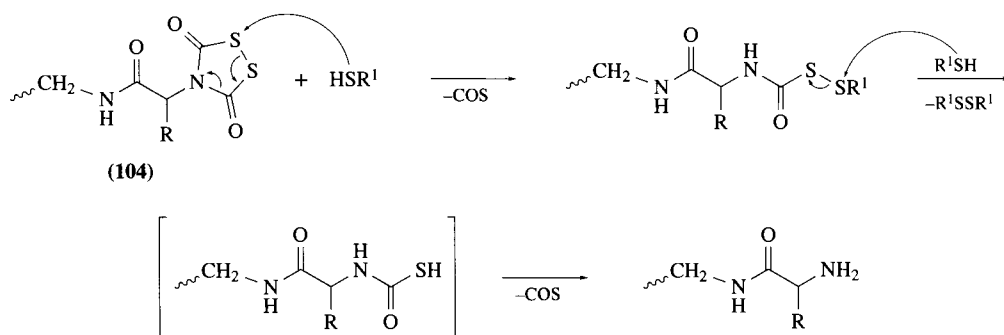
Scheme 16

Diimino-1,2,4-dithiazolidine (**103**) undergoes Dimroth rearrangement under the influence of $\text{P}(\text{OEt})_3$ which presumably coordinates at the sulfur atom <86JOC407>. Reduction by LiAlH_4 also appears to involve attack at sulfur <86JOC407>.



Scheme 17

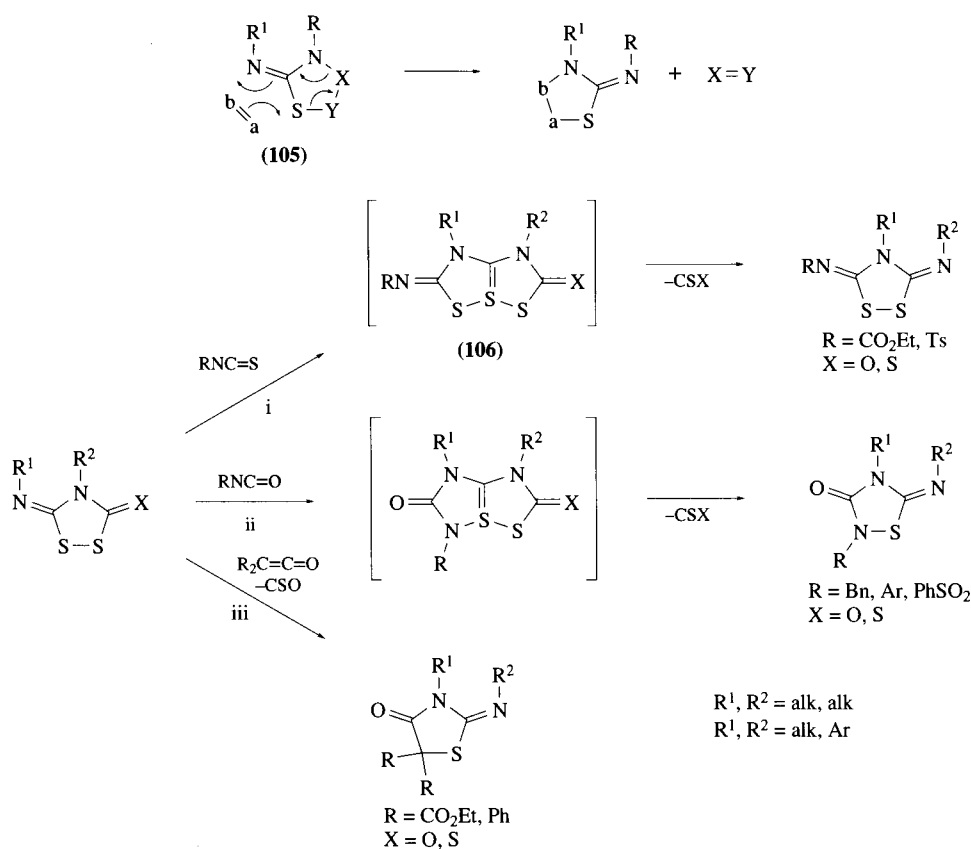
The known susceptibility of the 1,2,4-dithiazolidine ring to reductive cleavage of the SS bond is illustrated by reduction with glucose <88JOC1744> and H_2S <83H(20)1993, 90ACH29, 82IJC(B)649>. Thiols remove the dithiosuccinoyl protecting group (**104**) in peptide synthesis by cleaving the S-S linkage <85JA4936, 87MI 413-01, 90MI 413-01, 91MI 413-01>.



4.13.6.1.4 Cyclic transition state reactions with a second molecule

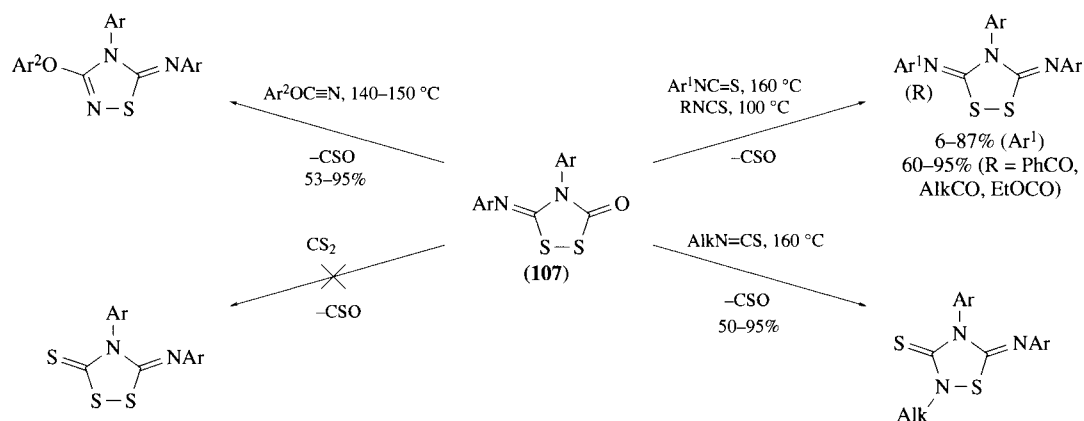
L'abbé had formulated a general rule on the basis of his extensive investigations of the reaction of sulfur-containing five-membered heterocycles with isocyanates and isothiocyanates: a heterocycle having an imino group conjugated with the ring sulfur atom (105) should interact with heteracumulenes by the pattern of cycloaddition–elimination with extrusion of the XY fragment. This has been substantiated again in several reactions (Scheme 19) <92JPR685, 83T2311, 90JHC1629>, and (Scheme 20) <90JHC1629, 92JPR685, 83T2311, 91JPR579>. There is some ^1H NMR spectral evidence for the heterapentalene intermediate (106) <90JHC1629>. In 1992 the rule was extended by the authors to take in structures containing a conjugated exocyclic sulfur atom and ring nitrogen atom as the sites for addition, as exemplified by reactions with ketenes and acetylenes in Scheme 21 <92JHC69>.

Excess of ArNCS in the reaction with (107) leads to all possible triarylsulfonated dithiazoline

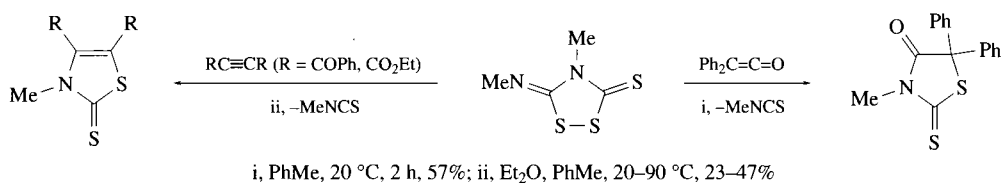


i, PhMe, reflux, 2 h–7 d, 66–73%; ii, PhMe, reflux, 4–7 d, 36–97%; iii, PhMe, 20 °C, 2 d

Scheme 19



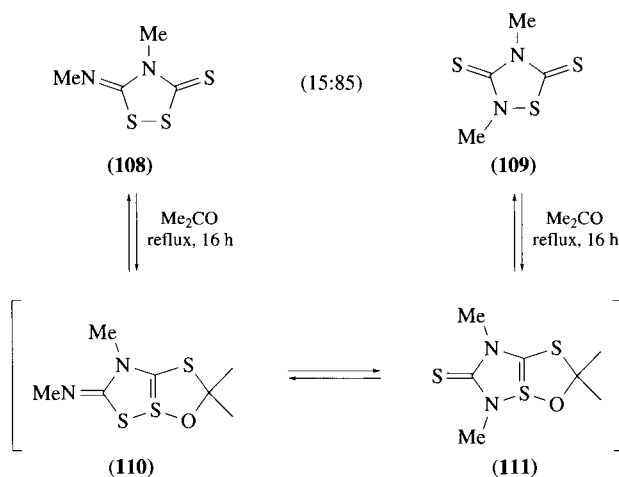
Scheme 20



Scheme 21

products due to their interconversion involving the starting Ar^1NCS and eliminated Ar^1NCS , both of which can react at either $\text{N}=\text{C}-\text{S}$ moiety in the heterocycle $\langle 91\text{JPR}579 \rangle$.

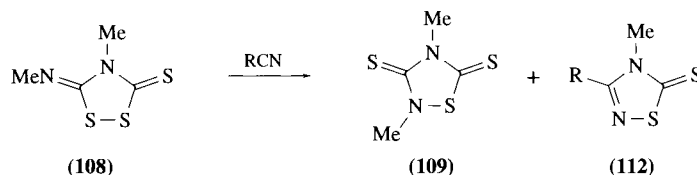
It has been inferred that acetone adds reversibly across the $\text{S}=\text{C}-\text{S}$ grouping to give heteropentalene-type adducts (**110**) and (**111**) which maintain an equilibrium between the two heterocyclic substrates (**108**) and (**109**) (Scheme 22) $\langle 92\text{JHC}69 \rangle$.



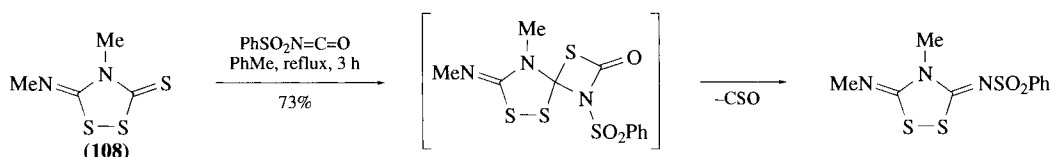
Scheme 22

Two products are isolated from the reaction of 4-methyl-5-methylimino-1,2,4-dithiazolidine-3-thione (**108**) with nitriles (Scheme 23): its 1,2,4-thiadiazolidine isomer (**109**) and a 1,2,4-thiadiazolidine derivative incorporating the nitrile unit (**112**). A sequence of 1,3-cycloaddition-elimination steps via heteropentalene intermediates is proposed for the process $\langle 91\text{JOC}3268 \rangle$.

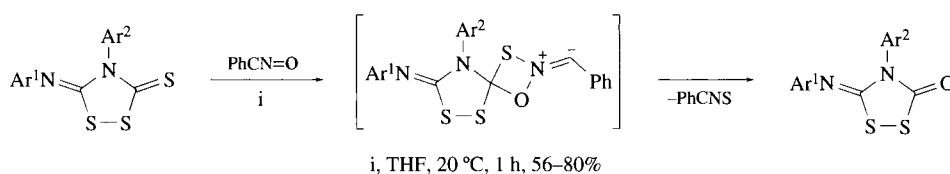
In some additions the thione group alone can also be a reaction site as with PhSO_2NCO which adds with its NC bond (Scheme 24) $\langle 92\text{JHC}69 \rangle$ and PhCNO (Scheme 25) $\langle 90\text{JPR}181 \rangle$.



Scheme 23



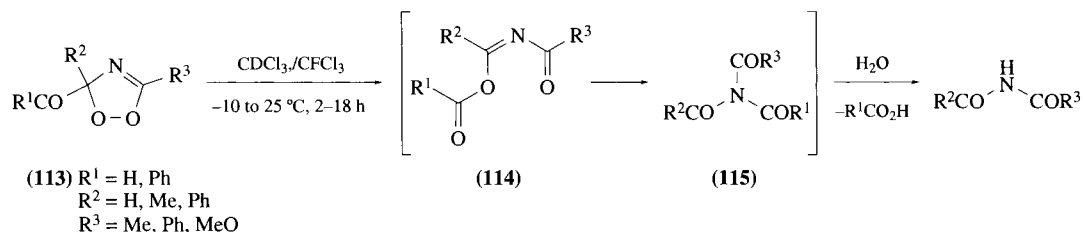
Scheme 24



Scheme 25

4.13.6.2 Reactions of Hydrogenated Derivatives of Fully Conjugated Ring Compounds

1,2,4-Dioxazolines (113) undergo a facile rearrangement to triacylamines (115) apparently via imino anhydrides (114); the reaction rate does not depend on solvent polarity (Scheme 26) <90JCS(P1)1011, 91JCS(P2)1085>.



Scheme 26

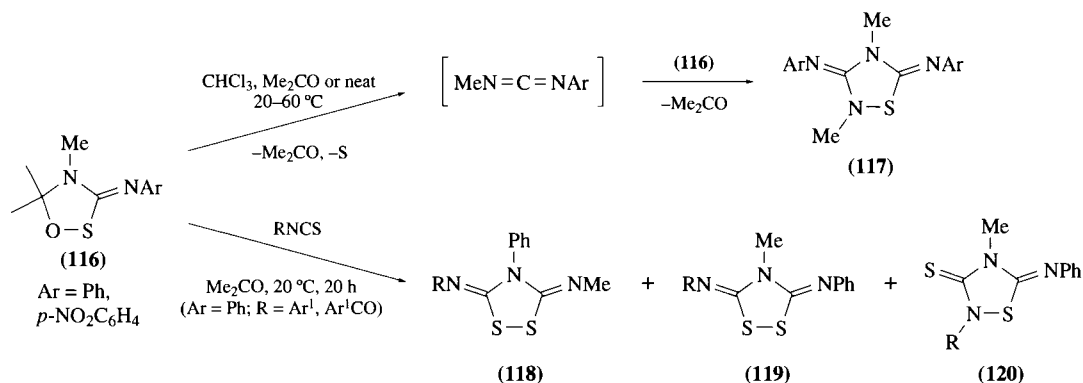
5,5-Dimethyl-4-methyl-3-phenylimino-1,2,4-oxathiazolidine (116; $\text{Ar} = \text{Ph}$) is converted into a 1,2,4-thiadiazolidine derivative (117; $\text{Ar} = \text{Ph}$) at room temperature either in the crystalline state or in solution as a result of fragmentation to acetone, sulfur, and *N*-methyl-*N*'-phenylcarbodiimide followed by cycloaddition of the latter to (116) and elimination of acetone (Scheme 27) <90JHC1993>. This mechanism is confirmed by reaction with added DCC or PhNCO which undergo addition–elimination with (116) (Scheme 27) <92JHC17>. In the reaction with isothiocyanates the expected product (118) of 1,3 cycloaddition–elimination appears but is accompanied by (119) and (120), the products of thermal transformations (Scheme 27) <90JHC1993>.

3-Trichloroacetylmino-1,2,4-oxathiazolidine (121) is transformed at room temperature into the 1,2,4-thiadiazolidine (124) apparently via (122) and formation of an intermediate carbodiimide (123) <92JHC17>.

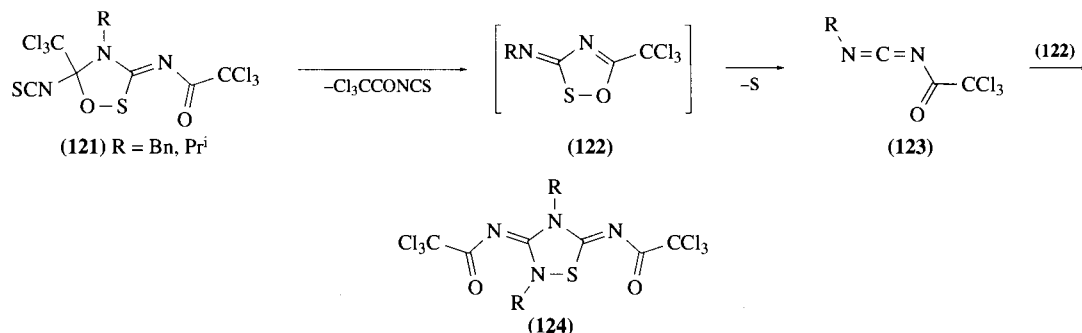
A Dimroth rearrangement occurs with 3-methylene-1,2,4-oxathiazolidines (125) (Equation (9)) <78AG480>.

Fully hydrogenated 1,2,4-dioxazolines (126) are remarkably stable and decomposition is only partial at 100°C ; in the presence of Ph_3P reaction is complete in 15 min (Scheme 29) <83TL3047>.

N-Methylation of 3,5-diphenyl-1,2,4-dioxazolidine is carried out by MeOTf in 80% yield <84TL3035>. The *N*-butyl derivative (126) gives a positive reaction with acidic KI solution and

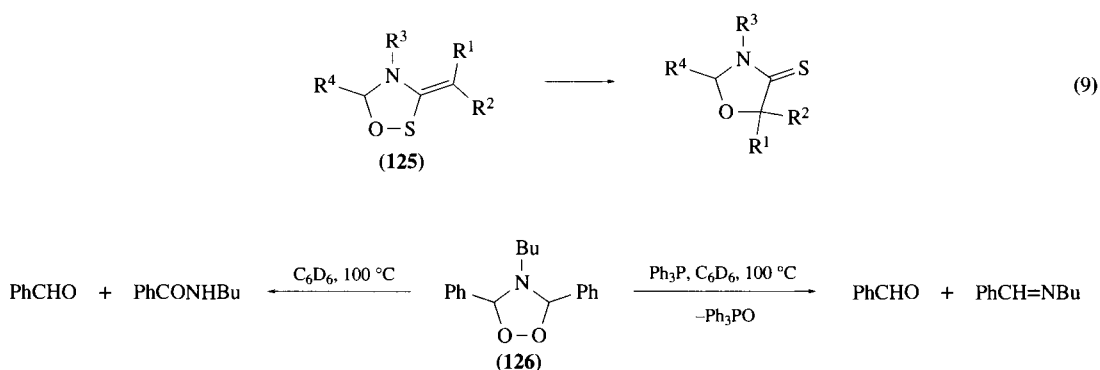


Scheme 27



Scheme 28

$\text{Fe}^{2+}\text{NH}_4(\text{SCN})_3$ <83TL3047>. 1,2,4-Oxathia (or dithia)zolidines *S*-dioxides (**50**) are susceptible to ambient moisture and sometimes to heat <91PS(57)203>.

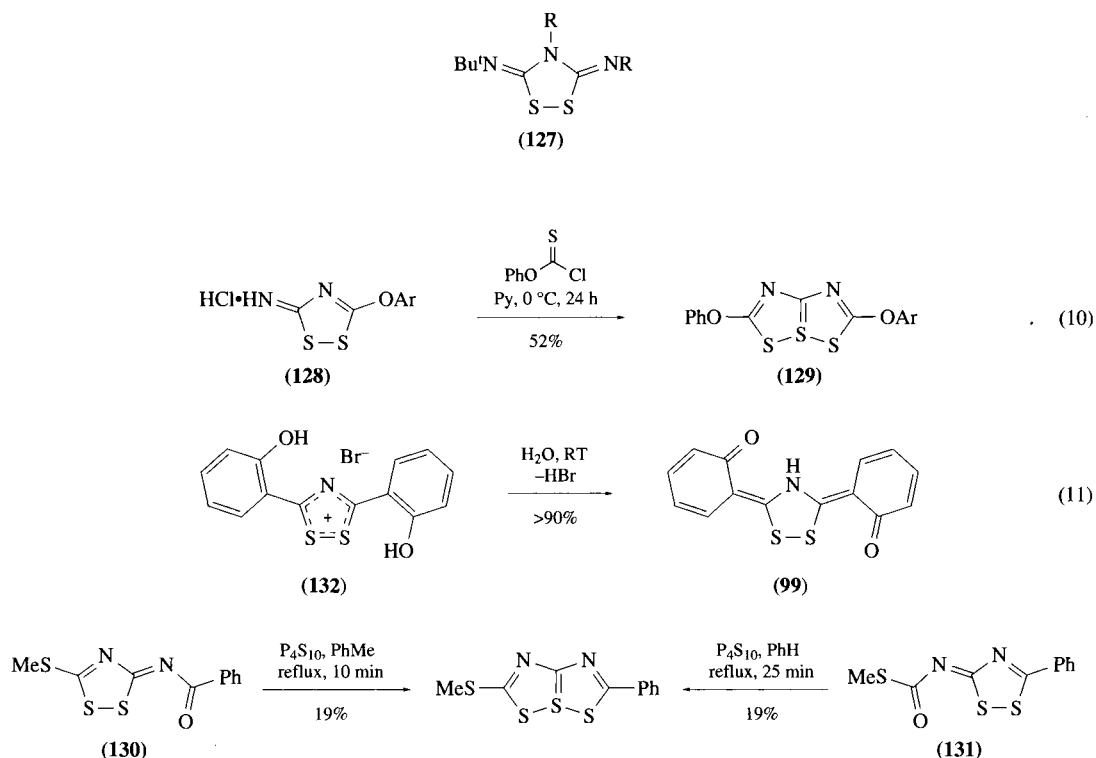


Scheme 29

4.13.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

3-*t*-Butylimino derivatives of 1,2,4-dithiazolidines (**127**; $\text{R} = \text{Ar}, \text{Bn}$) undergo de-*t*-butylation by strong acids <87JIC321>. The unsubstituted imino group of 5-aryloxy-1,2-dithiazolinimines (**128**) is thiocarbonylated and carbonylated by thioacyl or acyl chlorides and isocyanates; the first reagent gives rise to a trithiadiazapentalene system (**129**) (Equation (10)) <90JPR208>. This system can also be obtained by exchange of carbonyl oxygen with sulfur in 3-imido derivatives (**130**), (**131**) (Scheme 30) <88LA729>. Deprotonation of the 3,5-bis(o-hydroxyphenyl)-1,2,4-dithiazolium cation (**132**) leads

to a quinomethide type structure (**99**) with great synthetic potential (see Section 4.13.6.1.2) (Equation (11)) <86PHA283>. Alkylation of a phenylamino group in 1,2,4-dithiazoles is brought about by alkyl iodides in up to 52% yields <90IJC(B)937>.

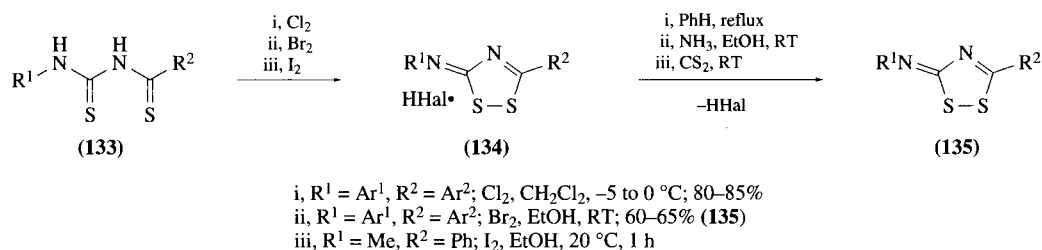


Scheme 30

4.13.8 RING SYNTHESIS CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

4.13.8.1 Formation of One Bond between Two Heteroatoms

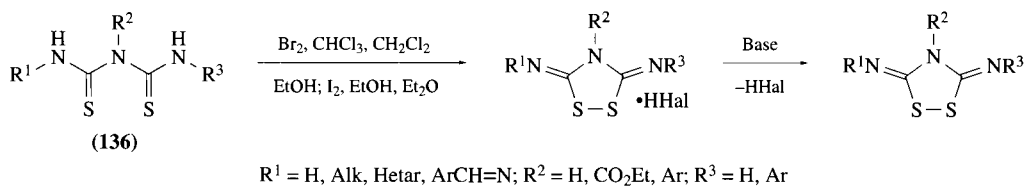
The old method of SS bond formation by oxidative cyclization of the *N*-thioacyl thioureas (**133**) still remains in use (Scheme 31). At 20 °C the sulfur atoms in (**133**) are substituted by Cl <81JGU1720, 82JIC663>. The oxidation is also effected by metabolically in the mycelia of *Pithium ultimum* Trow <88MI 413-01>.



Scheme 31

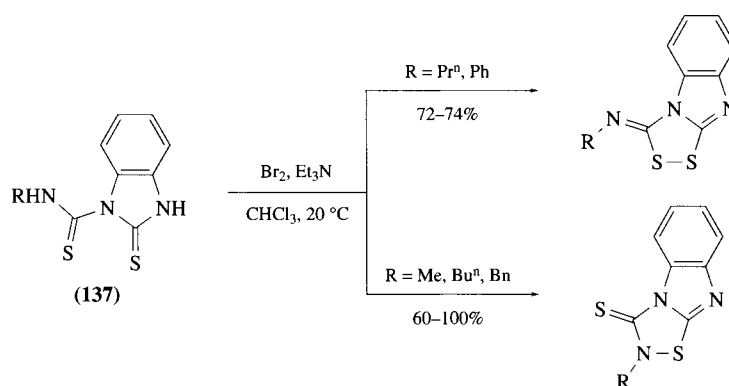
The dithiobiurets (**136**) are readily cyclized by Br₂ <83H(20)1993, 90JIC849, 91JPR579>, I₂ <90JIC223>, I₂ (R² = H) <82IJC(B)649>, at room temperature in high to quantitative yields (Scheme 32). The unsubstituted dithiobiuret is thought to be cyclized by KMnO₄ in 2-6N H₂SO₄ though the product

was not traced <84MI 413-02>. It is oxidized to 3,4-diamino-1,2,4-dithiazoline by metabolism in animals <82MI 413-04, 86MI 413-02>.



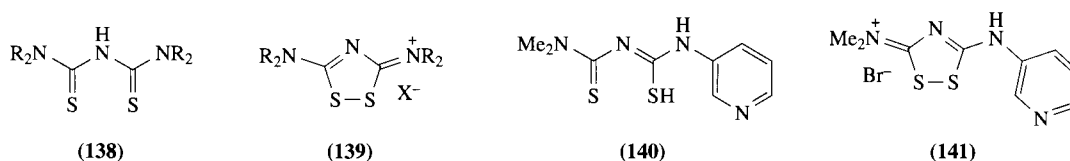
Scheme 32

The dithiobiuret moiety in structure (137) affords two types of sulfur-containing rings according to whether the sulfur or nitrogen atom of the exocyclic thioamido group becomes bonded to the sulfur atom of the ring thione group; this is governed by the R substituent (Scheme 33) <83T2311>. The interconversion of both products depends on the substituent R.



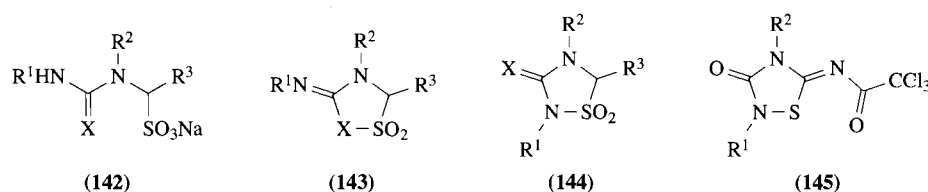
Scheme 33

Dithiobiurets (138) are oxidized by peroxy oxidants in the presence of various acids to the corresponding dithiazolylimmonium salts (139) <82SA(A)971, 87BCJ2686>. Delocalization in the latter appears to be confined to the NCNCN chain, hence the positive charge is located on the exocyclic amino group and the ring is devoid of aromatic character (see Section 4.13.3.1). Dithiobiuret (140) produced *in situ* is reported to be transformed into a dithiazolium salt (141) by 47% hydrobromic acid <82JAP82183770>.



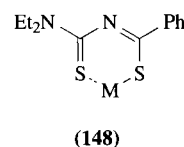
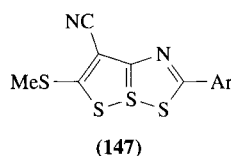
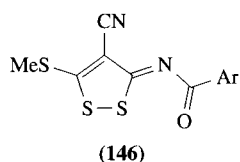
N-(α -Hydroxysulfonylalkyl)ureas or -thioureas in a salt form (142; X = O, S) (but not in a free acid form) can be subjected to nonoxidative 1,2,4-oxathiazolidine or -dithiazolidine ring closure to (143) by the action of SOCl₂ or PCl₅ <91PS(57)203>. No N—S ring closure occurs as no sulfohydantoines (144) were detected.

Formation of an unstable 1,2,4-oxathiazoline species (122) in the reaction of RN₃ (R = Prⁱ, Bn) with trichloroacetyl isothiocyanate was deduced from NMR spectral evidence and trapping experiments with isocyanates (RⁱNCO) to give (145). Further addition of trichloroacetyl isothiocyanate gave an unstable 1,2,4-oxathiazolidine (121) as a final product <92JHC17>.



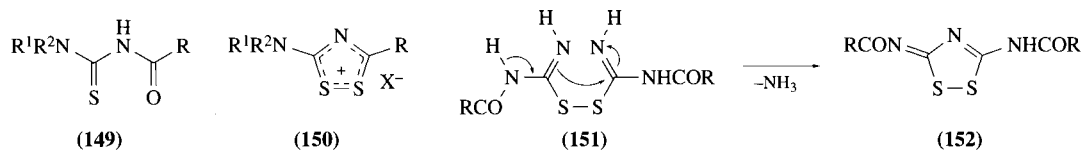
A new cyclic SS bond as in (147) is formed when the 3-acylimino group in 1,2-dithiacyclopentene (146) is sulfurized by 2,4-bis(phenylthio)-1,3-dithia-2,4-diphosphetane 2,4-disulfide <85CC1704>.

Cu^{2+} or Ni^{2+} Complexes of 1,1-diethyl-3-thiobenzoylthiourea (148) are oxidized to 1,2,4-dithiazolium salts (10) and (12) in which the heterocyclic ring is considered to be aromatic using Br_2 <90EGP280758, 89ZAAC(576)203, 91MIP2018945>, SOCl_2 <91MIP2018944> or electrochemically <91JPR537> (see Section 4.13.3.1) Analogous Cu^{2+} <91ZN(B)1113>, Ni^{2+} <89ZAAC(576)203, 90EGP280759> or Co^{3+} <90ZAAC(586)79> complexes of 1,1-diethyl-3-benzoylthiourea also give 1,2,4-dithiazolium salts (10)–(13) on treatment with SOCl_2 at room temperature or on brief heating in acetonitrile.

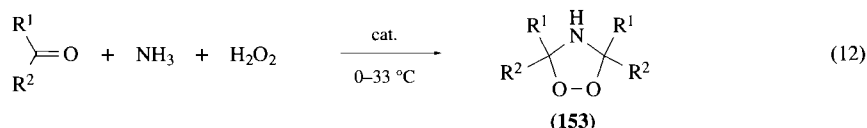


4.13.8.2 Formation of One Bond Adjacent to a Heteroatom

N-Acylthioureas (149) treated with Br_2 or H_2O_2 in a perchloric acid medium give 1,2,4-dithiazolium salts (150; $\text{X} = \text{ClO}_4^-$) <85T5371>. Oxidation of (149) to the 1,2,4-dithiazolium salts was also carried out electrochemically, the *N*-acylurea having been isolated as a by-product <91JPR537>. When disulfides (151), obtained by Br_2 oxidation of (149; $\text{R}^1 = \text{R}^2 = \text{H}$), are heated in AcOH 1,2,4-dithiazoles (152) are produced <85MI 413-01>.

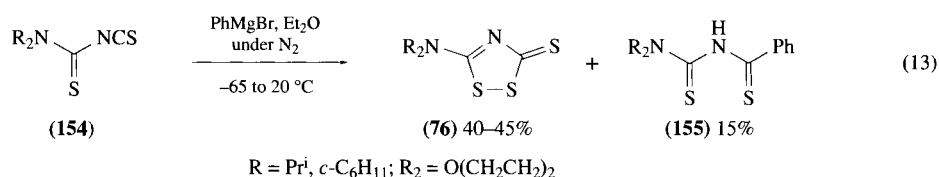


Oxidation of ketones by H_2O_2 in aqueous ammonia in the presence of the sodium salts of EDTA or 1,2-diaminocyclohexane tetra acetate as catalyst affords 1,2,4-dioxazolidines (153) in high yield (Equation (12)) <83JAP83121284, 88JAP8891363, 83JAP8318372, 91JMOC383, 91MI 413-02>.

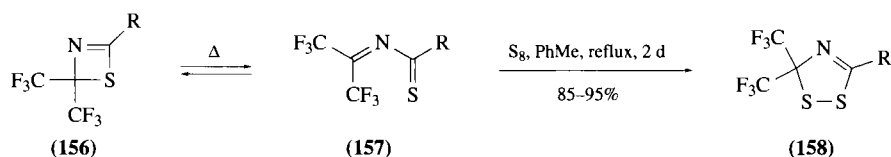


4.13.8.3 Formation of Two Bonds: Four-atom Fragments and Sulfur

Formally the reaction of aminothiocabamoyl isothiocyanates (154) with PhMgBr comes under this heading (Equation (13)) <82ZC377>. Bulky substituents R on the amino nitrogen favor the formation of (76) at the expense of the normal thioacyl thiourea (155). A more straightforward example of this type of ring closure is the direct interaction of (154) with elemental sulfur in pyridine at 80°C (96% yield of (76)) <72CB1568> or in CS_2 at 20°C (45%) <82ZC377>.



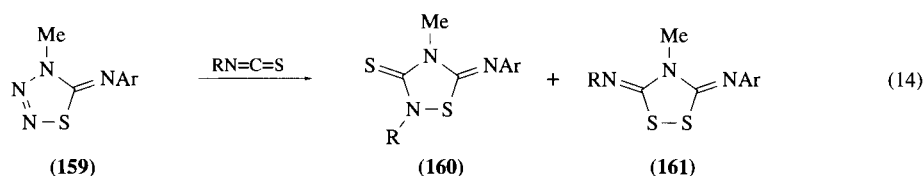
1,3-Thiazete (156) heated with elemental sulfur gives 1,2,4-dithiazoline (158) via its ring opened valence tautomer (157) (Scheme 34) <86CZ87>.



Scheme 34

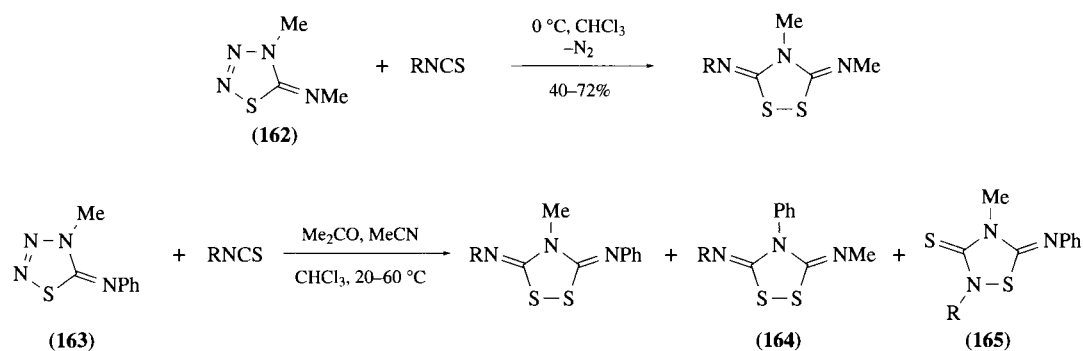
4.13.8.4 Formation of Two Bonds: [3 + 2] Atom Fragments by Cycloaddition

L'abbé and co-workers, in an extensive series of elegant investigations, have clarified the mechanism of the complex reaction of 4-methyl-5-arylimino-1,2,3-4-thiatriazoline (**159**) with isothiocyanates (usually a slow process in boiling CHCl_3 , requiring hours or days) leading to 1,2,4-dithiazolines (**161**) and 1,2,4-thiadiazolines (**160**) [88JHC1459, 89BSB879, 90BSB391, 90JHC199, 90JHC1993, 90T1281, 90JHC2133, 91BSB185, 93JCS(P1)27]. The finally proposed scheme involves a sequence of 1,3-cycloaddition-cycloeliminations [90JHC199]; for a full discussion see Section 4.19.6.4.1.

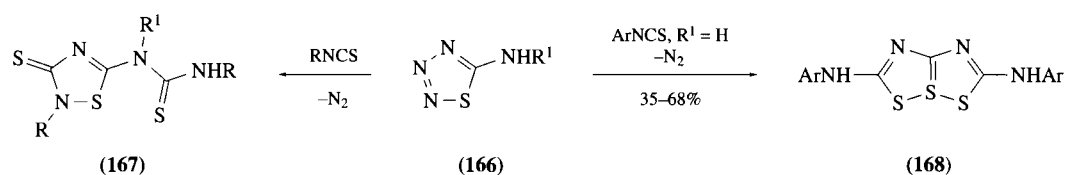


An important prerequisite in these reactions is the nucleophilicity of the imine nitrogen. Indeed, electron-withdrawing substituents in the aryl ring of (**159**) retard the reaction with isothiocyanates, whereas such substituents in the R group of the isothiocyanates enhance the reaction. No reaction occurs under the above chosen conditions (reflux in chloroform), when the aryl ring of (**159**) is replaced by a sulfonyl group [88BSB83].

With the all alkyl-substituted 5-imino-1,2,4-thiatriazoline (**162**) the reaction follows the normal course at 0°C [92JHC69]. At a higher temperature (**163**) also gives products of thermal transformations (**164**), (**165**) (Scheme 35) [90JHC1993]. 5-Aminothiatriazolines (**166**), lacking the substituent on heterocyclic nitrogen, react with isothiocyanates in the presence of a catalytic amount of DMAP to give products of type (**167**). When $\text{R}^1 = \text{H}$, reactions with alkyl isothiocyanates give (**167**) but aryl isothiocyanates give heterapentalenes (**168**) (Scheme 36) [89JPR115, 90EGP276286].



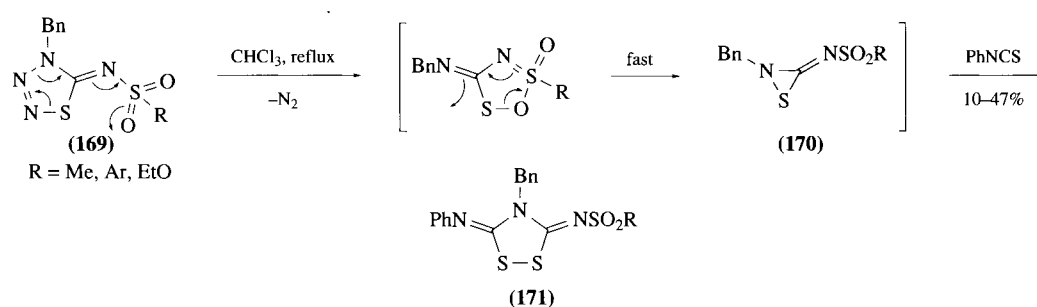
Scheme 35



Scheme 36

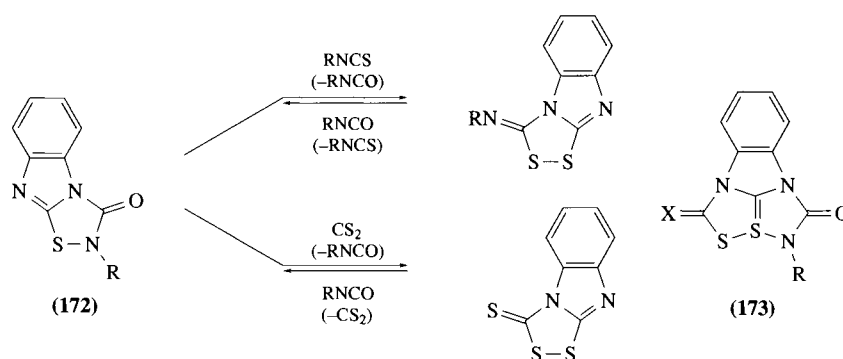
Sulfonylimine analogues of (159) i.e. (169) react with phenylisothiocyanate to give the normal of type of product (171) but evidently by a different mechanism involving sulfonyl group participation followed by intermediate thiaziridinimine (170) formation (Scheme 37) <90JHC2133>. This mechanism is supported by kinetic studies. Thus, the decomposition of (169) remains first order in the presence of phenylisothiocyanate, i.e. the latter does not change the mechanism of decomposition and enters the reaction in later stages <90JHC2133>. On the other hand general second-order kinetics was observed for the reaction of arylimine analogues (159) with isothiocyanates indicating participation of the latter in the early stages <78JOC4951>. The much lower activation energy for the reaction of (169) compared to that of (159) is consistent with anchimeric assistance by sulfonyl group.

The synthetic approaches to 1,2,4-dithiazoles developed prior to 1980 on the basis of reaction between 1,2,3,4-thiatriazolines of type (159) and isothiocyanates have been reviewed by L'abbé <82T3537>. Reactions proceeding through heterothiapentalene intermediates as discussed above have been named bond-switching rearrangements <80SR1>.



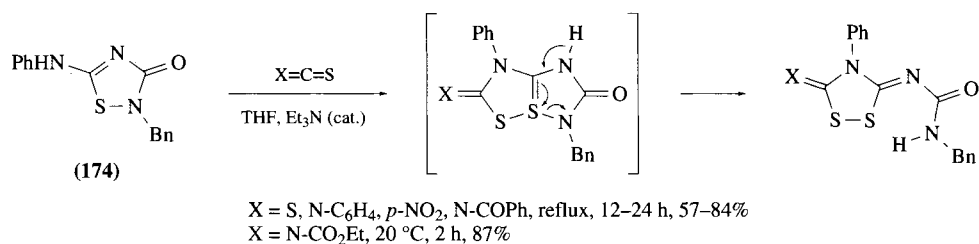
Scheme 37

A reaction with isothiocyanates (and CS₂) giving rise to a 1,2,4-dithiazolidine ring was also observed with the benzimidazo[1,2-*d*][1,2,4]thiadiazolidinone (172) which incorporates an isocyanate moiety (Scheme 38) <83T2311, 85JCS(P1)1007>. The reaction is reversed by the expelled isocyanate and an excess of the isothiocyanate (or CS₂) should be used. High yields are achieved under remarkably mild reaction conditions (20°C in CH₂Cl₂) suggesting a facile dissociation of (172) to give isocyanate which was, however, not observed by IR spectroscopy. An alternative mechanism via intermediate (173) was therefore proposed <85JCS(P1)1007>. Noncondensed 1,2,4-thiadiazolinones only give the analogous product in low yield with CS₂ <91JPR579>. 1,2,4-Thiadiazolidinethiones were also reported to react with CS₂ in a similar manner <87CE421>.

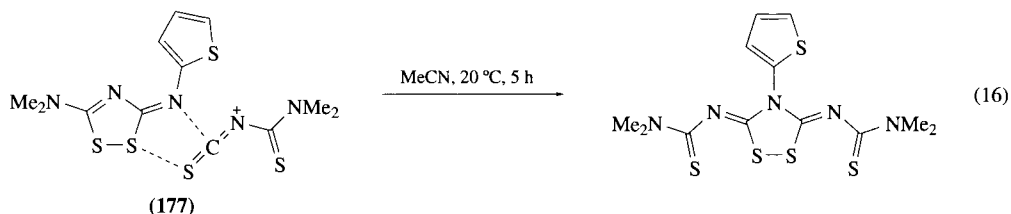
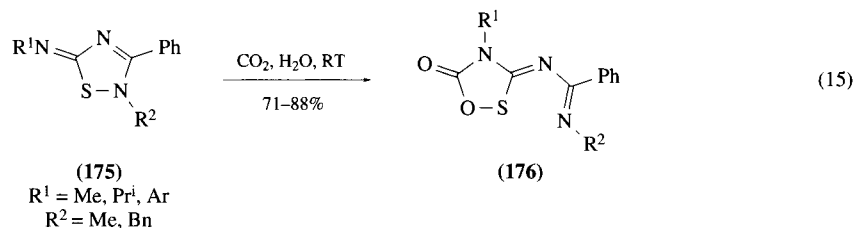


Scheme 38

1,2,4-Thiadiazolinone (174) undergoes a related reaction, however the incorporated isocyanate moiety is not fully expelled from the reaction product (Scheme 39) <92JHC451>. Also in the case of 1,2,4-thiadiazolinimine (175) a smooth 1,3-cycloaddition of CO₂ produces a 1,2,4-oxathiazolidinonimine (176) (Equation (15)) <86CB3737>. A similar behavior is exhibited by the dialkylamino dithiazole (177) (Equation (16)) <82JAP82183769>.

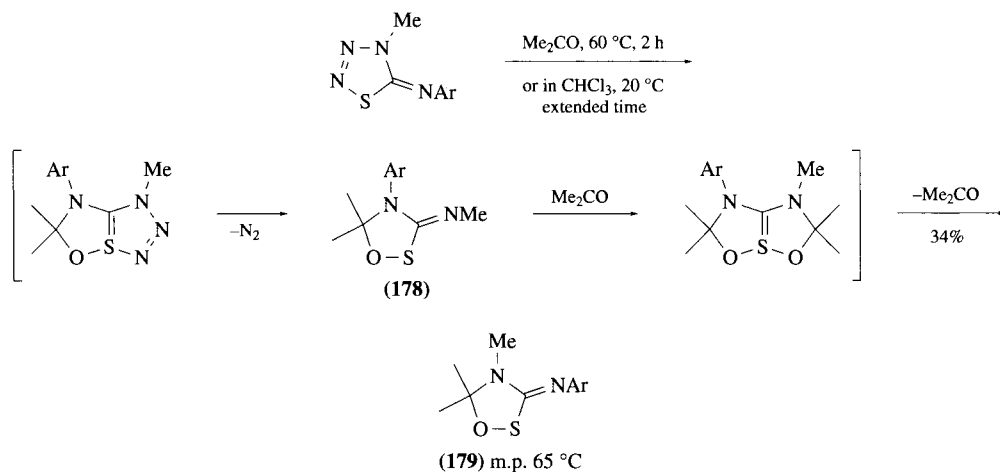


Scheme 39



Thiatriazoline (**159**) can add on acetone under mild conditions to give the 1,2,4-oxathiazoline ring (**179**), presumably via two successive 1,3-cycloadditions of acetone across the S—C=N grouping (Scheme 40) <90JHC1993>. An intermittent ¹H NMR signal δ 2.85 ppm in the reaction mixture was assigned to the intermediate (**178**).

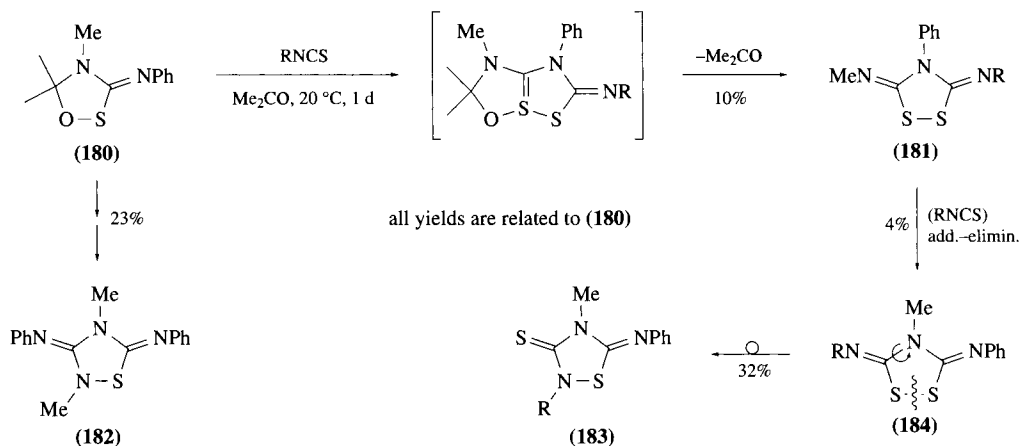
Reaction of (**159**) with other carbonyl compounds was monitored by ¹H NMR spectroscopy <90JHC1993>. Acetophenone and benzophenone in CDCl₃ at 60 °C gave within 2 h a small amount of (**179**) analogues but mainly thermal decomposition products of the latter. Benzaldehyde reacts at room temperature but the resulting analogue (**179**) decomposes completely.



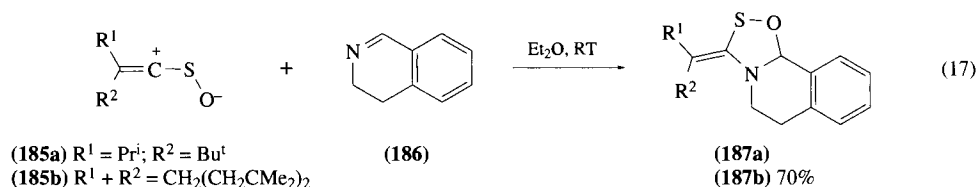
Scheme 40

1,2,4-Oxathiazolidinimine (**180**) containing the S—C=N thioamidate grouping can enter the cycloaddition–elimination reaction sequence with isothiocyanates to give 1,2,4-dithiazolidindimine (**181**) which in turn adds–eliminates RNCS to produce diimine (**184**) which isomerizes into thiadiazolidine (**183**). Another thiadiazolidine (**182**) is also formed directly from (**180**) which apparently

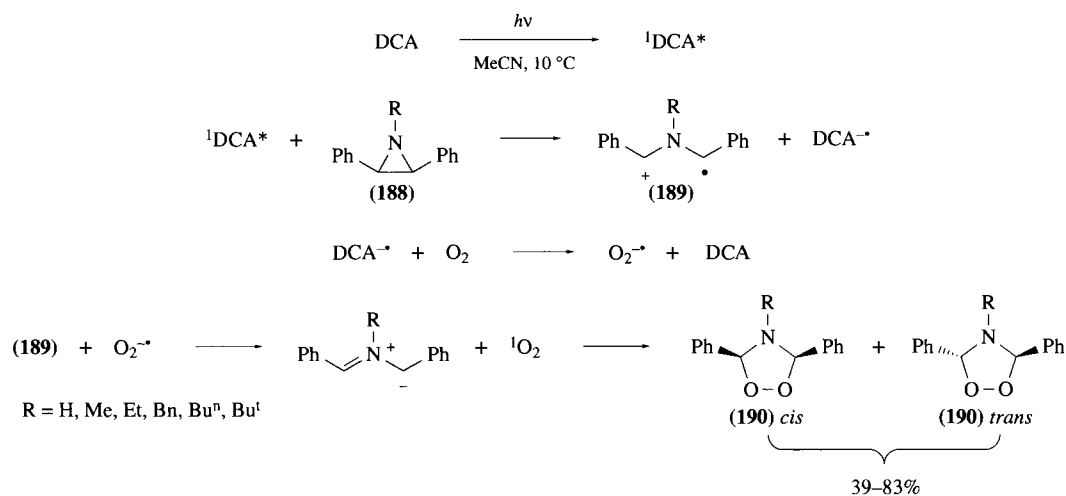
undergoes fragmentation to *N*-methyl-*N*-phenylcarbodiimide which in turn adds to (180) with acetone elimination. All four reaction products were identified (Scheme 41) <90JHC1993>. Thioketene *S*-oxides (185) add across CN double bond of imines, for example (186) to give 1,2,4-oxathiazolidines (187) (Equation (17)) <78AG480>.



Scheme 41

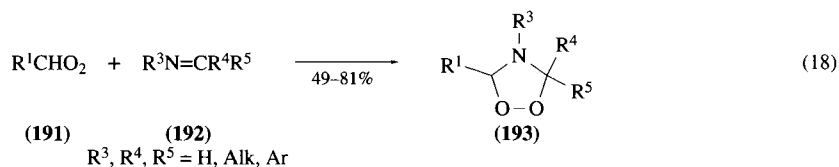


An ingenious method for synthesis of 1,2,4-oxathiazolidines (190) was devised on the basis of electron-transfer photooxygenation of aziridines (188) (Scheme 42) <83TL3047, 84TL3035>. 9,10-Dicyanoanthracene (DCA) as a sensitizer is promoted to a singlet excited state under irradiation by 450 W medium-pressure mercury lamp and accepts one electron from the aziridine and transfers it to O_2 . The ring-opened aziridine (189) takes the electron back from the oxygen species to give the azomethine ylide and $^1\text{O}_2$ which combine by 1,3-dipolar addition to give the final product (190). The starting aziridine (188) can not interact with singlet state oxygen directly as was evidenced by the fact that (188) was not oxidized when irradiated by a 400 W high-pressure sodium lamp in MeCN saturated with oxygen in the presence of a dye-sensitizer. Nor was (190) obtained by photolysis of (188) alone. The *cis* (190a): *trans* (190b) ratio of the product obtained is governed by steric interaction with the *N*-substituent: 100% *cis* (*N*-H), 100% *trans* (*N*-Bu^t), with intermediate values for other substituents.



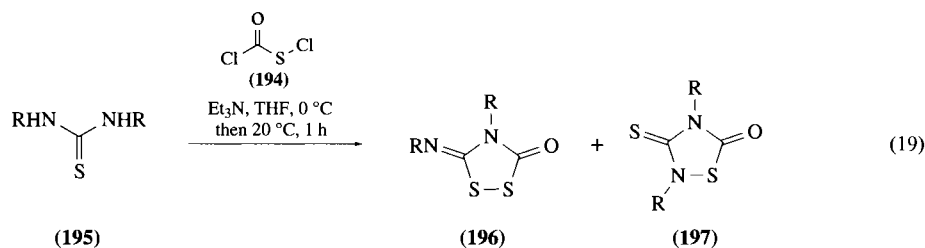
Scheme 42

Carbonyl oxides (**191**), generated *in situ* by ozonolysis of vinyl ethers readily add across the CN double bond of imines (**192**) to give 1,2,4-dioxazolidines (**193**) (Equation (18)) <88CC1550>. Alkyl substituted CN double bonds are more reactive than phenyl substituted ones. Ketones are far less reactive than imines.

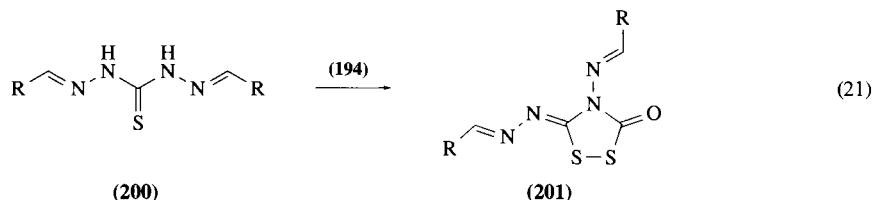
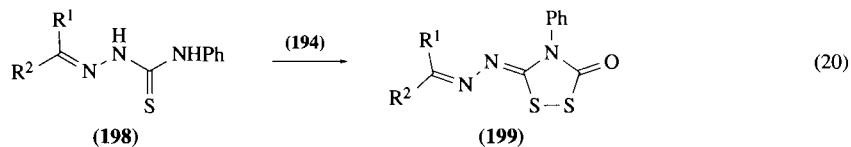


4.13.8.5 Formation of Two Bonds: [3 + 2] Atom Fragments by Other Processes

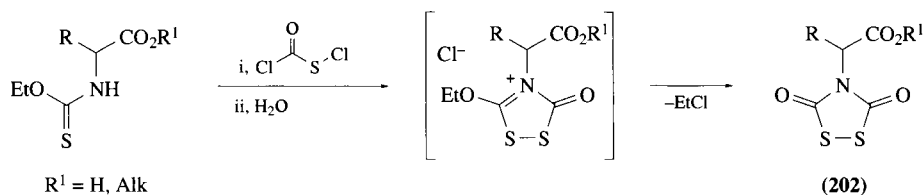
Chlorocarbonylsulphenyl chloride (**194**) and its derivatives at the carbonyl group are versatile reagents for the synthesis of sulfur-containing five-membered heterocycles, notably of the 1,2,4-dithiazole series. The outcome of reaction of sulfur-containing substrates with these reagents depends substantially on the nature of substituents (Equation (19)) <90JPR181, 91EGP294019>. Thus, aryl substituents in thioureas (**195**; R = Ar) favor 1,2,4-dithiazolidine ring (**196**) formation in the reaction with chlorocarbonylsulphenyl chloride whereas alkyl substituents lead to 1,2,4-thiadiazolidines (**197**). Both types of product result with mixed substituents, the second one predominating.



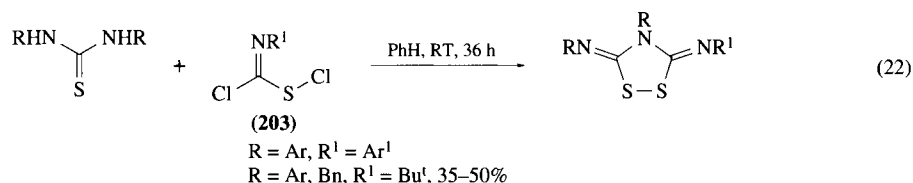
4-Phenylthiosemicarbazones (**198**) of aromatic aldehydes and ketones give 1,2,4-dithiazolidines (**199**) with the same reagent, whereas those of aliphatic ketones produce 1,2,4-triazolines only (Equation (20)) <91JHC1957>. Aromatic and heteroaromatic thiodihydrazones (**200**) in the same reaction conditions afford 1,2,4-dithiazolidines (**201**) (Equation (21)) <91JHC1957>.



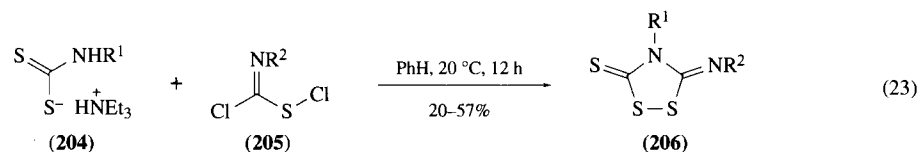
Reagent (**194**) can also be used to build the useful dithiasuccinoyl protecting group on to the amino group of amino acid derivatives as in (**202**) (Scheme 43) <77JA7363, 80JA3084, 85JA4936, 87MI 413-03, 90MI 413-01>. The reaction is also successful with alkyl and aryl substituents in place of the carboxylic acid entity <93JAP93139902>. The imino derivative of this reagent, *N*-substituted *S*-chloro-isothiocarbamoyl chloride (**203**) gives 1,2,4-dithiazolidines with thioureas (Equation (22)) <77IJC(B)1068, 87JIC321>.



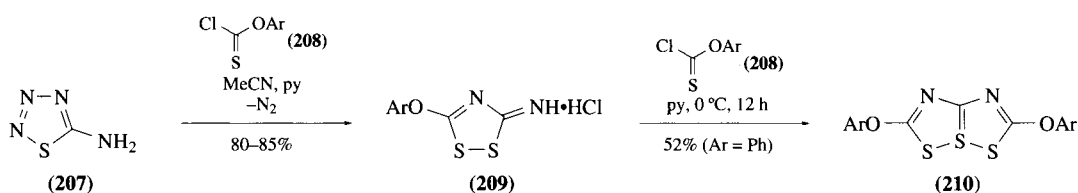
Scheme 43



The *N*-arylimino derivative (205; R² = Ar) on reaction with *N*-aryl substituted dithiocarbamates (204; R¹ = Ar) gives a dithiazolidine (206; R¹R² = Ar) in which the C—S entity of (205) has become attached across N—C—S grouping of (204) (Equation (23)). *N*-Alkyl imino derivatives (205; R² = alk) react with *N*-aryl substituted (204; R¹ = Ar) in the same sense to give (206; R¹ = Ar, R² = alk). Surprisingly the same product is formed in a cross experiment with *N*-aryl substituted (205; R² = Ar) and *N*-alkyl substituted (204; R¹ = alk). Similar crossover is observed when both reagents bear *N*-alkyl substituents and interconversion of the products by a Dimroth rearrangement was excluded <91JPR107>.

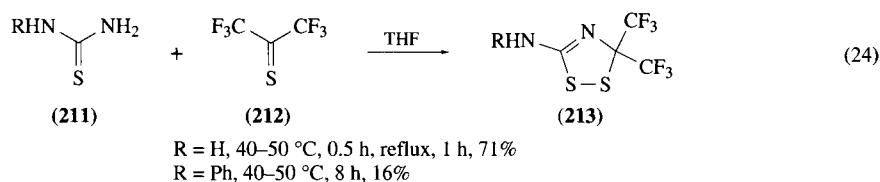


5-Amino-1,2,3,4-thiatriazole (207) when acylated with *O*-aryl chlorothioformate (208) transforms into an unstable 5-aryloxy-3-imino-1,2,4-dithiazole hydrochloride (209). Acylation of this compound produces 2,5-bis(aryloxy)-1,6,6αλ⁴-trithia-3,4-diazapentalene (210), which may be obtained more conveniently by acylating (207) with two equivalents of (208) (Scheme 44) <89M(120)997, 90JPR208>.



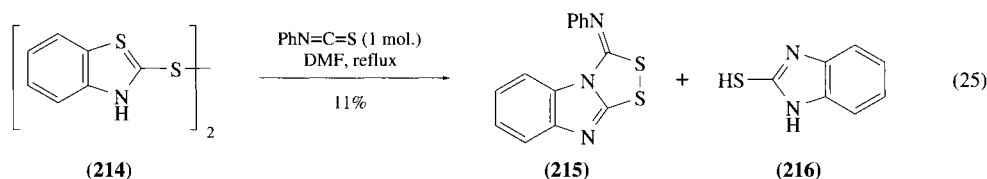
Scheme 44

Thioureas (211) combine with hexafluorothioacetone (212) to give 1,2,4-dithiazoline derivatives (213). The proposed mechanism involves nucleophilic attack by the nitrogen atom of thiourea on the carbon atom of the thione group in (212) (Equation (24)) <90CB691>.

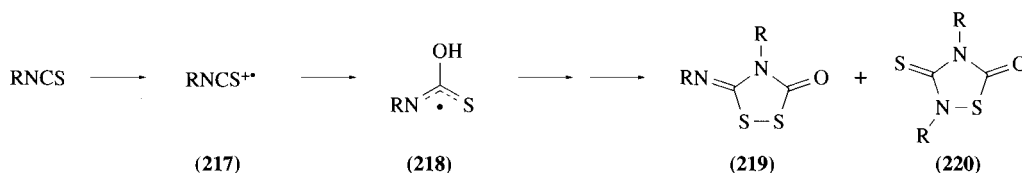


Bis(benzimidazol-2-yl)disulfide (214) treated with phenyl isothiocyanate gives the 1,2,4-dithiazole derivative (215) as a result of electrophilic attack by the isothiocyanate group on the nitrogen atom

of (214) accompanied by S—S bonding and displacement of benzimidazole-2-thiol (216) (Equation (25)). Less electrophilic alkyl isothiocyanates do not react <83T2311>.

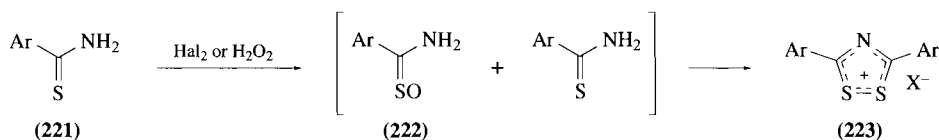


Primary and secondary alkyl isothiocyanates undergo electrochemical oxidation on a platinum anode in MeCN <87JOC2783> or CH₂Cl₂ <88JOC1744> to 1,2,4-dithiazolidines (219) and 1,2,4-thiadiazolidines (220) (Scheme 45). Cyclic voltammetry potentials are 2.05–2.25 V in MeCN and 1.6–1.85 V in CH₂Cl₂, preparative electrolysis was run at 2–2.4 V in MeCN and 1.80–1.85 V in CH₂Cl₂. The process is believed to begin with one electron anodic oxidation to a cation radical (217) followed by its chemical transformation to a radical (218) regarded as a branching point for three lines of further conversion into the final products (219) and (220): (1) dimerization, (2) combination with the initial isothiocyanate, and (3) a second one-electron oxidation to give the cation corresponding to (218) which combines with the initial isothiocyanate. Steric effects of the substituent R are important. The product (219) is predominant for R = Me, Et and exclusive for R = Prⁿ, Buⁿ, *c*-C₆H₁₁ in CH₂Cl₂ solvent; the total yield diminishes with longer alkyls. Reaction in nucleophilic MeCN solvent is far less selective because MeCN stabilizes carbocationoid intermediates and can also combine itself with isothiocyanates, producing thiadiazolidines. With secondary alkylisothiocyanates in MeCN and tertiary alkylisothiocyanates in both MeCN and CH₂Cl₂ the reaction takes a different course.

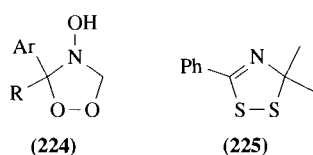


Scheme 45

Oxidation of arylthioamides (221) constitutes a most suitable and convenient method for preparation of 3,5-diaryl-1,2,4-dithiazolium salts (223) (Scheme 46) <85H(23)997>. The oxidation is believed to proceed via an oxide (222). The latter may also be used as a starting material on its own and allowed to react with an arylthioamide containing a different aryl group to obtain an unsymmetrically substituted diaryldithiazolium salt (223) <77LA1005>. There is some ¹H NMR spectral evidence for the 1,2,4-dioxazolines (224) as intermediates in the dye-sensitized photo-oxygenation of nitrones by singlet oxygen using 250 W sodium vapor lamp <89JOC3732, 93TL793>.

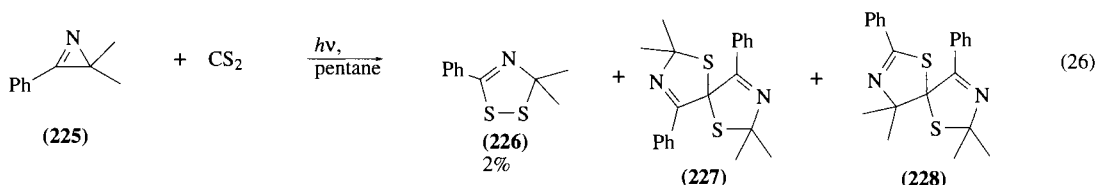


Scheme 46



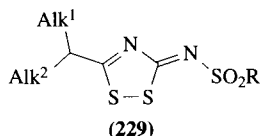
4.13.8.6 Formation of Three Bonds

Irradiation of 2,2-dimethyl-3-phenyl-2*H*-azirine (**225**) by a Hg lamp in the presence of CS₂ gave a 1,2,4-dithiazoline derivative (**226**) as a by-product to two thiazole derivatives (**227**) and (**228**) (Equation (26)) <82HCA1825>.



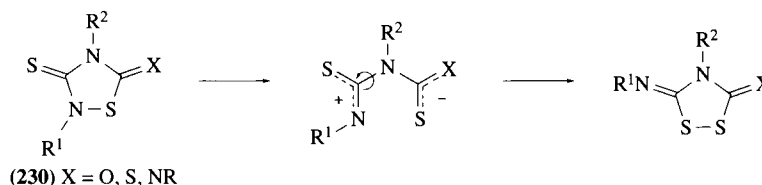
4.13.8.7 Formation of Four Bonds

Heating P₄S₁₀ with an excess of benzonitrile produces 3,5-diphenyl-1,2,4-dithiazolium salt (**13**), the anion being formed by incorporation of a nitrogen atom in place of sulfur in the cage-like P₄S₁₀ molecule <86ZAAC(542)123>. Butyronitrile and phenylacetone nitrile give similar results. Acetonitrile reacts very slowly yielding traces of the anion (maybe because of its low boiling point). Dialkyl thioketenes (preferably sterically hindered) with *N*-sulfonyl isocyanates yield *N*-sulfonylimino-1,2,4-dithiazolines (**229**) as minor products alongside the main [2 + 2] cycloaddition products (azetidinones) <88CB689>.



4.13.9 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

An important reaction under this heading is one related to the Dimroth rearrangement starting from derivatives of 1,2,4-thiadiazolidine series (**230**) (Scheme 47). The process is enhanced by acids (**230**; X = O, R¹ = Alk, R² = Ar) <90JPR181, 91EGP294019>, (**230**; X = S; R¹, R² = Alk) <91JPR107>, (**230**; X = NAr, R¹ = Alk, R² = Ar) <91JPR579>, bases (**230**; X = NAr; R¹, R² = Alk) <88JHC1459> and heat (**230**; X = O, R¹ = Alk, R² = Ar) <92JPR685>.

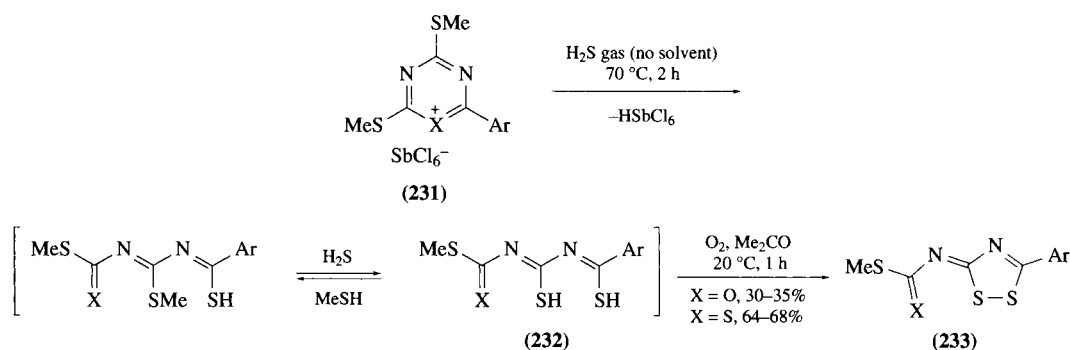


Scheme 47

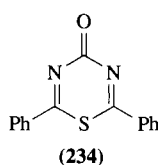
A reversible rearrangement of 1,2,4-thiadiazolidine (**109**) (Scheme 22) occurs in acetone with participation of the latter apparently via heterapentalene intermediate formed by reversible 1,3-cycloaddition of the carbonyl group to the S=C—S entity <92JHC69>.

2-Aryl-4,6-bis(alkylthio)-1,3,5-oxa(thia)diazenium salts (**231**) are converted to 1,2,4-dithiazolines (**233**) by H₂S presumably through ring opening under nucleophilic attack of H₂S on C-2 and oxidation of the dithiol intermediate (**232**) by atmospheric oxygen (Scheme 48) <85LA1874, 88LA729>.

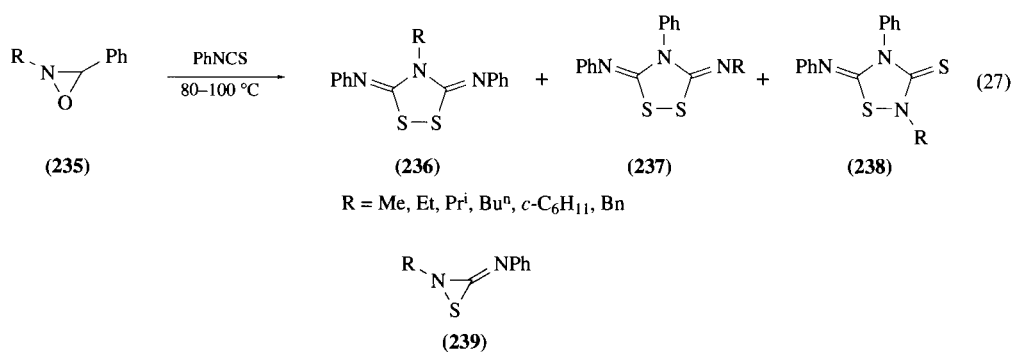
Thiadiazinone (**234**) is transformed into a trithiadiazapentalene (**25**; R = Ph) by the action of P_4S_{10} <84SUL127>.



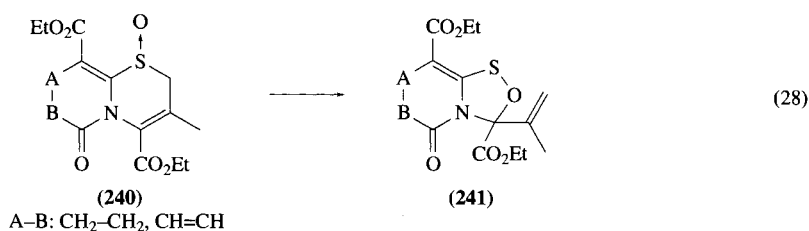
Scheme 48



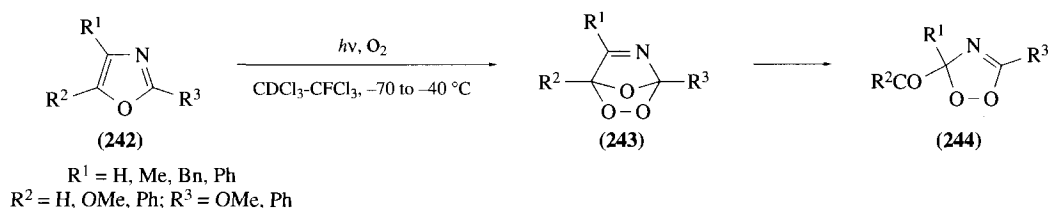
Oxaziridines (**235**) heated with phenylisothiocyanate at 80 – $100^\circ C$ afford 1,2,4-dithiazolidines (**236**), (**237**) and 1,2,4-thiadiazolidines (**238**) in proportions depending on R (Equation (27)). At a higher temperature (105 – $110^\circ C$, R = Bu^t , $c-C_6H_{11}$) the reaction takes another course <74JOC957, 86JOC407, 86BCJ987>. Thiaziridinimine (**239**) is postulated as an intermediate reacting with a second molecule of PhNCS.



Photolysis of fused 1,3-thiazine S-oxides (**240**) by a 125 W medium pressure lamp leads to stable 1,2,4-oxathiazolidines (**241**) presumably through a diradical intermediate (Equation (28)) <83CC199>.



Dye-sensitized photooxygenation of oxazoles (**242**) in aprotic solvents with 650 W halogen lamp leads to unstable 1,2,4-dioxazolines (**244**) via intermediate cyclic peroxides (**243**) (Scheme 49) <90JCS(P1)1011, 91JCS(P2)1085>.



Scheme 49

4.13.10 SURVEY OF RING SYNTHESIS

4.13.10.1 1,2,4-Dithiazole

1,2,4-Dithiazole systems have received most attention in synthesis.

Oxidative cyclization of dithioimides, one of the oldest methods dating back to 1893 [84CHEC-I(6)897], is still in use (see Section 4.13.8.1). The dithioimides may be used in form of *N*-thioacylthioureas (Scheme 31), dithiobiurets (136), (138), *N*-thioacyldithiocarbamates and mono- or dithioethers of all of them. The usual oxidants are Cl_2 , Br_2 [88IJC(B)967], I_2 , less conventional are H_2O_2 (or other peroxides), elemental sulfur [85JIC161] and atmospheric oxygen. Mild reaction conditions are usually sufficient to secure fair yields. This type of reaction may also be related to cyclization of thiocyanic acid in conc. H_2SO_4 with the supposed intermediate formation of dithioimide-like species [84JCE78]. Similarly transformation of the bis(alkylthio)-1,3,5-oxa(thia)diazinium cation (231) by H_2S into 1,2,4-dithiazoles supposedly via aerial oxidation of an intermediate *N*-thioacylthiourea and ring closure of 3-acylimino-1,2-dithialidines (146) by heating with dithiadiphosphetane (transforming acyl into thioacyl) are also examples. The final products in all these reactions are 1,2,4-dithiazoles with imino- and thione groups in 3 and 5 positions.

3-Amino-1,2,4-dithiazolium cations are obtained when the starting *N*-thioacylthioureas in the form of a metal chelate (148) are oxidized by Br_2 , SOCl_2 , or electrochemically on a Pt-anode (See Section 4.13.8.2). The same cations result from oxidation of *N*-acylthioureas (e.g. (149)) or their metal chelates and their formation from *N,N*-dimethylthionocarbamic acid derivatives with BrCN or KSCN and R_2NH is also described in an old patent [84CHEC-I(6)897]. 3,5-Diaryl-substituted cations are most conveniently prepared from arylthioamides (221) with halogen or H_2O_2 ; a less suitable preparation involves strong heating of aryl nitriles with P_4S_{10} .

Far less common is an oxidative cyclization proceeding through initial SS bonding. The oxidation of *N*-acylthioureas by Br_2 or H_2O_2 to give 1,2,4-dithiazoles (152) or their cations (150) depending on substituents and conditions used falls in this category. The thoroughly investigated electrochemical oxidation of alkylisothiocyanates is thought to proceed through formation of the SS bond prior to the ring closure (Scheme 45), whereas oxidation by Cl_2 or Br_2 , followed by hydrolysis is thought to involve an intermediate halodithiazolylium salt [84CHEC-I(6)897], both processes producing 3-imino-5-oxo-4-*R*-1,2,4-dithiazolidines.

Chlorocarbonylsulfonyl chloride and its imino derivative (see Section 4.13.8.5) have proved to be versatile and mild reagents for reaction with thioureas (Equations (19) and (22)), thioamides [84CHEC-I(6)897], thiosemicarbazones (198), formamides [84CHEC-I(6)897], amino acids esters [84CHEC-I(6)897] and their derivatives (Scheme 43), dithiocarbamates (Equation (23)) to give 1,2,4-dithiazolidines with oxo, thioxo, and imino groups in 3 and 5 positions in various combinations. Amongst these formation of the dithiosuccinoyl protecting group on amino acids (202) is worth noting [84CHEC-I(6)897]. The process involves addition of the CS entity of the reagent across NCS grouping of the above substrates with elimination of chlorine atoms. *O*-Aryl chlorothioformate (208) which combines with 5-amino-1,2,3,4-thiatriazole (207) to give 3-aryloxy-5-imino-1,2,4-dithiazole (209) followed by a repeated addition to form a symmetrical diaryloxy trithiadiazapentalene (210).

Reaction of 4-alkyl-5-imino-1,2,3,4-thiatriazolines with isothiocyanates gives 4-alkyl-3,5-diimino-1,2,4-dithiazolines and 1,2,4-thiadiazolines (Equation (14), Section 4.13.8.4) [84CHEC-I(6)897]. The extensive studies by L'abbé and coworkers have established the dependance of the process on substituents, solvents, temperature, and other chemical and physical factors and have shown that the mechanism involves alternating 1,3-cycloadditions–eliminations of RNCS through intermediate heterapentalene species. This pattern of 1,3-cycloaddition with RNCS to form 1,2,4-dithiazole ring is also realized with other heterocycles possessing an NCS grouping (Schemes 40 and 41; (214) or is envisaged in mechanisms involving such heterocycles). Other variants for the combining of $\text{C}=\text{S}$

bond and NCS grouping exist, for example the interaction between hexafluorothioacetone and thioureas to produce substituted 3-amino-5-bis(trifluoromethyl)-1,2,4-dithiazolines (**213**) and oxidative addition of CS₂ to isothiuronium salts to give 5-imino-3-thioxo-1,2,4-dithiazolidines (see Section 4.13.8.5) <84CHEC-I(6)897>.

Thioxo-1,2,4-dithiazolidines can be obtained from thioxo-1,2,4-thiadiazolidines by Dimroth rearrangement (Scheme 47) or reversibly by addition and elimination of acetone (Scheme 22). 1,2,4-Dithiazole type products are also obtained from thiocarbonyl isothiocyanates (**154**) by reaction with Cl₂ <84CHEC-I(6)897>, PhMgBr, S₈, or CS₂. Other routes include reactions of carbonyl isothiocyanates and thiocarbonyl isocyanates with P₄S₁₀ or S₈ <84CHEC-I(6)897> and sulfonyl isocyanates with dialkyl thioketenes. Phenylisothiocyanate heated with N,C-disubstituted oxaziridines affords 3,5-diimino-1,2,4-dithiazolidines (**226**, **227**). Other miscellaneous syntheses of 1,2,4-dithiazoline derivatives include cyclization of *N*-thioacyl hexafluoroacetoneimine to 5,5-bis(trifluoromethyl)-1,2,4-dithiazolines (**158**) when heated with P₄S₁₀ <84CHEC-I(6)897> or S₈, photoreaction between trisubstituted azirine and CS₂ to afford trisubstituted 1,2,4-dithiazoline (**226**) and formation of symmetrical diphenyl trithiadiazapentalene (**25**; R = Ph) by heating of 2,5-diphenyl-1,3,5-thiadiazine-4-one heated with P₄S₁₀.

4.13.10.2 1,2,4-Oxathiazolidines

1,2,4-Oxathiazolidines may be formed by 1,3-cycloaddition. Examples of the addition of carbonyl compounds across the SCN grouping include the reactions between CO₂ and 5-imino-1,2,4-thiadiazoles to give (**176**) in high yield and that between acetone and 5-imino-1,2,3,4-thiadiazolines to give (**179**) in low yield. A single example of addition of a C=N bond across a CSO grouping involves the reaction between cyclic imines and thioketene *S*-oxides <84CHEC-I(6)897>. Photorecyclization of condensed 1,3-thiazine *S*-oxides provides a route to condensed 1,2,4-oxathiazolidines (**241**) in good yields.

4.13.10.3 1,2,4-Dioxazolines and 1,2,4-Dioxazolidines

1,2,4-Dioxazolines and 1,2,4-dioxazolidines are synthesized by use of singlet oxygen, ozone, and peroxides, often through [2 + 3] cycloaddition. Electron-transfer photooxygenation of aziridines with a sensitizer proceeds through addition of singlet oxygen molecule to the ring-opened aziridine species to give 1,2,4-dioxazolidines in good yield (Scheme 42). Photoaddition of O₂ to 2-alkoxyoxazoles followed by a rearrangement leads to unstable 3-acyl-1,2,4-dioxazolines (**244**) <84CHEC-I(6)897>. Carbonyl oxides add to imines to give 4-substituted 1,2,4-dioxazolidines in good yield (Equation (18)). 4-Unsubstituted 1,2,4-dioxazolidines (**153**) are obtained in high yields by the catalytic reaction of aldehydes or ketones with H₂O₂ and NH₃ through intermediate formation of *N*-(α -hydroperoxyalkyl)imines (Equation (12)) <84CHEC-I(6)897>. The same compounds result by ozonolysis of alkenes in the presence of ammonia <84CHEC-I(6)897>. 4-Hydroxy-1,2,4-dioxazolidines (**224**) were only detected as intermediates in the dye-sensitized photooxygenation of ketonitrone. Percarbamic acid derivatives subjected to dehydrative cyclization by HCO₂H afford 1,2,4-dioxazoline-3-ones <84CHEC-I(6)897>.

4.13.11 IMPORTANT COMPOUNDS AND APPLICATIONS

3-Amino-1,2,4-dithiazoline-5-thiones (**7**; R₂ = H₂; H, Ac; H, alk; alk₂) increase the oxygen overpotential on the Pt anode (apparently by its strong chemisorption on the active surface centres) and, as a result, increase the initial rate of electrochemical synthesis of peroxydisulfate anion in 5 M H₂SO₄ and its current yield. These effective polarizers compare with the industrial promoter SCN⁻ in their optimal concentration ($\approx 10^{-2}$ mol dm⁻³), but rank somewhat below it in current yield <81EGP151186, 83CCC1956, 83EGP204714>. This type of compound (**7**; R₂ = H, H; H, Ac; H, Bz) was also used to catalyze the carbonylation of nitrobenzene by CO in methanol to methyl phenylurethan. They showed low activity (0.5–2.5% yields), but appreciable selectivity (60 to $\approx 100\%$ urethan in mixture with a co-produced aniline) <87ZPK1426>.

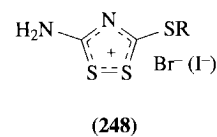
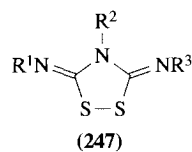
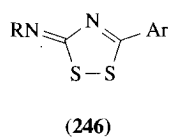
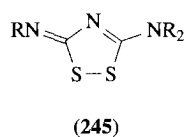
The ability of 2,5-diaryl-1,6,6 α ⁴-trithia-3,4-diazapentalenes (**73**) (see Section 4.13.5.3) to produce O₂^{-•} from O₂ in the process of electrochemical reduction was related by the authors <91CPB1914>

to the similar effect of some other heterapentalenes and the herbicide Paraquat in biological systems. The possibility that this ability is connected with the presence of hypervalent sulfur may be helpful in the search for biologically active substances, especially herbicides. This topic is reviewed <89YGK843>. The 2,5-bis(arylamino) substituted derivatives may be of interest as drugs, agrochemicals, and dye additives <90EGP276286>.

3-Amino-5-imino-1,2,4-dithiazoles (**245**) with Alk, Ar, and Bn substituents showed antifungal and insecticidal activities <87MI 413-02> but were more intensively investigated for their anti-convulsant and analgesic activities <82MI 413-05, 87MI 413-02, 92MI 413-01, 92MI 413-02, 92MI 413-03, 92MI 413-04>. The latter two activities were also exhibited by 3-aryl-5-imino analogues (**246**) with Ar and Bn substituents <82MI 413-05>. No fungicidal activity was found in (**246**; R = Me; Ar = Ph) <88MI 413-01>. 1,2,4-Dithiazoles (**245**) with an unsubstituted 3-amino group were claimed as microbicides and plant growth regulators <89EGP267655>, those with a monosubstituted 3-amino group were screened against bacteria <91JIC472>. Some 3,5-diimino-1,2,4-dithiazolidines (**247**) exhibited 100% fungicidal and acaricidal activity at ≈ 500 ppm <82JAP82183769>. 4-Substituted 1,2,4-dithiazolidine-3,5-diones are claimed as plant preservatives <93JAP93139902>.

1,2,4-Dithazolium salt (**141**) displays fungicidal and acaricidal activities <82JAP82183770>, and salts of the type (**248**) are shown to be inhibitors of biocorrosion of metals <90URP1587049>.

3-Amino-1,2,4-dithiazole-5-thione may be used for corrosion inhibition of Cu + Zn powder mixture <86MI 413-03> or for inhibition of polymer ageing <85URP1142485>; *N*-alkoxy derivatives inhibit corrosion of iron <91URP1650683, 82MI 413-06, 82MI 413-07>. 1,2,4-Dithiazolidines (**247**; R² = H, R¹ = R³ = Ar) display antiwear and antifriction properties <90MI 413-02, 92MI 413-05>. 1,2,4-Dithiazolidine derivatives (**247**) were proposed as antifoggants for silver halide photographic materials <88JAP8805535, 88JAP88281150, 92MI 413-06>. 3-Phenylimino-4-phenyl-1,2,4-dithiazolidine-5-thione is proposed as a sensitizer in color photography <82MIP8201260>. Some 1,2,4-dithiazolidines showed vulcanization properties <93MI 413-01>. 1,2,4-Dithiazolium derivatives (**10**) and (**12**) are thermochromic <91MIP2018944, 91MIP2018945>. 1,2,4-Dioxazoles of the type (**193**; R³ = H) are useful in textile bleaching compositions <85FRP2552123>.



4.14

1,4-Oxa/thia-2-azoles

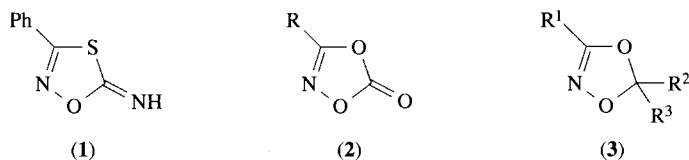
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4.14.1 INTRODUCTION

The chemistry of 1,4-(oxa/thia)-2-azoles, was founded in the late 1930s, when Musante first correctly suggested the 5-imino-2-phenyl 1,4,2-oxathiazole structure (**1**) for the product obtained from the reaction of ammonium thiocyanate and benzhydroximoyl chloride <38G331>. Later, Beck described the preparation of dioxazolones (**2**) and some of their properties <51CB688>, while the first nonconjugated dioxazole derivative (**3**) was prepared by Exner from hydroxamic acid and benzophenone diethylacetal <56CLY779>.

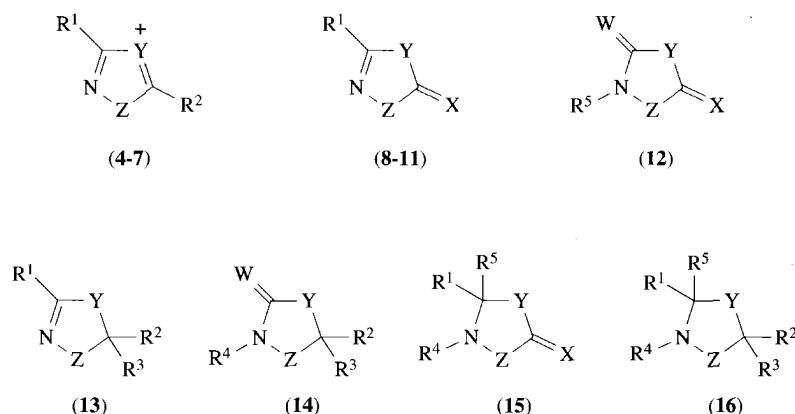


In general, there is a lack of review articles concerning these ring systems. In the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I), Sammes examined in a single chapter all possible structures of (oxa/thia)-azoles <84CHEC-I(6)897>; this still remains the only account on the subject. However, preparation of some of these ring systems, using the dipolar cycloaddition methodology, have been reported in review articles and books concerning nitrile oxides <B-71MI 414-01, B-84MI 414-01>, nitrile sulfides <89CSR33> or nitrones <75S205, B-84MI 414-02, B-88MI 414-01>. The accumulation of new material is one of the main reasons for the separate examination of 1,4-(oxa/thia)-2-azoles. Consequently, although this chapter will focus mainly on post-1980 data, earlier citations will also be included where appropriate.

4.14.1.1 Survey of Possible Structures

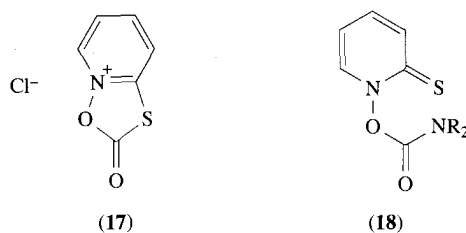
All possible general structures for 1,4-(oxa/thia)-2-azoles are given below (**4**)–(**16**). Fully conjugated rings may exist either as unsaturated monocationic rings or as such with exocyclic double bond(s) having anionic(s) O, S, NR, or CR₂ group(s) attached to ring carbon atoms.

Four possible structures may be proposed for the azolylium cations (**4**)–(**7**): 1,4,2-dioxazolium (**4**) (Y = Z = O); 1,4,2-dithiazolium (**5**) (Y = Z = S); 1,4,2-oxathiazolium (**6**) (Y = S, Z = O), and 1,3,4-oxathiazolium (**7**) (Y = O, Z = 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) (X = O, Y, Z = O and/or S), azolinethiones (9) (X = S; Y, Z = O and/or S), azolinimines (10) (X = NR, Y, Z = O and/or S) and azolinylenes (11) (X = CR₂, Y, Z = O and/or S). For the (oxa/thia) azolidines (12) (Y, Z = O and/or S, X, W = O, S, NR, or CR₂) 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 a *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.

There are no known examples of positively charged fully conjugated 1,4,2-dioxazolium rings (4) (Y = Z = O). In some instances of cations which have a fully conjugated dioxazole ring, the positive charge is located exclusively outside the ring (see Section 4.14.3.1 for azoniasallene cations). In practice, most of the known derivatives are dithiazolium salts (5), azolinones (8), and related compounds (9)–(11), as well as 5H-dihydro-1,4-(oxa/thia)-2-azoles (13) (Y, Z = O and/or S). However, examples of all other ring systems are known. Benzo-fused systems cannot exist, but there are possible bicyclic compounds with a bridgehead nitrogen atom. Although these compounds are examined elsewhere, 5-oxo-1,4,2-oxathiazolo[2,3-*a*]pyridinium chloride (17) should be mentioned, as it is widely used as an aminyl radical source in the form of N-hydroxypyridine-2-thione carbamates (18), e.g. the open-chain adduct with amines <85T3901, 90T2317>.



4.14.2 THEORETICAL METHODS

Data obtained from semi-empirical calculations at the AM1 level of approximation <85JA3902> on the ground-state geometries of some selected conjugated 1,4-(oxa/thia)-2-azoles are given in Table 1 <94UP 414-01>.

In all cases the oxathia derivatives appear to be at least 15 kcal mol⁻¹ more stable than their dithio analogues, though this cannot be a safe criterion for the assumption that they are more readily prepared. In general, dithiazolium salts appear to be slightly better donors and acceptors than their oxathia counterparts regarding their frontier molecular orbital eigenvalues. The LUMOs are mainly localized in the X—C5—Y region of the ring with pre-eminent C5 contribution thus supporting experimental evidence for the ring's reactivity towards nucleophiles (see Section 4.14.5.4). The HOMOs are generally widely delocalized predicting that reactions with electrophiles are rather unfavorable (see Section 4.14.5.3).

The introduction of substituents at C3 and C5 leads, in general, to charge removal from the corresponding carbon atom, and a subsequent drift of π -charge over the ring towards it, depressing

Table 1 AM1 data for 1,4-(oxa/thia)-2-azoles.

Structure type	Ring system			Substituents			Orbital energies ^a		Net charges					π -bond orders			
	X	Y	Z	R ¹	R ²	ΔH_f^b	HOMO	LUMO	Y	C5	Z	N	C2	X-C5	C5-Z	C5-Y	N-C2
(5)		S	S	H	H	208.9	-15.86	-6.91	+0.94	-0.91	+1.05	+0.17	-0.34		1.09	0.44	0.67
(5)		S	S	Ph	Ph	249.7	-12.73	-6.11	+0.73	-0.64	+0.93	-0.35	-0.13		0.45	0.36	0.63
(5)		S	S	Ph	NMe ₂	221.6	-12.60	-5.41	+0.56	-0.44	+0.68	-0.31	-0.09		0.28	0.25	0.73
(7)		O	S	H	H	194.6	-16.95	-7.16	-0.04	-0.33	+1.02	+0.09	+0.10		1.09	0.28	0.76
(7)		O	S	Ph	Ph	229.3	-12.87	-6.04	-0.10	-0.15	+0.83	-0.37	+0.21		0.50	0.23	0.68
(7)		O	S	Ph	NMe ₂	200.0	-12.78	-5.18	-0.15	-0.07	+0.67	-0.34	+0.21		0.31	0.18	0.74
(8)	O	O	O	H		-48.7	-11.47	-0.41	-0.19	+0.35	-0.13	-0.01	-0.04	0.84	0.15	0.15	0.76
(8)	O	O	S	H		-36.0	-9.90	-0.90	-0.22	+0.10	+0.37	-0.30	+0.02	0.91	0.15	0.14	0.84
(8)	O	S	S	H		-0.3	-9.24	-0.99	+0.23	-0.07	+0.33	-0.24	-0.27	0.90	0.16	0.15	0.82
(9)	S	O	S	H		25.1	-9.28	-1.24	-0.16	-0.28	+0.41	-0.30	+0.01	0.85	0.19	0.14	0.83
(9)	S	S	S	H		47.6	-9.00	-1.52	+0.36	-0.58	+0.44	-0.26	-0.30	0.81	0.20	0.18	0.80

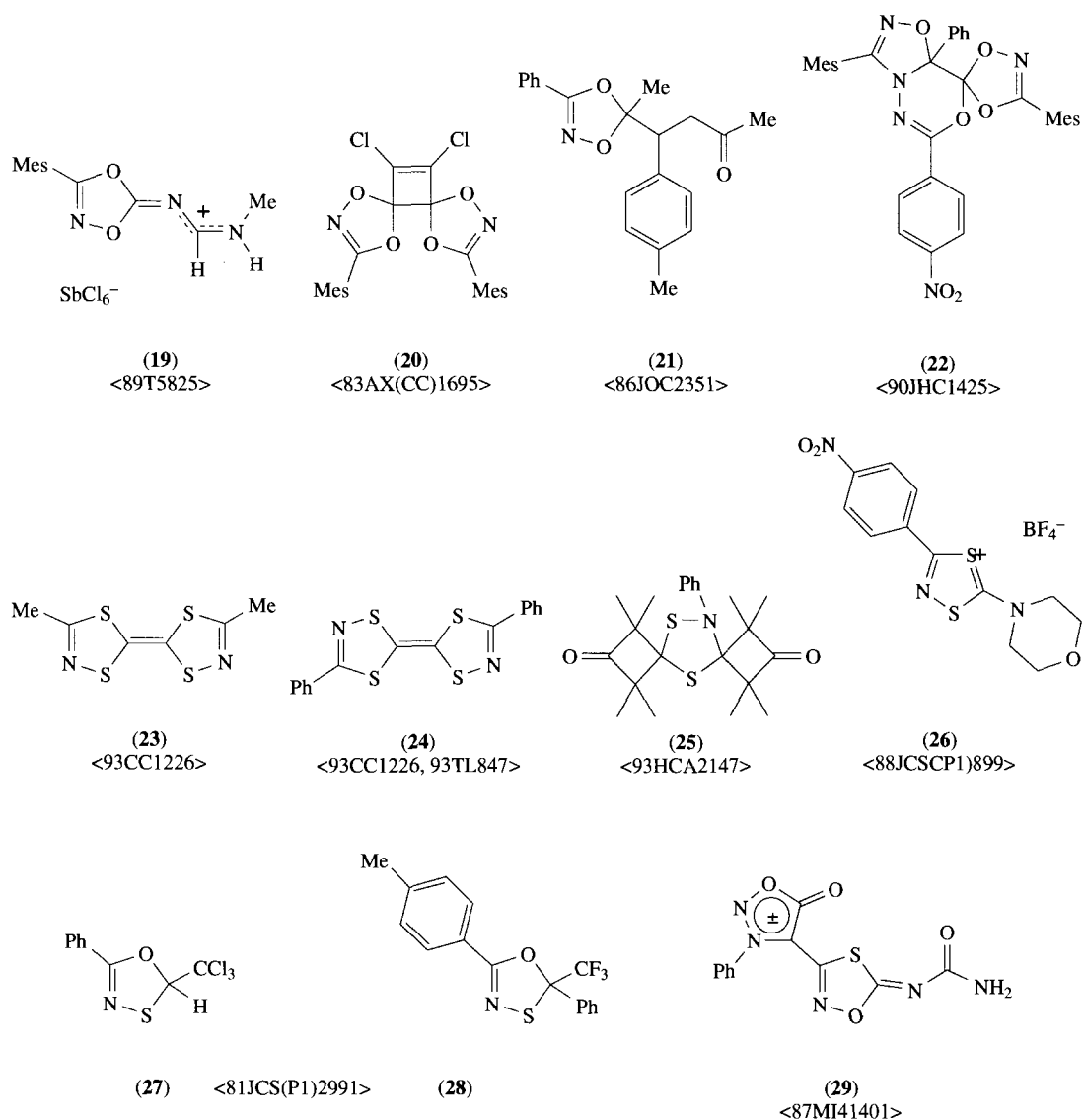
^aIn eV. ^bIn kcal mol⁻¹.

the C=N π -bond character (0.726 to 0.633 and 0.744 to 0.684 for dithia and oxathiazole rings, respectively).

4.14.3 EXPERIMENTAL STRUCTURAL METHODS

4.14.3.1 X-ray Diffraction

Below are listed various dioxazoles, dithiazoles and oxathiazoles, (19) to (29), the structures of which have been obtained by X-ray diffraction: (19) <89T5825>; (20) <83AX(C)1695>; (21) <86JOC2351>; (22) <90JHC1425>; (23) <93CC1226>; (24) <93CC1226, 93TL847>; (25) <93HCA2147>; (26) <88JCS(P1)899>; (27) and (28) <81JCS(P1)2991>; (29) <87MI 414-01>. Of particular interest are data for the cation (19), which indicates an almost ideal allylium rather than allenium cation structure (see also Section 4.14.4). A substantial bond shortening is observed for both C₅—O₄ (1.31 Å) and C₅—O₁ (1.31 Å) bonds, as a result of the sp^2 character of the C₅ atom and a bent central C—N—C unit (116.2°) with unequal C—N bond lengths; 1.27 Å for that adjacent to the ring bond, which presumably exhibits more double bond character and 1.34 Å for the other <89T5825>. All C=N and N—O bond lengths of dioxazoles (19–22) range between 1.27–1.28 Å and 1.42–1.43 Å respectively, while the C₃—O₄ bond lengths range between 1.36 and 1.39 Å. A significantly long C—C bond (1.63 Å), which connects the two dioxazole rings of compound (20), is observed and attributed to steric repulsions between the two rings <83AX(C)1695>.



In the tetrathiafulvalenes (**23**) and (**24**), the *trans*-diphenyl compound (**24**) is planar with the two phenyl groups also lying in the same plane. This causes a flattening of the five-membered ring and a shortening of the C=C double bond: 1.332 Å <93TL847>; 1.338 Å <93CC1226>. In contrast, the *cis*-dimethyl derivative (**23**) is not planar and the central C₂S₄ unit makes angles of 24.7 and 19.0° with the remaining S—N—C—S unit. The exocyclic C—N bond (1.297 Å) observed in the dithiazolium salt (**26**) indicates a considerable double-bond character, suggesting that most of the positive charge is located on the exocyclic nitrogen. Also both C—S bonds (C₅—S₁ = 1.733 Å and C₅—S₄ = 1.722 Å) are longer than those observed in other typical sulfur heteroaromatics, such as thiophenes or thiazoles <88JCS(P1)899>.

4.14.3.2 Electron Diffraction and Microwave Spectra

The molecular structure of parent 1,3,4-oxathiazolone (**30**) and its 5-methyl derivative (**31**) have been obtained by means of electron-diffraction measurements in combination with microwave spectra <82ACS(A)283>. Bond distances and angles for both compounds are listed in Table 2. From these results it is concluded that only minor changes have been caused in the ring geometry, by the methyl group. There are some differences in structure parameters of the parent compound between those reported previously <78ACS(A)1005> and those listed in Table 2, as a result of recalculation using a new set of force field constants.

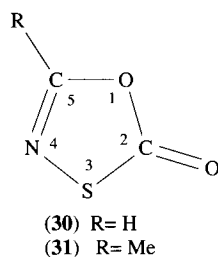


Table 2 Structural parameters and rotational constants of 1,3,4-oxathiazol-2-ones.

Bond lengths (Å)	(30)	(31)	Bond angles (°)	(30)	(31)	Rotational parameters (MHz)		
						(30)	(31)	
O ₁ —C ₂	1.398	1.391	C ₅ O ₁ C ₂	110.9	111.2	A	5583.3	4240.4
C ₂ —S ₃	1.773	1.768	O ₁ C ₂ S ₃	106.2	106.4	B	3643.3	2112.82
S ₃ —N ₄	1.687	1.685	C ₅ S ₃ N ₄	97.3	93.5	C	2204.8	1422.55
N ₄ —C ₅	1.283	1.289	S ₃ N ₄ C ₅	108.1	109.2			
C ₅ —O ₁	1.355	1.367	N ₄ C ₅ O ₁	121.2	119.3			
C ₅ —R ¹	1.107	1.486	R ¹ C ₅ O ₁	114.8	115.3			
C ₂ —O ₆	1.193	1.198	O ₁ C ₂ O ₆	123.4	123.6			

4.14.3.3 NMR Spectroscopy

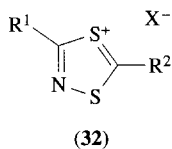
4.14.3.3.1 Proton NMR spectra

Representative examples of ring hydrogen chemical shifts are given in Table 3. In fact, only a few unsubstituted compounds are known and their chemical shifts vary depending upon the substitution and the degree of unsaturation of the ring. Of particular interest are the NMR spectra of 1,4,2-dithiazolium salts (**32**), which have been systematically studied by Sammes *et al.* <90JCS(P1)2465, 88JCS(P1)899, 92JCS(P1)2065>.

Table 3 Proton NMR data for dioxazole, dithiazole, and oxathiazole derivatives^a.

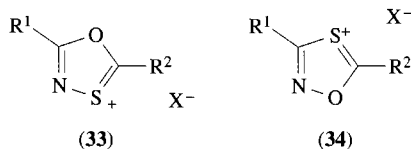
Structure type	Ring system				Substituents					Chemical shifts (δ , ppm)			Ref.
	X	Y	Z	W	R ¹	R ²	R ³	R ⁴	R ⁵	Ring hydrogens		Other	
										H-5	H-3		
(8)	O	S	S		H						8.847		92JCS(P1)2065
(9)	S	S	S		H						8.910		92JCS(P1)2065
(13)		O	O		Ph	H	CH ₂ CO ₂ Et				6.43 ^b	CH ₂ CO ₂ R 2.91 ^b	73CJC1368
(13)		O	O		Me	H	CH ₂ CO ₂ Et				6.25 ^c	CH ₂ CO ₂ R 2.80 ^c , 5-Me 2.03	73CJC1368
(13)		O	S		Ph	H	CCl ₃				6.44		81JCS(P1)2991
(13)		O	S		Ph	H	Ph				7.0		74ZN(B)284
(13)		S	O		Me	H	PhCH ₂ CH ₂				6.02 ^d	5-CH ₃ 2.19	84JOC573
(13)		S	S		H	H	SMe				6.445	2-SMe 2.097	92JCS(P1)2065
(13)		S	S		H	H	4-MeOC ₆ H ₄				6.19	7.75	90JCS(P1)2465
(13)		S	S		Ph	H	H				4.675		92JCS(P1)2065
(13)		S	S		Ph	H	1-pyrrolidine				6.85		88JCS(P1)899
(13)		S	SO ₂		N=CR ²	H	H				4.42		81JHC1309
(14)		O	O	NPh		H	Me	Bu ^t			5.50		86JOC732
(14)		O	O	NBu ^t		H	Bu ^t	Bu ^t			4.94		86JOC732
(14)		S	SO ₂	NR ^e		H	H	Me			4.21	NMe 3.31	77TL1729
(15)	C(CF ₃) ₂	S	O		Ph			Me	H		5.83	NMe 2.95	70JOC3470
(15)	C(CF ₃) ₂	S	O		Ph			H	H		6.05 ^f	NH 6.53 ^f	70JOC3470
(16)		O	O		Bu ^t	H	Bu ^t	Ph	H		4.96 ^g	4.58 ^g	80JCR(S)122
(16)		S	S		H	H	H	4-ClC ₆ H ₄	H		3.95 ^g	4.61	85M1153
(16)		S	O		Me		(CH ₂) ₁₁	OTBDMS	H		4.86	5-CH ₃ 1.46	84JOC573

^aUnless otherwise stated solvent is CDCl₃. ^bAB system, $J = 5.0$ Hz. ^cAB system, $J = 5.2$ Hz. ^dTriplet, $J = 6.2$ Hz. ^eR = Pr₂N—C=S. ^fDoublet, $J = 12$ Hz. ^gNot assigned in the text. ^hTBDMS-*t*-butyldimethylsilyl group.



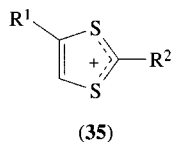
These cations are formally heteroaromatic with 6π electrons, hence both their ^1H and ^{13}C NMR data have some significance, regarding the π -electron delocalization of the ring system, especially in the cases of the parent compound and derivatives without substituents at C-3 and C-5.

In Table 4 are given some ^1H and ^{13}C NMR spectral data for ring protons and carbon for both dithiazolium (32) and oxathiazolium salts (33) and (34). A δ downfield shift for both H-3 and H-5 is generally observed, parallel to the decreasing ability of substituents at C-5 to support a positive charge, a fact which is consistent with an increasing π -electron delocalization and thus of aromaticity of the ring system. Moreover $\delta_{3\text{-H}}$ is more sensitive to change by substitution than $\delta_{5\text{-H}}$. However, the large difference between $\delta_{3\text{-H}}$ and $\delta_{5\text{-H}}$ in the parent cation (ca. 1.7 ppm), in spite of the electronegativity of the ring nitrogen, suggests a limited delocalization, i.e. the positive charge is located mainly near C-5 <92JCS(P1)2065>. Even more limited seems to be the positive charge delocalization for the oxathiazolium cations (33) and (34) as evidenced from comparisons between ^1H NMR spectra of these cations and 1,4,2-dithiazolium analogues with the same substituents <91TL3771>.



4.14.3.3.2 Carbon-13 NMR spectroscopy

In Table 5 the various C-3 and C-5 chemical shifts of representative examples of 1,4-(oxa/thia)-2-azoles are given. As regards the conjugated compounds (8)–(11) $\delta_{\text{C-5}}$ and $\delta_{\text{C-3}}$ are found to vary from 153 to 175 ppm and from 150 to 218 ppm, respectively. Analogous $\delta_{\text{C-5}}$ are found for the dihydro compound (13) and (14) (146–171 ppm), while the $\delta_{\text{C-3}}$ is more affected by the substitution varying from 46 to 118 ppm. The potentially aromatic character of (oxa/thia)azolium cations is further supported by ^{13}C NMR data (see Table 4). As for the proton signals, in cases where the positive charge is located predominantly inside the heterocyclic ring, a downfield shift is observed if compared to cases where the C-5 substituent (e.g. an alkylamino group) is able to support a positive charge <92JCS(P1)2065>. The degree of delocalization for 1,4,2-dithiazolium salts (32) is higher than that of 1,3,4- (33) and 1,4,2-oxathiazolium salts (34) <90TL5935, 91TL4329>, but lower than that of the closely related 1,3-dithiolium salts (35) <92JCS(P1)2065>.



4.14.3.3.3 Nitrogen-15 NMR spectroscopy

No data on ^{15}N chemical shifts have yet been reported for any class of 1,4-(oxa/thia)-2-azoles.

4.14.3.3.4 Fluorine-19 NMR spectroscopy

The ^{19}F NMR spectra (CClF_3 internal reference) of some 1,3,4-dioxazolidines (36) show a characteristic A_3B_2 pattern with $\delta_{\text{A}} = -68.8$ (m), $\delta_{\text{B}} = -68.2$ (m), $J_{\text{AB}} = 7$ Hz ($\text{R} = \text{Me}$) <82JA4034> and $\delta_{\text{A}} = -68.14$ (m), $\delta_{\text{B}} = -67.35$ (m), $J_{\text{AB}} = 7$ Hz ($\text{R} = \text{Et}$) <86JOC4466>. Other ^{19}F chemical shifts

Table 4 Proton and carbon-13 NMR data for dithiazolium (32) and oxathiazolium salts (33) and (34).

Structure type	Substituents			Chemical shifts (δ , ppm)						Ref.	
				Ring protons		Other		Ring carbons			Other
	R^1	R^2	Anion	H-3	H-5	3-Me	5-SMe	C-3	C-5		
(32)	Ph ^{a,b}	H	BF ₄ ⁻		12.335						92JCS(P1)2065
(32)	4-ClC ₆ H ₅ ^a	H	ClO ₄ ⁻		12.360			188.26	195.55		92JCS(P1)2065
(32)	H ^a	H	BF ₄ ⁻	10.803 ^c	12.506 ^c			172.05	195.70		92JCS(P1)2065
(32)	H ^d	4-MeOC ₆ H ₄	ClO ₄ ⁻	9.980				168.16 ^d	211.34		90JCS(P1)2465
(32)	H ^e	SMe	BF ₄ ⁻	9.987			3.185	169.89 ^f	211.45 ^g	29.35 (5-SMe) ^e	92JCS(P1)2065
(32)	H ^e	1-piperidino	BF ₄ ⁻	9.098				158.05	193.91	29.35 (5-SMe) ^e	92JCS(P1)2065
(32)	Me ^c	1-piperidino	BF ₄ ⁻			2.705 (3-Me)		168.52	195.15	22.55 (3-Me)	92JCS(P1)2065
(32)	Me ^c	MeS	BF ₄ ⁻			2.990 (3-Me)	3.149	182.40	222.10	22.01 (3-Me)	92JCS(P1)2065
(34)	Me ^a	Ph	BF ₄ ⁻			3.03		170.02	211.93		91TL4329
(34)	Me ^a	SMe	ClO ₄			3.27	2.91	169.72	218.82		91TL4329
(33)	H ^a	4-MeC ₆ H ₄	ClO ₄	9.08				158.86 ⁱ	205.59		90TL5935
(33)	Me ^a	1-piperidino	ClO ₄				2.61	163.74 ⁱ	181.91		90TL5935

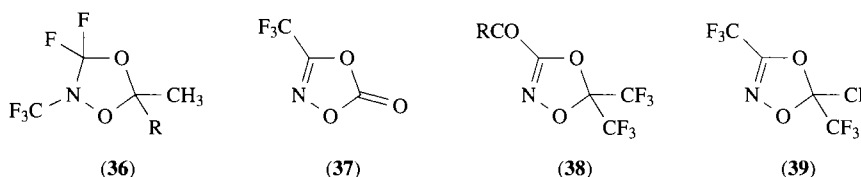
^aIn CF₃CO₂D/CD₃NO₂. ^bUnstable, no ¹³C NMR data available. ^c⁴J_{HH} 0.55 ± 0.11. ^dIn CF₃CO₂D. ^eIn CD₃CN. ^f¹J_{CH} 226.8 ± 0.5. ^g³J_{CH} 6.8 and 3.6. ^h¹J_{CH} 224 ± 1. ⁱThe numbering starts from atom Z.

Table 5 Carbon-13 NMR data for dioxazoles, dithiazoles, and oxathiazoles.^b

Structure type	Ring system				Substituents				Chemical shift (δ , ppm)			Ref.
	X	Y	Z	W	R ¹	R ²	R ³	R ⁴	C-3	C-5	Other	
(8)	O	S	S		H				153.37	196.91		92JCS(P1)2065
(8)	O	S	S		Me				164.00	198.95		92JCS(P1)2065
(8)	O	O	S		Me				158.70	174.20		81JCS(P1)2991
(8)	O	O	S		Ph				157.40	173.7		81JCS(P1)2991
(9)	S	S	S		H				160.16	217.10		92JCS(P1)2065
(9)	S	S	S		Me				172.06	220.41		92JCS(P1)2065
(9)	S	S	S		Ph				172.58	218.98		92JCS(P1)2065
(10)	NCO ₂ Et	S	S		Ph				161.6 ^a	198.2	160.7(CO) ^a	85JCS(P1)1205
(11)	CCl ₂	O	S		Ph				158.10	150.3	81.1(CCl ₂)	85JCS(P1)1517
(13)		O	O		4-NO ₂ C ₆ H ₅	CCl ₃	CCl ₃		159.0	115.3	96.8(CCl ₃)	85JCS(P1)1517
(13)		O	O		Ph	Me	Alk		158.0	118.6		86JOC2351
(13)		S	S		Ph	Ph	Ph		159.38	81.80		91JCS(P1)183
(13)		S	S		4-NO ₂ C ₆ H ₄	Ph	OEt		156.13	115.98		91JCS(P1)183
(13)		S	S		Ph	H	H		162.11	38.98(t)		92JCS(P1)2065
(13)		S	S		Ph	H	SMe		157.48	62.11		92JCS(P1)2065
(13)		S	SO ₂		PhNHC(Ph)=N	H	H		170.7	51.6		81JHC1309
(13)		O	S		Ph	CCl ₃	H		157.1	95.9		81JCS(P1)2991
(13)		O	S		Me	CCl ₃	H		157.6	95.9		81JCS(P1)2991
(13)		O	S		Ph	CCl ₃	CCl ₃		156.1	112.2		81JCS(P1)2991
(13)		S	O		Me	OMe	MeOCS		151.1	127.9	207.8 (C=S)	86CZ338
(14)		O	O	NPh		H	Me	Bu ¹	150.5	99.4		86JOC732
(14)		O	O	NBu ¹		Me	Me	Bu ¹	147.9	105.9		86JOC732
(14)		S	SO ₂	NPh		H	H	Me	145.7	46.2		78JOC4951

^aNot assigned. ^bNumbering starts from atom z.

for fluorinated substituents are as expected. Thus the dioxazolone (37) give $\delta_F = -69.3$ <83JOC3845> the dioxazoles (38) δ_F from -79.9 to -80.76 and (39) δ_F -68.0 and -82.4 <84JOC919>.

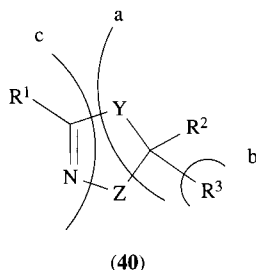


4.14.3.4 UV spectroscopy

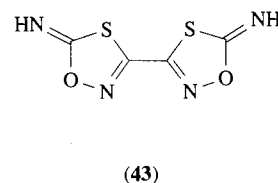
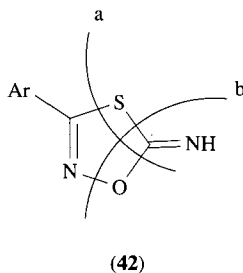
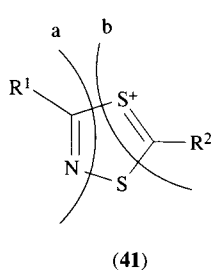
Because of its decreasing use there is little UV data on 1,4-(oxa/thia)-2-azoles. However, some data, gathered mainly from the experimental sections of published papers, is presented in Table 6.

4.14.3.5 Mass Spectrometry

Fragmentation patterns of 1,4-(oxa/thia)-2-azoles show considerable variations depending upon the arrangement of heteroatoms, the degree of unsaturation and the nature of substituents. In many cases, a retro 1,3-dipolar cycloaddition pathway predominates. Numerous examples of this fragmentation pattern have been reported. It should be mentioned that for dioxazoles ($Y = Z = O$) <74OMS(9)1017> and oxathiazoles ($Y = O, Z = S$) (40) <74ZN(B)284, 81JCS(P1)2991> this cycloreversion process (path (a)) predominates while in dithiazoles, it is a minor pathway.



Usually dithiazoles give the dithiazolium cation as most abundant peak (path (b)) <91JCS(P1)183, 92JCS(P1)2065> which is further fragmented by path (c). In 5-alkylamino dithiazolium salts (41; $R_2 = NR_2$) parent ions are frequently absent <88JCS(P1)899>, or of moderate intensity <92BCJ920>, prominent ions being those which correspond to $R_2NC\equiv S^+$, $RC\equiv N^+$ while ions $R_2NCS_2^+$ and R_2N^+ are also frequently observed. Cycloreversion also predominates in the imino compounds (42) where expulsion of HNCS (path (a)) and also of HNCO (path (b)), give rise to metastable ions <83JHC301>. An analogous fragmentation pattern is invoked for the bis-imino oxathiazole derivative (43) <88MI 414-02>.



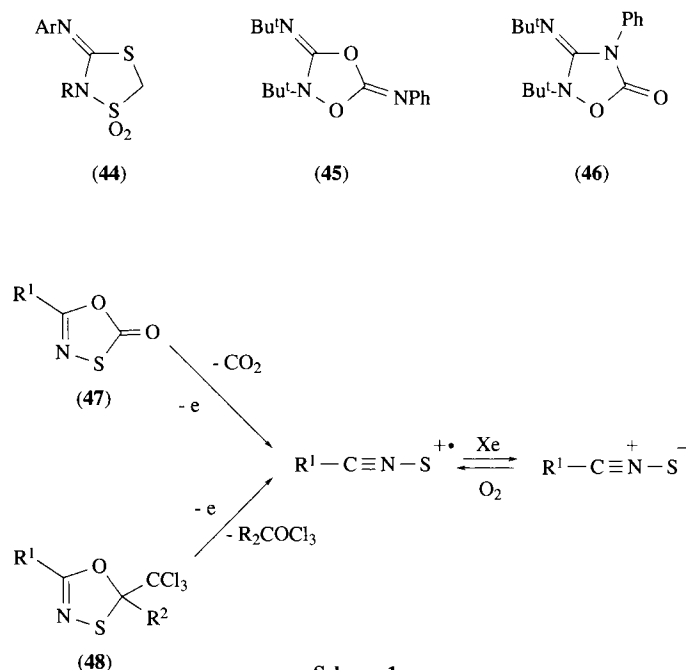
The dithiazolidine (44) <77CCC2672> and dioxazolidine (45) <69JOC2269> are ring systems in which the fragmentation pattern, has been used to affirm the structures. In the latter case the absence of CO_2 primary loss allows differentiation from the isomeric oxadiazolidone (46) co-product. A new technique, e.g. the neutralization-reionization mass spectrometry (NRMS) in combination with

Table 6 UV absorption maxima for dioxazoles, dithiazoles, and oxathiazoles.

Structure type	Ring system			Substituents			$\lambda_{max}(\log \epsilon)$ (nm)	Solvent	Ref.
	X	Y	Z	R ¹	R ²	R ³			
(5)		S	S	NEt ₂	1-pyrrolidino		243 (4.19), 340 (3.78)	EtOH 95%	88JCS(P1)899
(5)		S	S	Ar	NR ₂		213–223 (4.03–4.27), 2.34–244 (4.04–4.43), 247–262 (4.08–4.23)	EtOH 95%	88JCS(P1)899
							286–309 (4.04–4.20), 247–262 (4.08–4.23), 286–309 (4.04–4.20)	EtOH 95%	88JCS(P1)899
(8)	O	O	S	Ph			269 (3.81)	EtOH	78JCS(P1)1445
(8)	O	S	S	H			235 (3.54)	EtOH 95%	92JCS(P1)2065
(9)	S	S	S	H			229 (3.86), 268 (3.36), 339 (4.14)	EtOH 95%	92JCS(P1)2065
(9)	S	S	S	Me			232 (4.71), 262 (4.23), 342 (5.08)	EtOH 95%	92JCS(P1)2065
(9)	S	S	S	4-Cl-C ₆ H ₅			258 (4.35), 352 (4.21)	EtOH 95%	92JCS(P1)2065
(9)	S	S	O	Ph			300 (–)	CH ₂ Cl ₂	78JCS(P1)1445
(9)	S	S	S	Ph			257 (4.21), 294 (3.7), 353 (4.12), 362 (4.1)	EtOH	84CHEC-I(6)908
(10)	NH	O	S	H			272 (–)	CH ₂ Cl ₂	78JCS(P1)1445
(11)	CHPh	S	SO ₂	Mes			296 (4.36)	EtOH	78BCJ1805
(13)		O	O	Ph	Ph	H	234 (3.64), 267 (3.96)	EtOH	72CB2805
(13)		O	O	Ph	Me	H	216 (3.76), 268 (3.83)	EtOH	67TL331
(13)		S	S	Ph	^a	^a	213 (4.53), 230 (4.70), 239 (4.67), 278 (4.25), 287sh (4.21), 306sh (3.98), 278 (4.25), 287sh (4.21), 306sh (3.98)	Dioxane	74JOC2885
(24) ^b							260 (3.51), 284 (4.75), 319 (4.4), 410 (3.67)	Cyclohexane	93TL847

^aR²R³ = 2,2'-biphenylene. ^bStructure (24), see text.

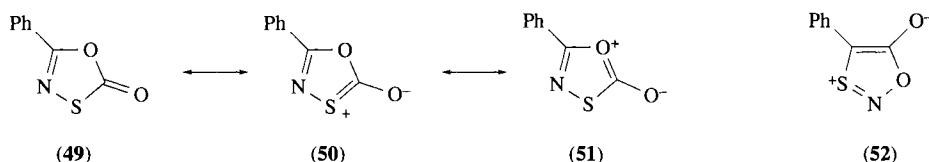
collision activation mass spectrometry <87CRV485> has been used to establish the formation of nitrile sulfide intermediate. Using this technique on oxathiazolones (**47**; $R^1 = \text{H, Me, Ph}$) and some oxathiazoline derivatives (**48**) <91CRV363, 91TL1487>, it has been reported that the nitrile sulfide fragments do not isomerize to isocyanic acid at least at the microsecond time scale of experiments (Scheme 1).



4.14.3.6 IR Spectroscopy

IR spectroscopy is rather more useful for functional group identification than for characterizing a particular ring system. Indeed the remark has been made that there are no apparent common peaks assignable to the dithiazoline ring <91JCS(P1)183> and most of the reported IR data is given without assignments to specific bond vibrations. However, data for $\nu_{\text{C=O}}$, $\nu_{\text{C=S}}$, and $\nu_{\text{C=N}}$ bonds for rings containing such groups are usually assigned and representative examples are given in Table 7.

In two particular cases, that of parent oxathiazolone (**30**; $R = \text{H}$) <78ACS(A)1005> and its 5-methyl derivative (**31**) <82ACS(A)283> both IR and Raman spectra have been interpreted in terms of C_s symmetry. The observed C=O bond lengths of oxathiazolones (**30**) and (**31**), respectively 1.193 ($R = \text{H}$) and 1.198 Å ($R = \text{Me}$) (see Section 4.14.3.2) do not agree with the integral intensity measurements of the C=O band of oxathiazolone (**49**). The latter appears to be highly polarized, comparable to the isomeric mesoion (**52**), a fact suggesting that mesoionic resonance structures (**50**) and (**51**) are of some importance <73ACS2161>.



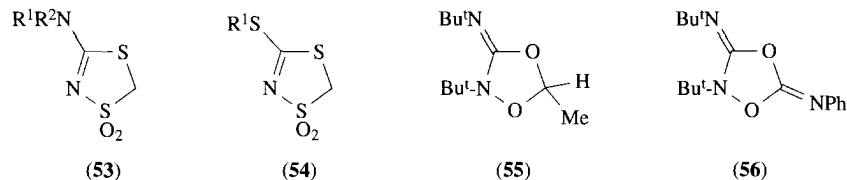
Doubts about C=N stretching vibrations of dithiazolines (**53**) and (**54**) and of the 3-imino-dithiazolidine (**44**) appeared, when Dickoré *et al.* <62AG(E)594> reported that they can be distinguished as they have $\nu_{\text{C=N}}$ between 1550–1590 and 1630 cm^{-1} respectively, but later workers assigned a $\nu_{\text{C=N}}$ near 1600 cm^{-1} for compounds which were claimed to be of type (**44**) though

Table 7 IR stretching vibrations (cm^{-1}) for C=O, C=S, and C=N bonds in dioxazoles, dithiazoles, and oxathiazoles.

Structure type	Ring system				Substituents					IR frequencies (cm^{-1})			Others	Ref.
	X	Y	Z	W	R ¹	R ²	R ³	R ⁴	R ⁵	$\nu_{\text{C=O}}$	$\nu_{\text{C=S}}$	$\nu_{\text{C=N}}$		
(8)	O	O	O		H(CH ₃) ₂					1880, 1835			1375, 1180, 1150 ^a	88JOC2674
(8)	O	O	O		Ph ₂ C(OH)					1860, 1830		1630		82LA211
(8)	O	O	O		CF ₃					1887		1640		83JOC3845
(8)	O	O	S		H					1809, 1747		1576	Raman, 1806, 1740, 1573	78ACS(A)1005
(8)	O	O	S		Me					1762, 1743		1624	Raman, 1755, 1741, 1622	82ACS(A)283
(8)	O	O	S		Ph					1745		1560		83MI 414-01
(8)	O	S	S		H					1706, 1657		1630	1489, 843, 796, 613 ^a	92JCS(P1)2065
(8)	O	S	O		2,4,6-Me ₃ C ₆ H ₂					1796			1741, 1052, 900, 857, 725 ^a	66JOC2417
(9)	S	O	O		Ph						1260–1315 ^b	^c		68TL319
(9)	S	S	S		H						1075		3024, 2943, 1479, 1028, 790	92JCS(P1)2065
(10)	NH	S	O		Ar							1650–1630		83JHC301
(10)	NSO ₂ Ph	S	O		Ph							1586, 1570	1327, 1158(SO ₂)	75TI537
(10)	NPh	S	S		1-pyrrolidine							1660		87CZ339
(10)	NCOPh	S	S		Ph							^c	1606, 1421, 1315, 1281 ^a	88BCJ4043
(11)	CCl ₂	O	S		Ph							1650	1610(C=C)	85JCS(P1)1517
(11)	PhCH	S	SO ₂		MeNH							1620	3200(NH)1290 and 1160(SO ₂)	78BCJ1805
(12)	NPh	O	O	Bu ^t N				Bu ^t				^c	1775, 1700(C=N)	69JOC2269
(13)		O	O		Ph	CCl ₃	H					1635	1122(C—O), 853(N—O)	72CB2805
(13)		O	O		Ph	Me	MeCOCH ₂					1615	1710(C=O)	86JOC2351
(13)		O	O		CF ₃	Cl	CF ₃					1661		84JOC919
(13)		S	O		Me	CSOMe	OMe					1510		86CZ338
(13)		O	S		Me	CCl ₃	CCl ₃					1650		81JCS(P1)2291
(14)		O	O	Bu ^t N		H	Me	Bu ^t				1710		86JOC732
(15)	C(CF ₃) ₂	S	O		Ph			H	H				3185(NH), 1621(C=C)	70JOC3470

^aNot assigned to specific vibration. ^bDoublet between 1260 and 1315 cm^{-1} . ^cNot recorded.

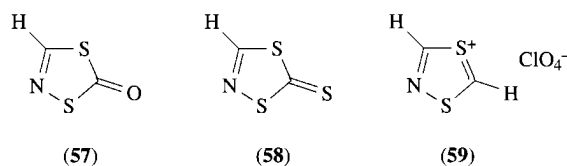
prepared by the same way as compound (53) <77CCC2672> (see Section 4.14.4). The imino oxazolidines (55) and (56) show $\nu_{\text{C}=\text{N}}$ at 1710 cm^{-1} <86JOC732> 1775 cm^{-1} , and 1700 cm^{-1} <69JOC2269>, respectively. A full assignment has also been reported for the bisoxathiazoline (43) <88MI 414-02>.



4.14.4 THERMODYNAMIC ASPECTS

4.14.4.1 Intermolecular Forces

Most of the parent 1,4-(oxa/thia)-2-azoles are unknown with the exception of the 1,3,4-oxathiazol-2-one (30) (b.p. $47\text{--}48^\circ\text{C}/12\text{ mmHg}$ <78ACS(A)1005>, $40^\circ\text{C}/10\text{ mmHg}$ <80CB1790>), 1,4,2-dithiazol-5-one (57), 1,4,2-dithiazol-5-thione (58) appearing as oils, and the unsubstituted 1,4,2-dithiazolium salt (59) as an unstable precipitate <90JCS(P1)808, 92JCS(P1)2065>. In general, all rings discussed in this chapter are heavily substituted, so generalizations about their inter- and intramolecular associations or chromatographic behavior are not available.



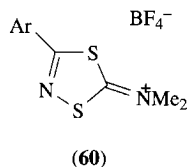
4.14.4.2 Stability and Aromaticity

All conjugated 1,4-(oxa/thia)-2-azoles may be formally considered as aromatic systems. The question of the aromaticity of 1,4,2-dithiazolium cations <92JCS(P1)2065> and ring current, has already been discussed (see Section 4.14.3.3.1 and 4.14.3.3.2). Indeed, there is a positive charge delocalization, although this is limited and less than that of the closely related 1,3-dithiolium cations. All these salts are not stable and at least in one case an explosion occurred during the isolation procedure <92JCS(P1)2065>. Explosions have also been reported during isolation of 1,4,2-oxathiazolium perchlorates <91TL4329> and in the preparation of trifluoromethyl isocyanate from 5-trifluoromethyl-1,3,4-dioxazol-2-one <83JOC3845>.

4.14.4.3 Conformation

Rotational energy barrier measurements performed for the $\text{C}=\text{NMe}_2$ of the dithiazolium salt (60) ($\text{Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4$) give $\Delta G^\ddagger = 95.5 \pm 0.7\text{ kJ mol}^{-1}$ <88JCS(P1)899> (^1H NMR signals at δ 3.803 and 3.92 coalesced at $431 \pm 2\text{ K}$). This value seems to be rather large for an imminium group attached to a potential aromatic ring and suggests a restricted rotation around the exocyclic $\text{C}=\text{N}$ bond

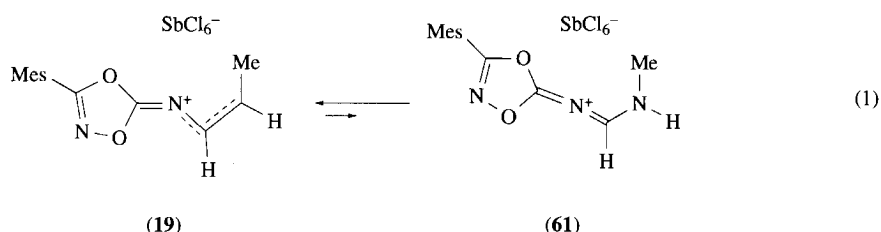
indicating that most of the positive charge lies on the exocyclic nitrogen atom in accordance with X-ray data (see Section 4.14.3.1). Some data concerning hindered internal rotation in 5-(N,N-dimethylamino)-1,3,4-oxathiazole 3,3-dioxide are also available <68CC1245>.



4.14.4.4 Tautomerism

There is uncertainty about the structures of dithiazole dioxides formulated as (53) <62AG(E)594, 78BCJ1805> and as (44) by others using ms data <77CCC2672, 77CCC2680>. Dickoré's assignment was based on the fact that the same derivative (53; $R^1 = R^2 = \text{Me}$) was obtained both by methylation of the monomethyl derivative ($R^1 = \text{Me}$, $R^2 = \text{H}$) and by aminolysis of the thioether (54) with Me_2NH . Moreover, compound (44) ($\text{Ar} = 4\text{-ClC}_6\text{H}_4$, $R = \text{Me}$) unambiguously prepared from secondary chloromethane sulfonamide, proved to be different from that prepared by methylation of compound (53) ($R^1 = 4\text{-ClC}_6\text{H}_4$, $R^2 = \text{H}$) <62AG(E)594>.

As evidenced from x-ray data, azoniaallene cations (61) adopt the less sterically demanding allylium valence tautomeric conformation (19) in accordance with Wurthwein's calculations <84CB3365, 84JOC2971> which predict that this is the more stable conformation for amino substituted azoniaallene cations (Equation (1)).



4.14.5 REACTIVITY OF FULLY CONJUGATED RINGS

4.14.5.1 General Survey of Reactivity

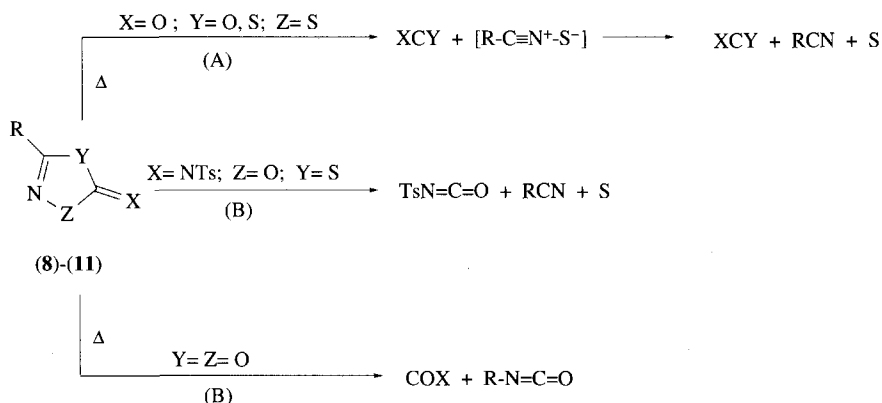
Fully conjugated 1,4-(oxa/thia)-2-azoles are electrophilic in character and this is mainly expressed by their tendency to react exclusively with nucleophiles. The site of nucleophilic attack is either the partly positively charged ring carbon atom of the azolylium cations, or the sp^2 ring carbon of the exocyclic double bond. The other carbon atom of the ring seems to be unreactive.

There are no reports on electrophilic attack at ring carbon or nitrogen. Regarding ring sulfur atom, it has been reported that oxathiazolones (49), act as sulfur sources in their reaction with $\text{Mn}(\text{CO})_5$ yielding a sulfido cluster of the type $[\text{Mn}_3(\text{CO})_9(\mu_3\text{-S})_2]$ by elimination of PhCN and CO_2 <93OM1009>.

4.14.5.2 Unimolecular Thermal and Photochemical Reactions

4.14.5.2.1 Thermal reactions

Thermolytic reactions are known for all azolone structures (8)–(11). Thermolysis may be regarded as a six-electron thermally allowed process and follows two major pathways, both extruding YCX or ZCX fragments (Scheme 2).

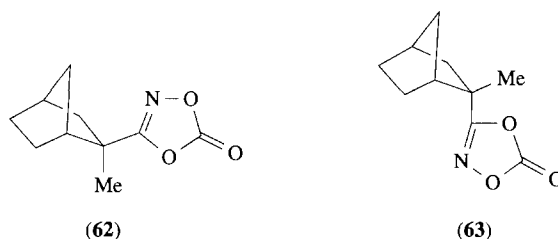


Scheme 2

The first pathway (A) is usually followed by 1,3,4-oxathiazolones (8) ($X = Y = O$, $Z = S$). The nitrile sulfide formed has a transient existence, but it can be trapped in the presence of a suitable dipolarophile (see also Section 4.14.5.6). Usually it breaks down to a nitrile and sulfur $\langle 89\text{CSR}33 \rangle$, except the parent which gives isocyanic acid $\langle 84\text{CHEC-I}(6)913 \rangle$. The decarboxylation of oxathiazolones is the method of choice to obtain nitrile sulfides and a great variety of substituted compounds have been tested as nitrile sulfide precursors. The thermal fragmentation also occurs with polymer bound 1,3,4-oxathiazol-2-one derivatives affording the nitrile sulfide functionality linked to the polymer chain $\langle 83\text{CC}901, 89\text{CSR}33 \rangle$.

Dithiazolones (8) ($X = O$, $Y = Z = S$) are more stable than oxathiazolones and decompose slowly under more drastic conditions (higher temperature and prolonged heating) to give nitrile sulfide $\langle 82\text{TL}5453 \rangle$, by extrusion of COS. Moreover, dichloromethylene oxathiazole ($X = \text{CCl}_2$, $Y = O$, $Z = O$) also yields nitrile sulfide, which has been trapped by DMAD and PhCN, though attempts to trap the dichloroketene failed, probably because of its limited thermal stability $\langle 85\text{JCS(P1)}1517 \rangle$. The dithiazole thione (9) ($X = Y = Z = S$) appears to be stable but in the presence of a dipolarophile is decomposed according to another route (see Section 4.14.5.6).

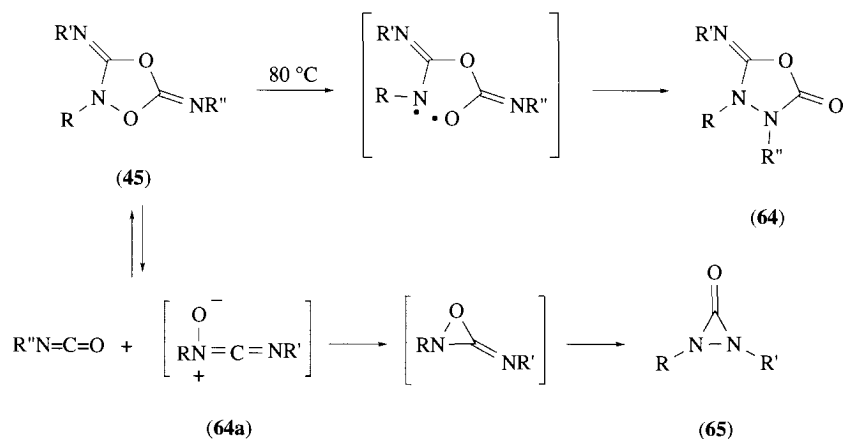
The second pathway (B) is followed by dioxazolones (8) ($X = Y = Z = O$) and conjugated derivatives having $Z = O$. The XYZ fragment is usually CO_2 but it can be an isocyanate as in the case of 5-tosylimino-1,4,2-oxathiazole (10) ($X = \text{NTs}$, $Y = S$, $Z = O$) $\langle 75\text{T}1537 \rangle$. Formally, an acyl nitrene fragment is produced which further rearranges to an isocyanate. The nitrene was considered as the initially formed intermediate, its existence apparently being supported by various trapping experiments $\langle 68\text{TL}319, 73\text{CC}586, 74\text{JCS(P1)}460 \rangle$ until Sauer *et al.* observed a second-order kinetics for the thermal decomposition of dioxazolones in the presence of nucleophiles, a fact ruling out an acyl nitrene which demands a first-order rate-determining decomposition. Moreover, thermolysis of dioxazolones leading to nitrile oxides, which in turn might be rearranged to isocyanate, is excluded by labeling experiments using ^{18}O . Thus the likely pathway involved is a concerted CO_2 extrusion and rearrangement. This process is followed with absolute retention of the configuration of the migrating group, as exemplified in the thermolyses of stereochemically pure exo- and endo-dioxazole compounds (62) and (63) $\langle 87\text{MI} 414-02 \rangle$.



In the absence of nucleophiles thermal decomposition of 5-*t*-butyl and 5-isopropyl-1,3,4-dioxazol-2-ones follow first-order kinetics with activation energies, obtained from Arrhenius plots, ranging

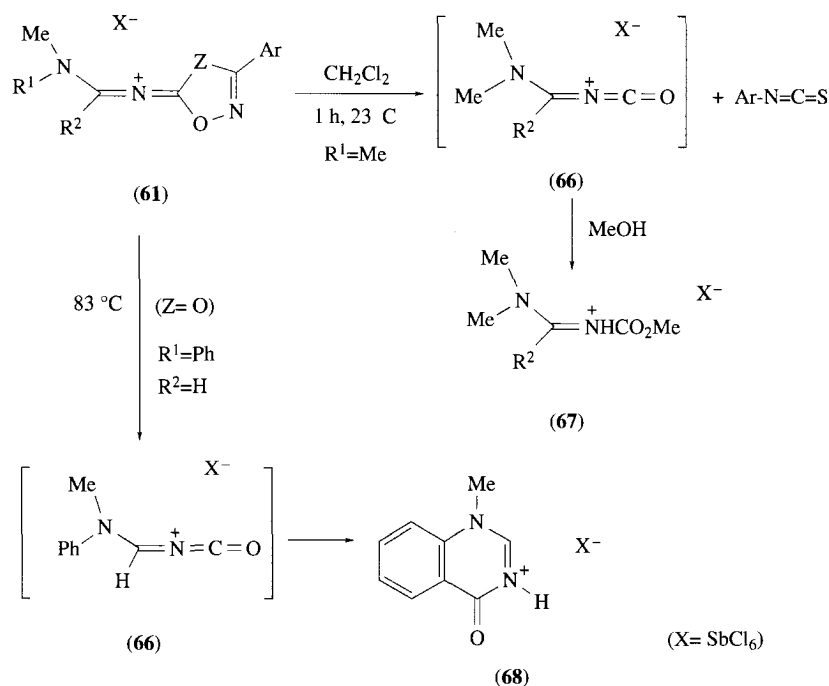
from 21.6 to 23.5 kcal mol⁻¹ <88JOC2674>. The rates are affected by substitution (isopropyl derivative decomposed faster than the *t*-butyl one) and the solvent polarity, being larger in a polar (DMF) than a less polar solvent (diglyme).

The imino dioxazolidine derivatives (**45**) are thermally isomerized to oxadiazolinone (**64**) and also decomposed, probably via a retro-1,3-dipolar cycloaddition mode (Scheme 3) <75JOC3112>, to phenyl isocyanate and the transient 1,3-dipole (**64a**), which in turn rearranges to the diaziridinone (**65**).



Scheme 3

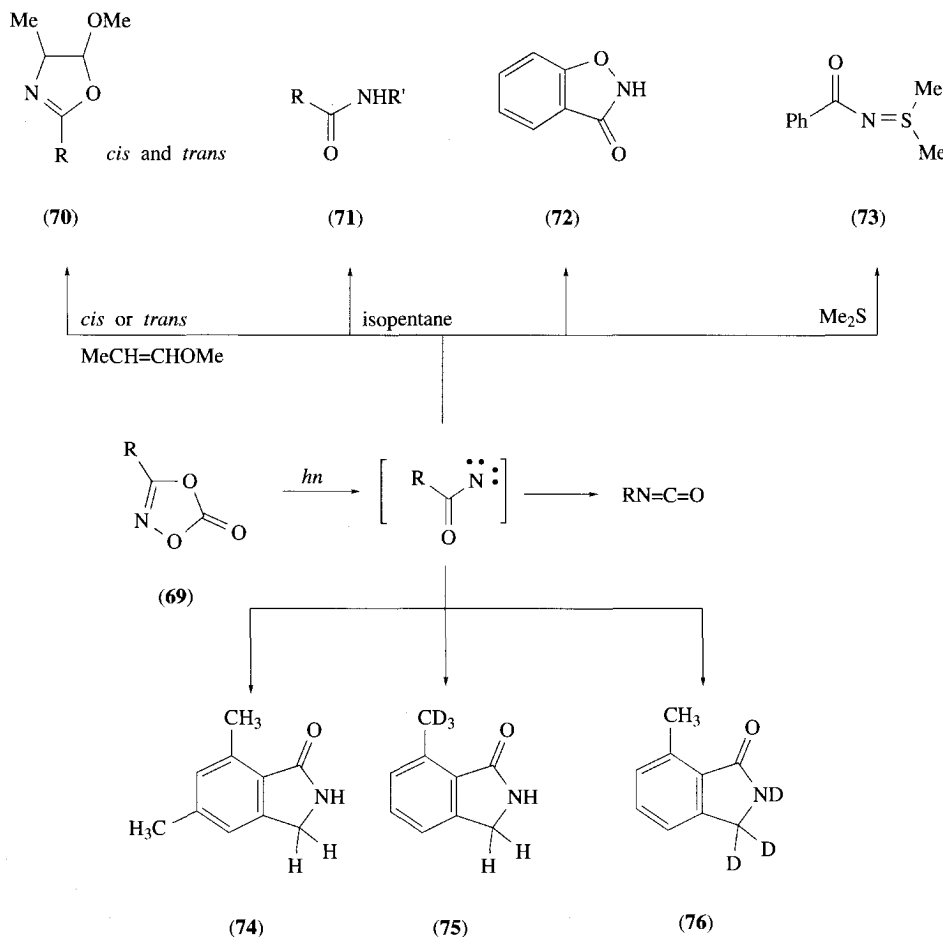
Furthermore, a cycloreversion has been observed in the case of the thermally labile azoniaallene salts (**61**) (Z = O, S). When Z = S, this proceeds within an hour at room temperature to yield the aryl isothiocyanate and the charged cumulene (**66**) which is isolated as the acyliminium salt (**67**) <91CB2537>. When Z = O and R¹ = Ph, cycloreversion occurs at 83 °C (refluxing 1,2-dichloroethane) to give the aryl isocyanate and (**66**), which is further cyclized to the quinazolinium salt (**68**) (Scheme 4) <89TS5825>.



Scheme 4

4.14.5.2.2 Photochemical reactions

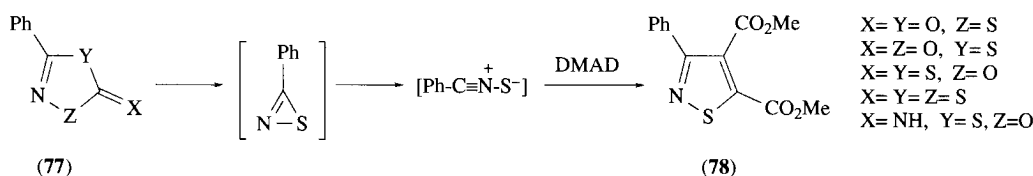
The photofragmentation of azolones also follows two pathways, typically analogous to those of thermolysis. In general, 1,3,4-dioxazol-2-ones (**69**) extrude CO₂ and the resulting N-acylnitrene intermediates may either be trapped or rearrange to isocyanates. In the presence of *cis*- or *trans*-1-methoxypropene, both *cis*- and *trans*-oxazolidine derivatives (**70**) are obtained, presumably from *cis*- and *trans*-N-acyl aziridine, through an open-chain common intermediate (Scheme 5) <90ZOR1757>.



Scheme 5

Insertion reaction into the CH bond is an unambiguous way to trap a nitrene intermediate and a number of such intermolecular or intramolecular insertion reactions have been carried out. Photolysis in the presence of isopentane, affording the amides (**71**), permits the study into the selectivity of insertion of the nitrene, which is found to be $3^\circ > 2^\circ > 1^\circ$. When R is the 2-hydroxyphenyl group cyclization is preferred to Wolff rearrangement and gives the benzisoxazolone (**72**), while for R¹ = Ph the sulfinates (**73**) is formed in anhydrous Me₂S. Moreover, the 5-mesityl dioxazolone (**69**; R¹ = 2,4,6-Me₃C₆H₂) affords the isoindolinone (**74**) through an intramolecular insertion reaction and mesityl isocyanate <74TL2565, 84CHEC-I(6)914>. It has been found from competition experiments, using isopentane as a nitrene trap and the photolysis of benzoyl azide as a standard nitrene source, that the competition constant for the insertion into the tertiary and secondary CH bond is independent of the precursor used, i.e. both dioxazolone and acyl azide passed through the same nitrene intermediate. Also both nitrene sources show the same small isotope effect in the formation of isoindole derivatives (**75**) and (**76**) when deuterium-labeled compounds are used <87MI 414-02, 87TL1097>.

The photolysis of thiazolinone or thiazolinethione derivatives (**77**), having at least one sulfur atom in the ring, (Scheme 6) proceeds like the thermolysis and involves extrusion of a small molecule (CO₂, COS, CS₂, HCNO), to give an unstable antiaromatic thiazirine, which in turn rearranges to the also unstable nitrile sulfide. The latter has been trapped with DMAD to give the isothiazole (**78**) (<75JA6197, 78JCS(P1)1445, 89CSR33>).



Scheme 6

4.14.5.3 Electrophilic Attack at Carbon, Nitrogen, and Sulfur

As previously noted, no electrophilic attack at ring carbon, nitrogen, and sulfur has been reported with the exception of a sulfonium ylide intermediate formed from reaction of 1,3,4-oxathiazole-2-ones with a carbene, which will be discussed later (see Section 4.14.5.5).

4.14.5.4 Nucleophilic Attack at Carbon

4.14.5.4.1 Conjugated systems with exocyclic double bond and nucleophiles

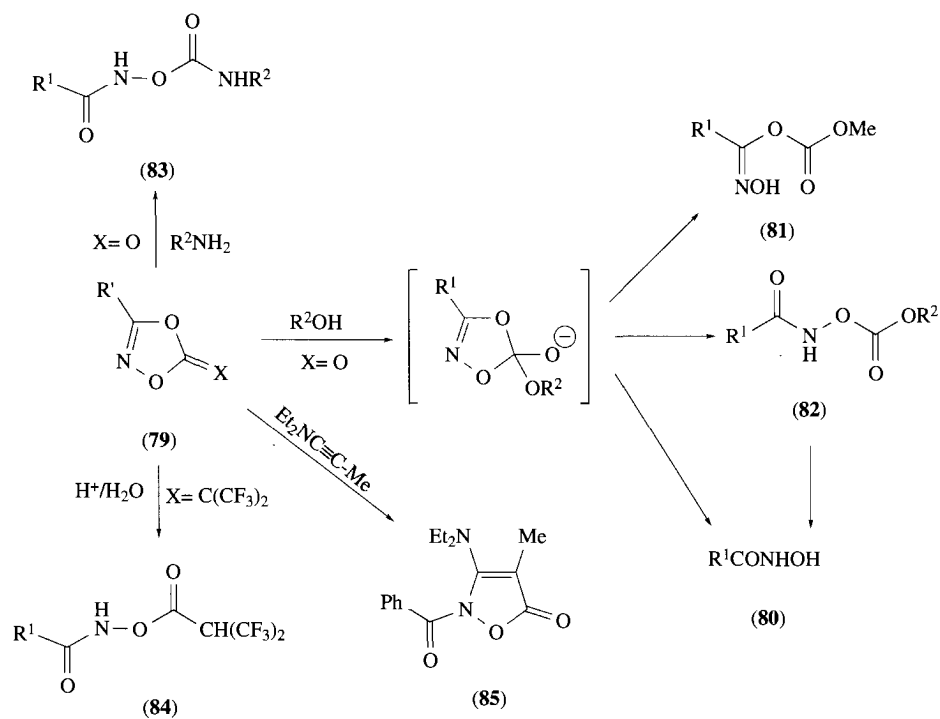
The exocyclic C=O of 1,3,4-dioxazol-2-ones (**79**) ($X = O$) is susceptible towards attack by nucleophiles leading to ring open products. Thus they can be regarded as mixed anhydrides of carbonic and hydroxamic acids and are readily hydrolyzed to hydroxamic acids (**80**) <51CB688, 88JOC2674>. On the other hand, methanolysis affords either the adduct ester (**81**) <83JOC3845> or alkoxy carbonyl hydroxamates (**82**; $R^1 = Ar_2P(O)CH_2$, $R^2 = Me$) <78ZOB1465> depending upon the ring fission mode. The hydroxamates (**82**; $R^1 = Pr^i$, Bu^t ; $R^2 = Me$) formed under acidic methanolysis cannot be isolated and decompose further to hydroxamic acid (Scheme 7). Pseudo first-order kinetics were observed for both hydrolysis and methanolysis with rate constants 1.4×10^{-2} and $1.7 \times 10^{-2} \text{ min}^{-1}$ ($R^1 = Pr^i$ and Bu^t) for hydrolysis and 5×10^{-1} and $4.2 \times 10^{-3} \text{ min}^{-1}$ (R is the same) for methanolysis. In an analogous way, aniline and benzylamine afford the carbamoyl hydroxamate (**83**; $R^1 = Bu^t$, $R^2 = Ph$) <88JOC2674>. Dioxazolone derivatives having an α -hydroxy group at C-5 also give the carbamoyl hydroxamates (**83**) with benzylamine, while with 3-chloroaniline the product (**83**) is further decomposed <82LA211>. In an analogous way, the azonylene (**79**) ($X = C(CF_3)_3$, $Y = Z = O$), as a ketene acetal, is ring opened in acidic media to give the alkoxy carbonyl hydroxamates (**84**) <69DOK(185)837, 70IZV2140> while the dioxazolone (**79**; $R^1 = Ph$, $X = Y = Z = O$) reacts with diethylaminopropyne to give the isoxazolone (**85**) <73TL233>.

The behavior of both isomeric 1,4,2- and 1,3,4-oxathiazole derivatives, with an exocyclic double bond, towards nucleophiles is different from that of dioxazolone derivatives (**79**), in the sense that ring cleavage is usually followed by subsequent fragmentation of the ring (Scheme 8).

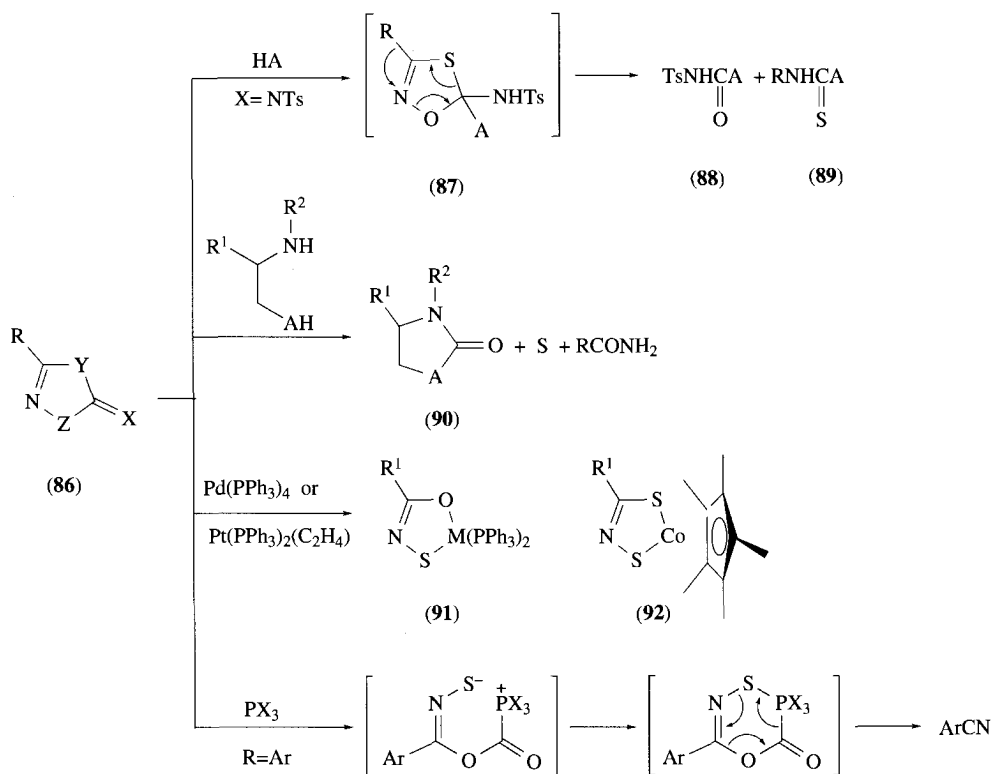
Thus, from the 5-imino oxathiazoline (**86**; $R^1 = Ph$, $X = NTs$, $Y = S$, $Z = O$) on treatment with methanol or dimethylamine the primary adducts (**87**) are ring opened with rearrangement of the aryl group to give the urethane ($A = OMe$) or urea ($A = NMe_2$) derivatives (**88**) and (**89**) <75T1537>. The 1,3,4-oxathiazolones (**86**) ($X = Y = O$, $Z = S$) prove to be useful cyclocarbonylating reagents and react readily with 1,2-amino alcohols or 1,2-diamines, to give respectively oxazolinone ($A = O$) or imidazolinone ($A = NR$) derivatives (**90**) in good yields <83S1032>. Treatment of (**86**) ($X = Y = O$, $Z = S$) with $Pt(PPh_3)_2(C_2H_4)$ or $Pd(PPh_3)_4$ affords the metallocycles (**91**) ($M = Pd$ or Pt , $X = (PPh_3)_2$) <80CB1790>, while with $Co(Cp)(CO)_2$ ($Cp = \text{pentamethylcyclopentadienyl}$) the cobaltadithiazole (**92**) is formed <92CL243>. This compound is also formed from $Co(Cp)(CO)_2$ and 2-alkylamino-dithiazolium salts. Reaction with trialkyl phosphites ($X = OMe$) or triphenylphosphine ($X = Ph$) leads to oxathiazolone ring break down to give aryl nitriles according to the proposed sequence (Scheme 8) <83MI 414-01>.

4.14.5.4.2 Reactions of 1,4-(oxa/thia)-2-azolium salts and nucleophiles

All 1,4-(oxa/thia)-2-azolium salts are, in general, electrophilic species. Some of them, especially those where the positive charge is expected to locate predominantly inside the heterocyclic ring, are extremely electrophilic. Both kinds of oxathiazolium salts (**6**) and (**7**) exhibit this high electrophilic character, being attacked by solvents more nucleophilic than trifluoroacetic acid and nitromethane

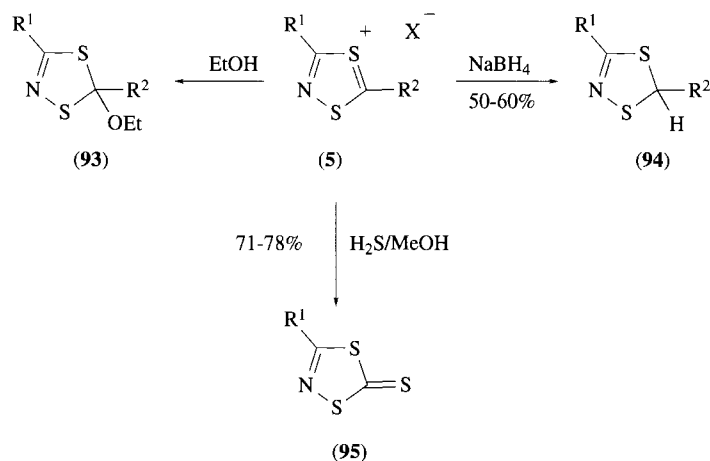


Scheme 7



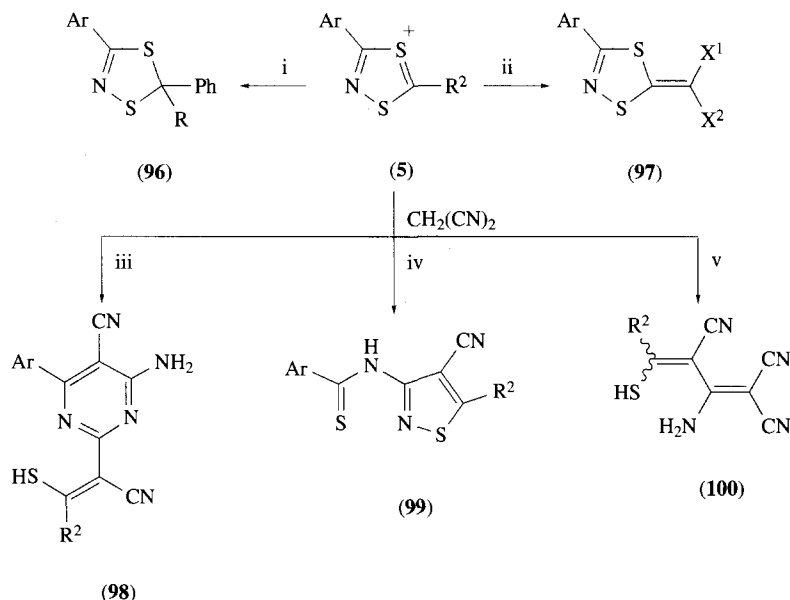
Scheme 8

and decompose within a few days, in the solid state, even over P_4O_{10} (90TL5935, 91TL4329). Dithiazolium salts (5) are more stable and provide the main source of azolium cation chemistry. However, they are also highly electrophilic and attempts to recrystallize them from ethanol give the 5H-dithiazole derivative (93; $R^1 = R^2 = Ar$) (88CC852). Sodium borohydride reduction also gives 5H-dithiazole derivatives (94) (88JCS(P1)899, 92JCS(P1)2065) and treatment with H_2S affords the thiones (95), including the parent compound ($R^1 = H$) (Scheme 9) (90JCS(P1)808, 92JCS(P1)2065).



Scheme 9

Active methylene compounds attack the more electrophilic C-5 position of 1,4,2-dithiazolium salts (see Section 4.14.2) to give various products as outlined in Scheme 10. The reaction course is greatly affected by the applied conditions (base and solvent used) as well as by the nature of the substrate itself.

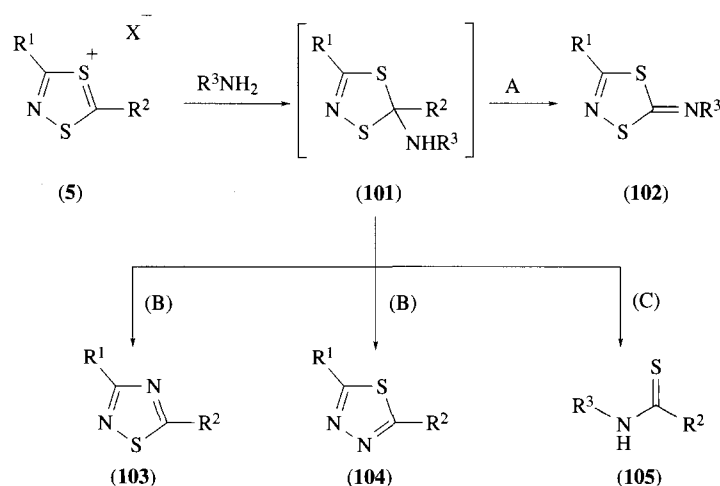


Scheme 10

The primary adducts (96) (path(i)) are isolated in a few instances, e.g. ($R^2 = Ph$) $CH_2(CO_2Me)_2/NEt_3$ or indanone/ NEt_3 or N,N -dimethylaniline alone (90BCJ2933). However, the reactions usually proceed further, either by displacement of the C-5 substituent (path(ii)) or even by ring opening and subsequent transformations (paths(iii) and (iv)) or by ring fragmentation (path (v)). Thus, malononitrile acts as a nucleophile with the alkylamino salt (5) ($R^2 = NR_2$), yielding, in the presence of a relatively weak base (e.g. pyridine or γ -picoline), the dicyanomethylene derivative (97) ($X^1 = X^2 = CN$). With a stronger base (NEt_3), the dithiazole ring is opened and depending on the

C-5 substituent either a pyrimidine (**98**) (when $R^2 = NR_2$) or an isothiazole (**99**) (when $R^2 = Ar$) are finally obtained. Sodium hydride as base resulted in ring fragmentation to give the open-chain adduct (**100**). Multistep mechanisms are proposed for these transformations <89BCJ1086>. The behavior of methylthio and dialkylamino salts (**5**; $R^2 = SMe$ and NR_2 , respectively) is quite similar and both give with carbon nucleophiles (e.g. Meldrum's acid) the same alkylidene derivative (**97**) ($X^1, X^2 = \text{Meldrum's acid residue}$) <85CC696, 88JCS(P1)899>.

Yonemoto and Shibuya and co-workers systematically studied the behavior of dithiazolium salts towards various amino nucleophiles and examined all factors (substituents at C-3 and C-5, strength of base used, nature of base, solvent polarity) which may affect the composition of the final products <88BCJ4043, 90BCJ2933>. The initial attack always takes place at C-5 of the cation, but the primary adduct (**101**) has not been isolated and undergoes further transformation. Three possible fission modes have been recognized which are given in Scheme 11. However in some instances more than one path may be followed, resulting in mixtures of the reaction products. Path (A) requires a removable R^2 group (e.g. NR_2) and when aniline or hydrazine derivatives ($R^3 = Ph, NHPh, NHCOPh, NHCONHPh$), are used as nucleophiles, in the absence of a base, the 5-imino dithiazoles (**102**) are formed as the only reaction products (80–90%). It should be noted that Paton and co-workers first reported the formation of the phenylimino compound (**102**) from dithiazolium salts (**5**; $R^1 = Ph, R^2 = SMe$) and aniline <85CC696>.

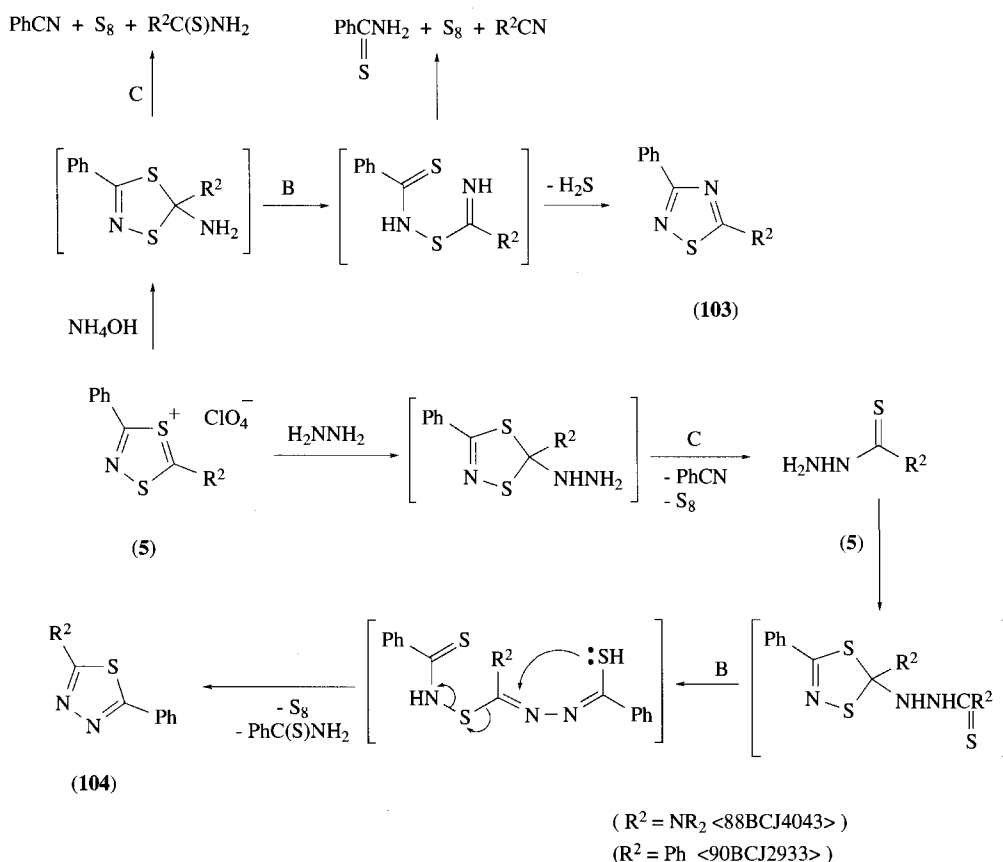


Scheme 11

Path (B) proceeds by proton abstraction followed by C—S bond cleavage to give open-chain intermediates, which either undergo recyclization to the thiadiazoles (**103**) (for $R^3 = H$), and (**104**) (for $R^3 = NH_2$), or yield decomposition products: $R^2 = NR_2$ <88BCJ4043>; $R^2 = Ph$ <90BCJ2933>. According to path (C), the primary adduct undergoes a spontaneous fragmentation affording thiourea (for $R^2 = NR_2$) <88BCJ4043> or thiobenzamide (for $R^2 = Ar$) (**105**) <90BCJ2933>, a nitrile and sulfur. Usually paths (B) and (C) both proceed in parallel as illustrated in Scheme 12 for the reactions with ammonia and hydrazine hydrate as nucleophiles ($R^1 = Ph, R^2 = NR_2$ <88BCJ4043>; $R^1 = R^2 = Ph$ <90BCJ2933>). The strength of the base used substantially affects the reaction mode. An extreme example is that of benzoylhydrazine, which in the absence of a base follows path (A), and in the presence of NEt_3 path (C). Moreover, with *p*-toluidine as a nucleophile, path (C) becomes increasingly important as the pK_a value of the base and the solvent polarity are raised.

4.14.5.4.3 Ring-expansion reactions

Ring-expansion reactions of dithiazolium salts leading to incorporation of a nitrogen into the dithiazole ring can also occur via an initial nucleophilic attack of the expanding reagent at C-5. Depending on the reagent used, further transformations affording dithiadiazines (**106**), (**107**), or (**108**), novel classes of 8π -electron ring systems with four heteroatoms, occurs as shown in Scheme 13. The 1,4,2,6-dithiadiazine derivative (**106**) is obtained <89CL89>, when a nitrene intermediate (**109**) is involved (route(i)) while the other isomer (**107**) or (**108**) is obtained, either from sulfenamides as expanding reagent via the intermediate (**110**) <88BCJ2232, 88JAP(K)63218682>, or through the



Scheme 12

nitrenium ion intermediate (**111**) (route(iii)) <89CL89, 90BCJ2933, 90JAP(K)0267276>. It should be noted that analogous expansion reactions have been observed in other classes of dithiolium and oxathiolium cations <89CL89, 92BCJ668>.

4.14.5.5 Reactions with Electron-deficient Species and at Surfaces

Rhodium(II) catalyzed the addition of the carbene formed from methyl diazoacetoacetate, to the oxathiazolone (**112**; $\text{R} = 4\text{-MeOC}_6\text{H}_4$) gives the 1,4,3-oxathiazine derivative (**113**) in low yield (6%), this probably proceeds through the intermediate sulfonium ylide (**114**), by decarboxylation and ring closure, either concomitantly or sequentially (Scheme 14) <90JCR(S)343>.

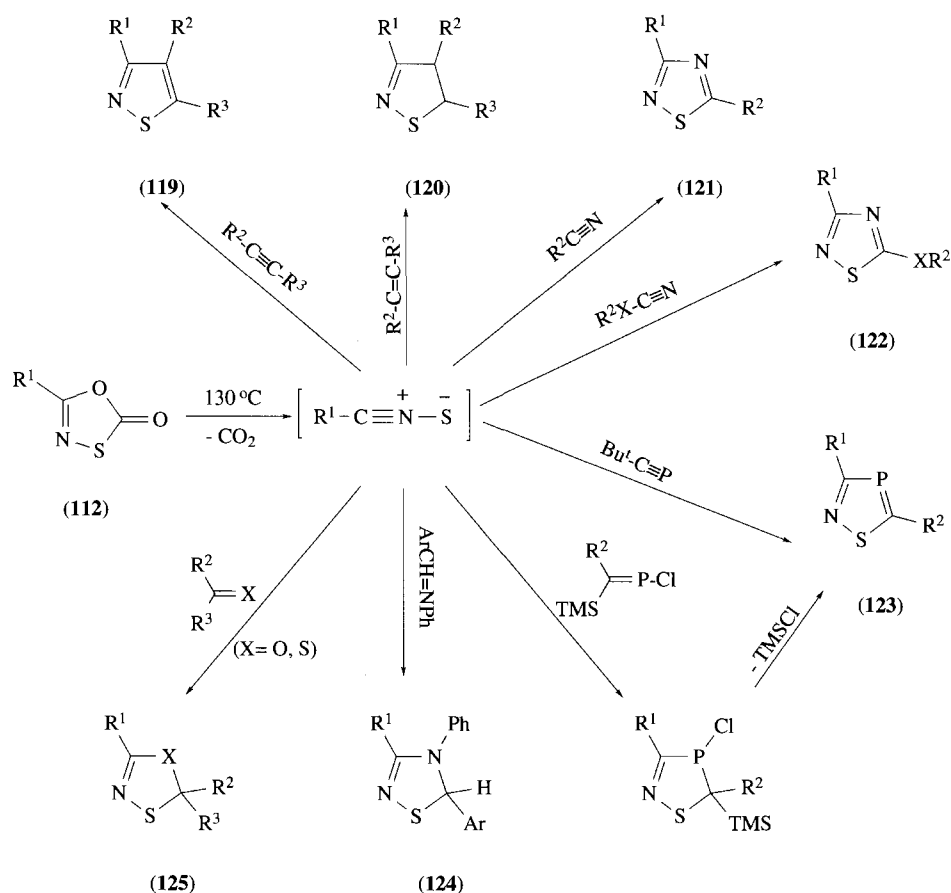
Hydrogenation of 1,3,4-dioxazol-2-ones over Raney nickel results in N—O bond cleavage to give amides and CO_2 <51CB688>. A reductive dimerization of dithiazolium salts (**5**; $\text{R}^1 = \text{Me}$, Ph ; $\text{R}^2 = \text{SMe}$, $\text{X} = \text{BF}_4$) with zinc dust affords mixtures of adducts (**115**) and (**116**) which upon thermolysis give *cis*- (**117**) and *trans*- (**118**) tetrathiadiazafulvalenes, a hitherto unknown class of compounds (Scheme 15) <93CC1226>. Tetrathiadiazafulvalenes, in low yield, through the treatment of C-5 unsubstituted dithiazolium salts ($\text{R}^2 = \text{H}$, $\text{X} = \text{ClO}_4^-$) with NEt_3 <93TL847>, a method already used for the preparation of the closely related tetrathiafulvalenes from the corresponding 1,3-dithiolium salts <91CSR355>. The tetrathiadiazafulvalenes are less potent electron donors than the corresponding tetrathiafulvalenes, as evidenced from cyclic voltammetry measurements performed on compounds (**118**; $\text{R}^1 = \text{Me}$, Ph) <93CC1226, 93TL847>.

4.14.5.6 Reactions with Cyclic Transition States

As reported before (see Section 4.14.5.2), 1,3,4-oxathiazolone (**112**) undergoes ring fragmentation readily on heating to give nitrile sulfides, a very unstable class of 1,3-dipoles. A considerable part



of its chemistry is focused on nitrile sulfide generation and trapping reactions and this is covered in a review article <89CSR33> on nitrile sulfide chemistry and summarized in Scheme 16. It is well established, from kinetic measurements, that during thermolysis of oxathiazolones in the presence of a trapping dipolarophile (DMAD), CO₂ is lost first, to give the nitrile sulfide prior to the cycloaddition to the alkyne <78JOC3742, 84CHEC-I(6)919>. Nitrile sulfide cycloadditions are HOMO dipole-controlled reactions, therefore, dipolarophiles, strongly activated by electron-withdrawing groups, are needed for their trapping; the order of reactivity is increased in the order of decreasing LUMO energies. A few reports of the regioselectivity have appeared <89CSR33>.

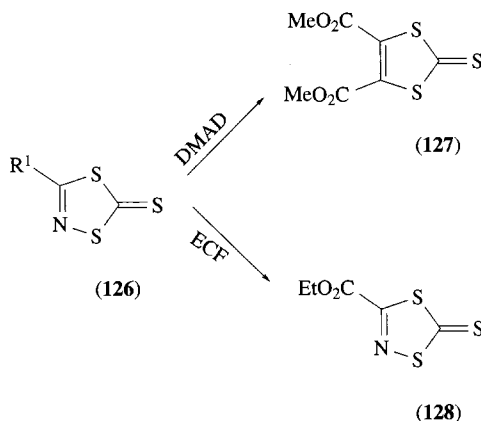


Scheme 16

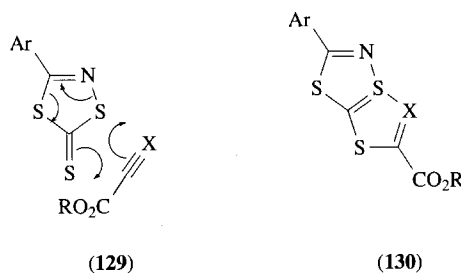
Reactions with electron-poor alkynes or alkenes, for example, DMAD and other various alkynoic esters, quinones or norbornene derivatives, afford isothiazole (119) and 4,5-dihydroisothiazole derivatives (120). The latter are formed with retention of the configuration, although in some instances, as in the case of maleate and fumarate esters, both give the same *trans*-isothiazole carboxylate <89CSR33>. Nitriles are also reactive dipolarophiles, especially those having electron-withdrawing substituents, affording thiadiazoles (121) <81JOC771, 89CSR33>. Ethyl cyanofornate (ECF), a particularly useful nitrile sulfide trap even for polymer bound derivatives, as well as α -ketonitriles <84T681> and trifluoroacetonitrile are the most reactive nitriles <86PS(26)151>. Moreover, arylthio- and arylselenocyanates <87JCS(P1)607>, although less reactive, give the corresponding 5-arythio or arylseleno-1,3,4-thiadiazoles (122) (X = S, Se). The C=P or C≡P bonds are also sufficiently strong dipolarophiles and 2,2-dimethylpropyldynephosphane <87S689> or 1-chloro-2-trimethylsilylphosphalkenes <88TL4535> afford the thiazaphospholes (123). There are a few reported examples of trapping reactions with imines to give the dihydrothiadiazoles (124) in very low yields <86JCR(S)156>. The reactions with C=O and C=S bonds yielding (oxa/thia) azoles (125) are discussed later (see Section 4.14.9.3).

Dithiazolethiones (126) are thermally stable at least under reflux in xylene (see Section 4.14.5.2.1). However, on heating in the presence of DMAD or ethyl cyanofornate, the dithiol 2-thiones (127)

and dithiazol-5-thiones (**128**) respectively are obtained (Scheme 17). The formation of both adducts, involves cycloaddition to the exocyclic and one of the ring sulfur atoms, followed by nitrile expulsion. The reaction is either concerted, termed in this particular case a $[2' + (1,2,3)]$ cyclodismutation or cyclosubstitution, via transition-state (**129**), or proceeds by a two-step mechanism via the hyper-valent sulfur intermediate (**130**) <85JCS(P1)1205>.



Scheme 17



The thione group of dithiazoethiones is a very reactive heterodipolarophile. In Scheme 18 are given cycloadditions with nitrile oxides <67BSF2239>, diphenylnitrilimine, and ethyl azidoformate <85JCS(P1)1205>. The primary adducts are spiro derivatives, but only compound (**131**), which is obtained from nitrile oxides is isolable at low temperature. All are decomposed to give respectively compounds (**132**)–(**134**) and occasionally nitriles and sulfur. Compound (**134**) reacts further with nitrilimine affording compound (**135**) which is also isolated.

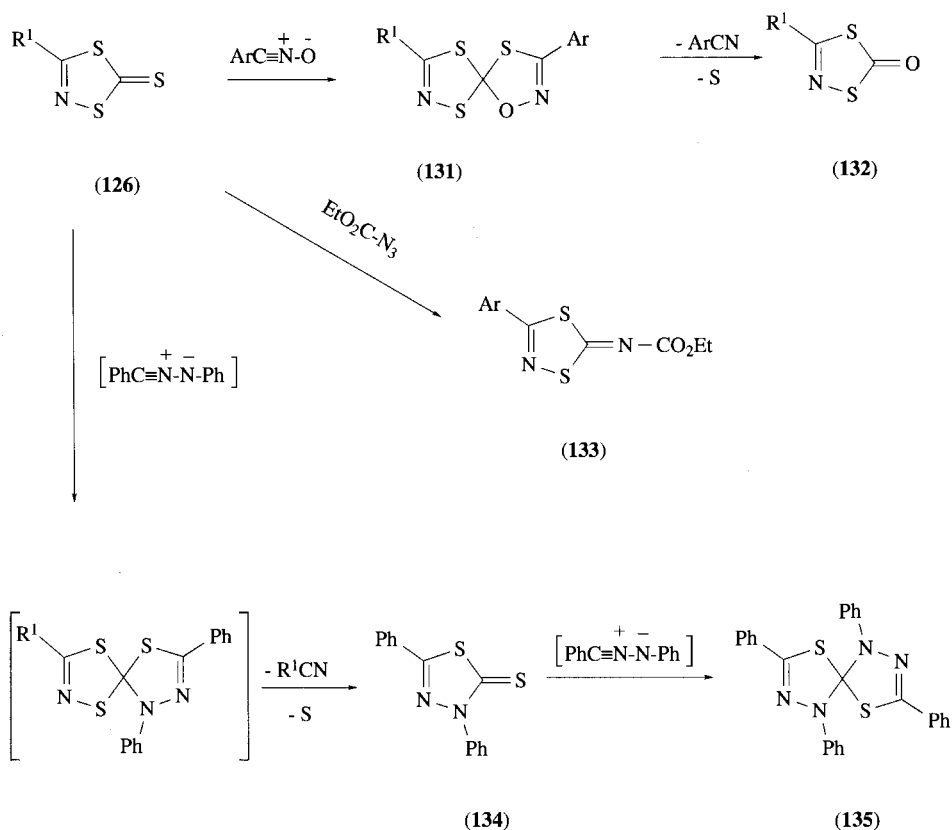
4.14.6 REACTIVITY OF NONCONJUGATED RINGS

In this section are included reactions concerning both dihydro and tetrahydro derivatives of the general structures (**13**)–(**16**).

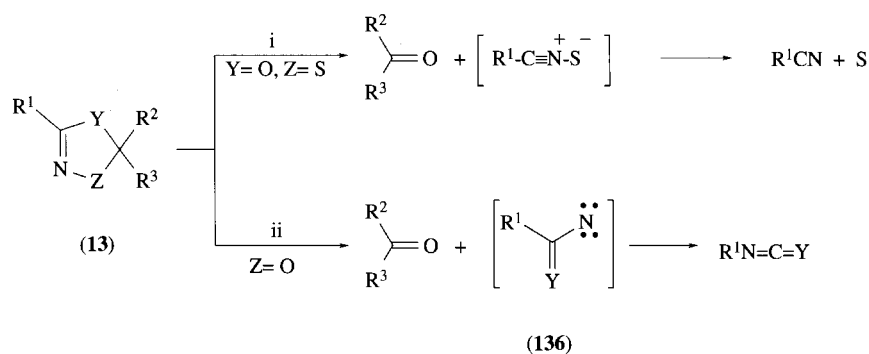
4.14.6.1 Unimolecular Thermal and Photochemical Reactions

4.14.6.1.1 Thermal decomposition of azolines

Azolines of type (**13**) undergo thermal decomposition in an analogous way to that already discussed for azolones (see Section 4.14.5.2) (Scheme 19). Path (i) is followed by those azolines having $Z = S$ and path (ii) by those with $Z = O$. Path (i) is a typical retro-1,3-dipolar cycloaddition process, via an intermediate nitrile sulfide, while path (ii) might involve an acyl ($Y = Z = O$) or thioacyl ($Y = S, Z = O$) nitrene intermediate (**136**), which in turn rearranges to iso(thio)cyanate. However, no systematic attempts to trap this possible nitrene intermediate seem to have been made, and so a concerted pathway for the fragmentation cannot be ruled out.



Scheme 18



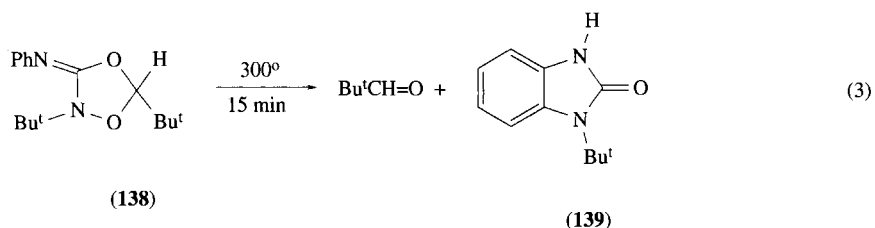
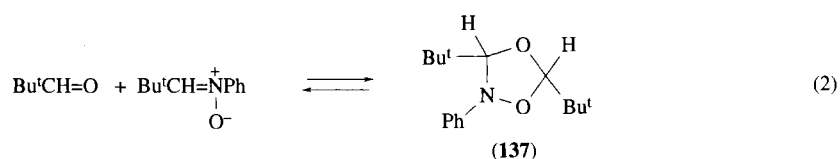
Scheme 19

The 1,3,4-oxathiazolines (13) ($\text{Y} = \text{O}$, $\text{Z} = \text{S}$) decompose slowly on heating and at higher temperature than the corresponding azolones $\langle 89\text{CSR}33 \rangle$ to give, in the absence of trapping dipolarophile, carbonyl compounds, nitriles and sulfur (path (i)). The rate of decomposition is unaffected by dipolarophiles (if present) but is dependent on substituents, being rapid for $\text{R}^2 = \text{R}^3 = \text{CCl}_3$ and slow for $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{CCl}_3$. Moreover, the rate increases with electron-donating substituents at C-5, consistent with a partial positive charge developing at this atom in the transition state $\langle 85\text{JCS}(\text{P}1)1517 \rangle$. The 1,4,2-oxathiazolines (13) ($\text{Y} = \text{S}$, $\text{Z} = \text{O}$) are also thermally labile and decompose on heating (path (ii)) to give carbonyl compounds and arylisothiocyanates $\langle 84\text{CHEC-I}(6)925$, $84\text{JCS}(\text{P}1)2641 \rangle$. Since 1,4,2-oxathiazolines can be formed by cycloaddition of nitrile oxides to thio-carbonyl compounds (see Section 4.14.9.3) their thermolysis offers an attractive way to transform a $\text{C}=\text{S}$ to a $\text{C}=\text{O}$ bond especially in compounds sensitive to the usual reagents $\langle 79\text{CB}1873 \rangle$. 1,3,4-Dioxazolines ($\text{Y} = \text{Z} = \text{O}$) also decompose to carbonyl compound and isocyanates. An early kinetic study of their thermal decomposition in the presence of an excess of Bu_2NH showed that it was first

order with respect to dioxazoline. Rate constants were dependent on the nature of the ketone formed and increased in the order $\text{Ph}_2\text{CO} > \text{PhCOMe} > \text{Me}_2\text{CO}$ <67BCJ664>. As regards the dithiazolines, there is no report on their thermal decomposition.

4.14.6.1.2 Thermolysis of azolidine derivatives

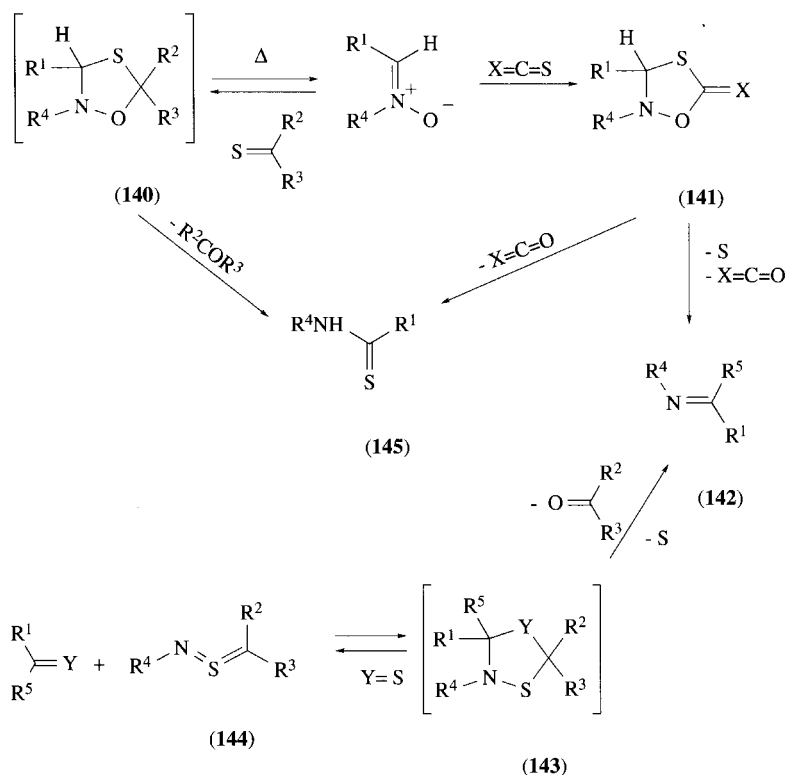
Compounds of structures (14)–(16) are in general less studied than all other classes of (oxa/thia)-2-azoles, either because of difficulty in their preparation or their thermal instability. Some of them are stable, but others are nonisolable reactive intermediates <75S205>. The dioxazolidine (137) is reversibly dissociated to the nitron and pivalaldehyde <80JCR(S)122> (Equation (2)); the dioxazolidine (138) is more stable, but decomposes on heating at 300°C to yield the pivalaldehyde ($\text{Bu}^t\text{CH}=\text{O}$) and the benzimidazolone (139) (Equation (3)) <86JOC732>.



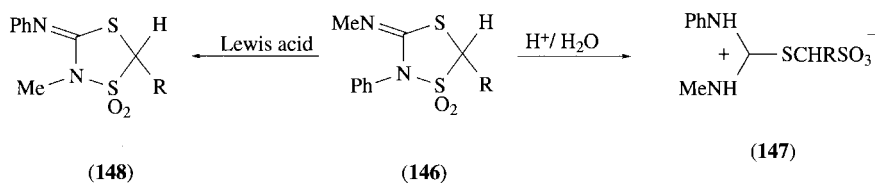
The oxathiazoline derivatives (140) and (141) ($\text{X} = \text{S}$) are usually nonisolable intermediates of reactions between nitrones and thiocarbonyl compounds. However, those oxathiazolines (140), obtained from aliphatic thioketones, are isolable but reversibly dissociated compounds (Scheme 20) <75S205>. Also isolable are the azonylene compounds (141) ($\text{X} = \text{C}(\text{CF}_3)_3$), which decompose over several days at room temperature, to the imine (142; $\text{R}^1 = \text{H}$, $\text{R}^4 = \text{Me}$ or OMe , $\text{R}^5 = \text{Ph}$) <70JOC3470> and the dithiazolidine (143) ($\text{Y} = \text{S}$), which is reversibly dissociated to the starting thione-S-imide (144) and aromatic thiones <80BCJ1023>. The analogous 1,3,4-oxathiazolidine derivative (143) ($\text{Y} = \text{O}$) instantly decomposed to the imine (142). Imine derivatives (142) are also formed from carbon disulfide and C,N-diphenylnitron or heteroaromatic N-oxides <75S205>, presumably through the nonisolable oxathiazolidine thione derivatives (141) ($\text{X} = \text{S}$). However, reactions of aliphatic aldonitrones with 1,1'-thiocarbonyldiimidazole ($\text{R}^2 = \text{R}^3 = 1\text{-imidazolyl}$) <85CJC951> and with CS_2 or benzoylisothiocyanate afford thioamides (145), presumably through the nonisolable intermediates (140) and (141) <75S205>; these transformations offer a useful way to convert an aldehyde to a thioamide.

4.14.6.2 Electrophilic Attack at Ring Carbon and Nitrogen

The ring carbons of all possible 1,4-(oxa/thia)-2-azoles are not expected to be attacked by electrophiles and indeed no such reactions have yet been reported. Alkylations which were supposed to take place at the ring nitrogen of 1,3,4-dithiazolines (44; $\text{R} = \text{H}$), either directly with diazomethane or methyl iodide, or by alkylations and acylations of the corresponding sodium salts <77CCC2680>, have been already discussed (Section 4.14.3.6). Protonation at the ring nitrogen of sultams (146) is claimed to cause hydrolysis to the betaine (147), while Dimroth rearrangement to the isomeric compound (148) is also performed under Lewis acid catalysis (Scheme 21) <78JOC4951>.



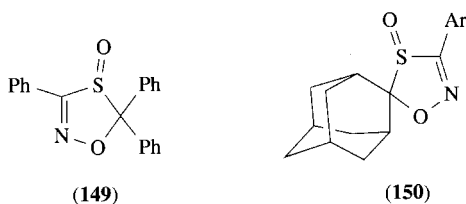
Scheme 20



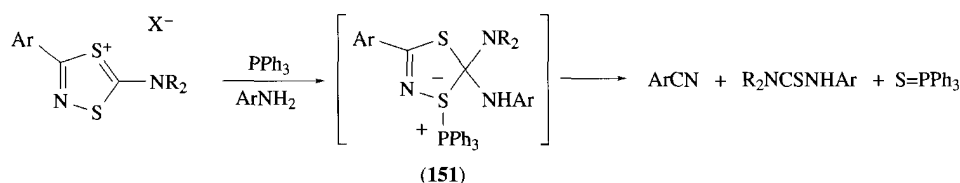
Scheme 21

4.14.6.3 Attack at Ring Sulfur

Electrophilic attack at the ring sulfur of oxathiazolines by certain oxidizing reagents has been reported to give sulfoxy compounds. Thus oxathiazoline-S-oxides (149) and (150) have been obtained by oxidation with acidic KMnO_4 <72CB2815> and with MCPBA <84JCS(P1)2641> respectively.



The presence of Ph_3P as a base in the reaction of 1,4,2-dithiazolium salts with amino nucleophiles promotes ring fragmentation, probably by attack at the primary adduct yielding (151) and assisting sulfur expulsion as $\text{Ph}_3\text{P}=\text{S}$ (Scheme 22) <88BCJ4043>.

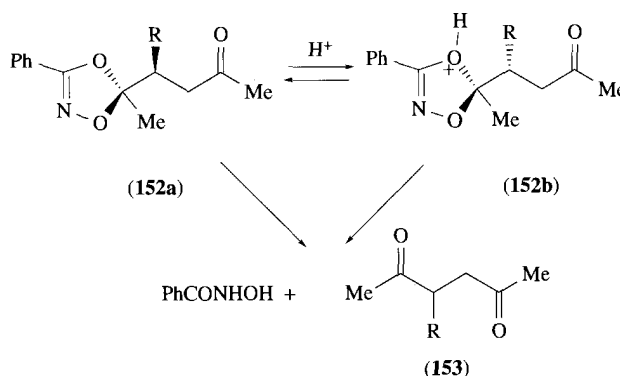


Scheme 22

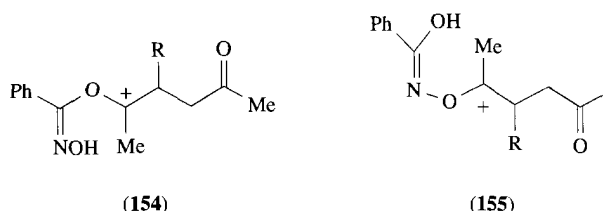
4.14.6.4 Nucleophilic Attack at Ring Carbon

4.14.6.4.1 Azolines

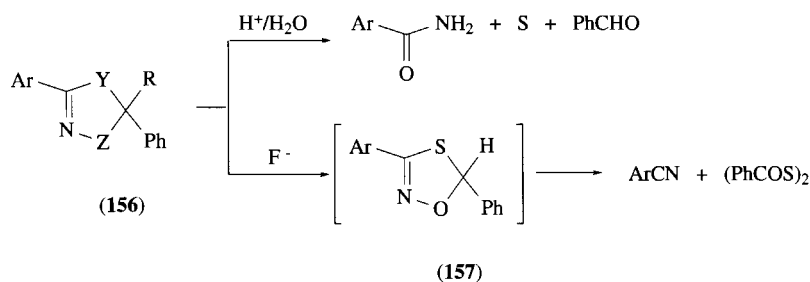
Although triphenyl-1,3,4-dioxazoline (**3**; $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Ph}$) exhibits an exceptional stability towards hydrolytic ring fission, being hydrolyzed only on boiling with 60% HI $\langle 56\text{CLY}779 \rangle$, other alkyl substituted dioxazolines are more susceptible to hydrolysis either by acetic acid $\langle 72\text{CB}2805 \rangle$ or alcoholic alkali $\langle 78\text{ZC}57 \rangle$ to give the hydroxamic acids and carbonyl compounds. The dioxazolyl ketones (**152**) are hydrolyzed, under neutral conditions, by refluxing with 1:1 aqueous EtOH, to the internally substituted γ -diketones (**153**) (see also Section 4.14.7). When diastereomerically pure compounds (**152**) are used, epimerizations at the tertiary carbon atom have been observed (Scheme 23) during hydrolysis. This suggests a recyclization equilibrium via cations (**154**) and/or (**155**), formed by protonation at ring oxygen atoms and subsequent ring opening, which must be recycled to the epimers (**152a**) and (**152b**) faster than they are quenched by water $\langle 86\text{JOC}2351 \rangle$. However some derivatives, having R electron withdrawing, did not hydrolyze, probably as a result of destabilization of intermediate cations (**154**) and (**155**).



Scheme 23

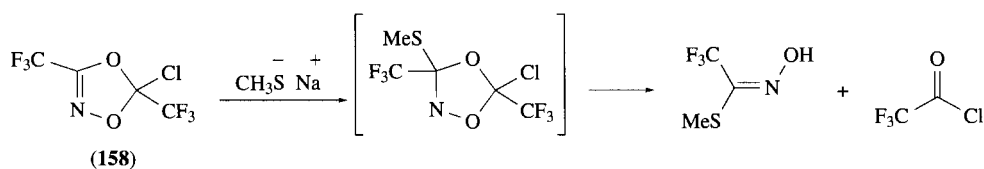


Acidic hydrolysis of oxathiazoline (**156**) ($\text{Y} = \text{O}$, $\text{Z} = \text{S}$, $\text{R} = \text{H}$), results in ring cleavage to give amides, benzaldehyde and sulfur $\langle 74\text{ZN}(\text{B})284 \rangle$, while fluoride anion promoted desilylation of the isomeric ring ($\text{Y} = \text{S}$, $\text{Z} = \text{O}$, $\text{R} = \text{TMS}$) $\langle 81\text{CC}822, 90\text{H}(31)47 \rangle$ affords a nitrile and benzoylsulfide (Scheme 24). For the latter reaction, the nonisolable intermediate (**157**) is invoked to explain the fragmentation although presumably this actually proceeds via the anion at the tertiary carbon.

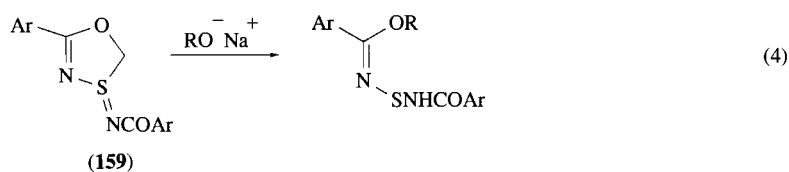


Scheme 24

For all the above examples, the nucleophilic attack takes place at the tertiary carbon atom of the (oxa/thia)azoline ring. However in two particular cases, namely for the fluoromethyl substituted dioxazoline (**158**) <84JOC919> and the unusual oxathiazoline (**159**) <74ZOR39>, the nucleophiles attack at the sp^2 ring carbon according to Scheme 25, and Equation (4)).

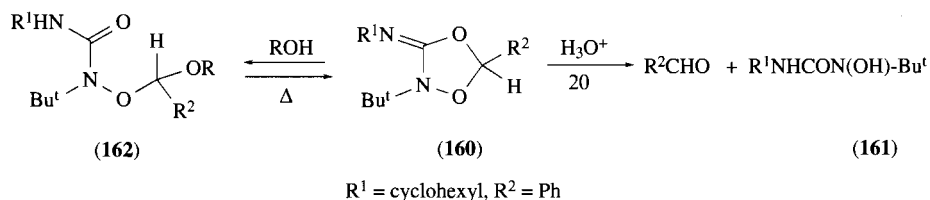


Scheme 25

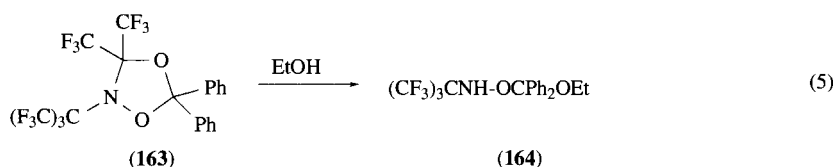


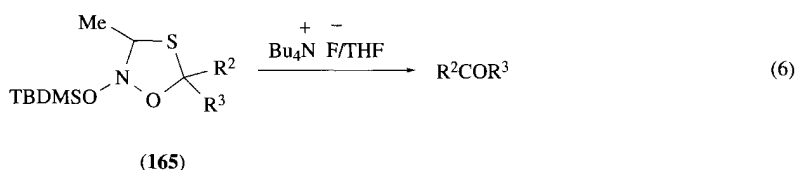
4.14.6.4.2 Azolidines

Acid hydrolysis of the imino dioxazolidine (**160**; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Bu}^t$) affords pivalaldehyde and the N-hydroxyurea derivative (**161**), while methanolysis or acetolysis of (**160**) ($\text{R}^1 = \text{cyclohexyl}$, $\text{R}^2 = \text{Ph}$) gives the open-chain compound (**162**; $\text{R}^2 = \text{cyclohexyl}$, $\text{R}^3 = \text{Ph}$, $\text{R} = \text{Me}$ or MeCO) <86JOC732>. On heating (250°C) (**162**) cyclizes to the starting dioxazolidine (Scheme 26). In a similar way (Equation (5)) the dioxazolidine (**163**) on solvolysis with EtOH gives the disubstituted hydroxylamine (**164**) <79IZV1788>. The fluoride anion-promoted ring cleavage of oxathiazolidine (**165**) to carbonyl compounds <84JOC573> has been suggested as an alternative way to transform a thiocarbonyl to a carbonyl group (Equation (6)).



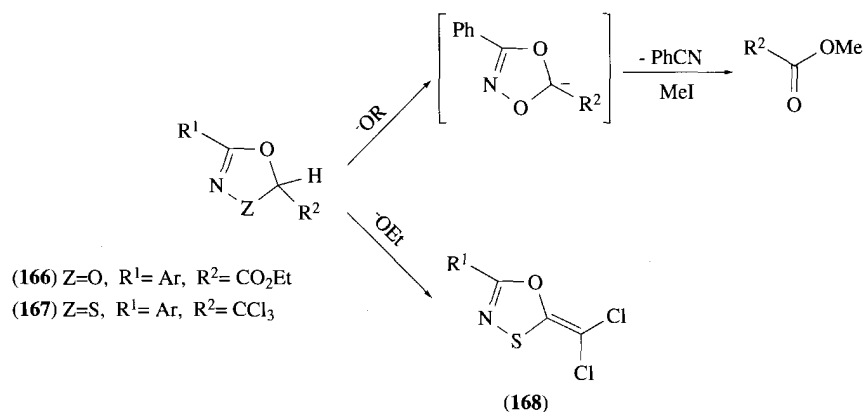
Scheme 26





4.14.6.5 Attack at Ring Hydrogen

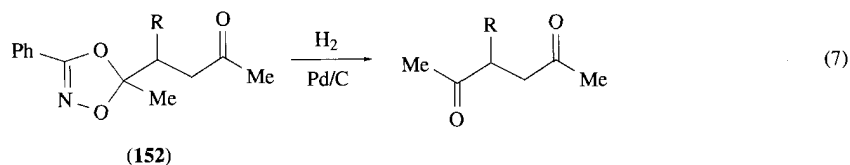
Deprotonation of 1,3,4-dioxazolines (**166**) with a strong base (Bu^tOK) results in ring fragmentation to give nitriles and the carboxylate anion $\langle 72\text{CB}2805, 91\text{SL}189 \rangle$, which in turn is converted to carboxylic acid derivatives. Since 1,3,4-dioxazolines (**166**) are formed from aldehydes and nitrile oxides, this reaction may form the basis of a conversion of aldehydes to carboxylic acids without the use of conventional oxidizing agents $\langle 91\text{SL}189 \rangle$. In the case of oxathiazoline (**167**) dehydrochlorination affords the azonylene derivative (**168**) (Scheme 27) $\langle 85\text{JCS}(\text{P}1)1517 \rangle$.



Scheme 27

4.14.6.6 Reactions at Surfaces

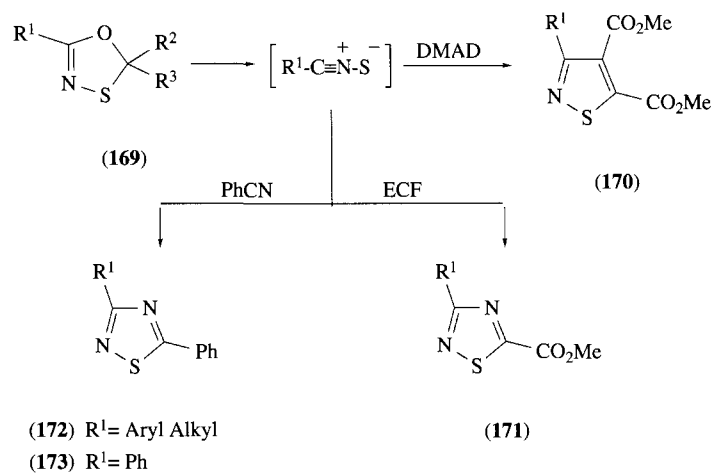
1,3,4-Dioxazoline or dioxazolidine rings may be useful as protecting groups for carbonyl functionalities. In two particular cases, that of dioxazolyl ketone (**152**) (Equation (7)) $\langle 86\text{JOC}2351 \rangle$ and of dioxazolidine (**137**) $\langle 80\text{JCR}(\text{S})122 \rangle$, the ring is cleaved by catalytic hydrogenation (H_2/Pd) to liberate the carbonyl group. However the resistance to reduction of 2,2,5-triphenyl-1,3,4-dioxazole with Zn/AcOH , Al/Hg , Et_2O , Na/Hg , EtOH has been reported $\langle 56\text{CLY}779 \rangle$.



4.14.6.7 Reactions with Cyclic Transition States

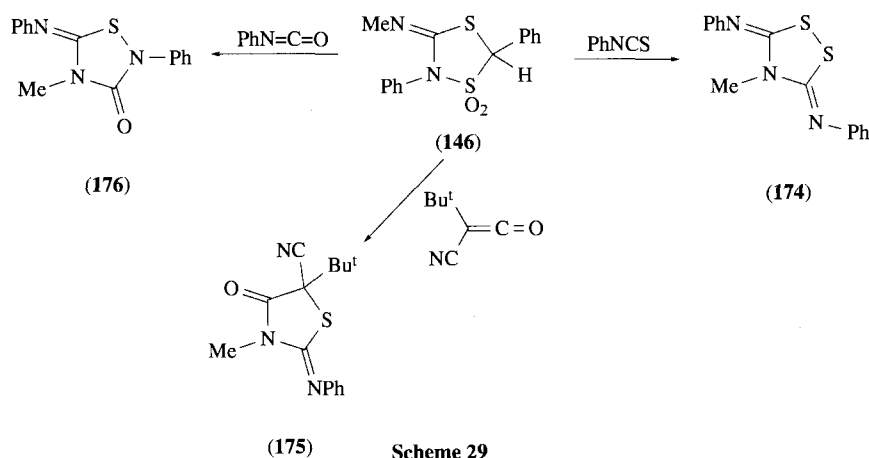
As reported before (see Section 4.14.6.1, Scheme 19), thermolysis of oxathiazolines (**169**) proceeds via a retro 1,3-dipolar cycloaddition to produce the carbonyl compound and the nitrile sulfide intermediate. Trapping reactions have been carried out with DMAD, ECF (ethyl cyano formate), and benzonitrile to give respectively isothiazoles (**170**) and thiadiazoles (**171**) and (**172**). However in two particular cases ($\text{R}^1 = 4\text{-MeOC}_6\text{H}_4$, $4\text{-ClC}_6\text{H}_4$, thermolysis in the presence of benzonitrile gives (**172**) and the thiadiazole (**173**) in very low yields. It has been suggested that the latter arises

from the presence of benzonitrile sulfide formed from PhCN and atomic sulfur or by sulfur transfer from the initially formed nitrile sulfide to PhCN. Subsequent cycloaddition of the benzonitrile sulfide to PhCN accounts for (173) (Scheme 28) <85JCS(P1)1517>.



Scheme 28

The sultam (146) yields the 1,2,4-dithiazolidine (174), thiazolidine (175) or 1,2,4-thiadiazolidine derivatives (176) on heating with an excess of several heterocumulene dipolarophiles (Scheme 29). It is formally acting as a masked 1,3-dipole resulting from elimination of the sulfene moiety ($PhCH=SO_2$) <78JOC4951>.



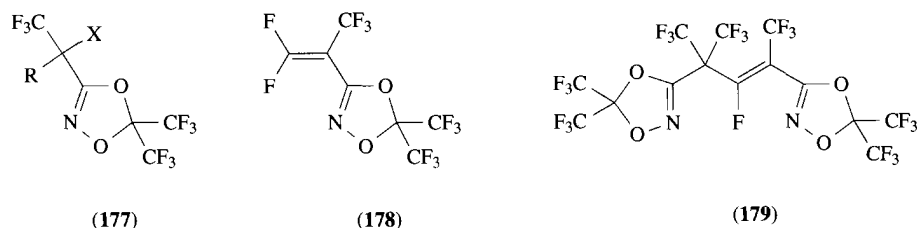
Scheme 29

4.14.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

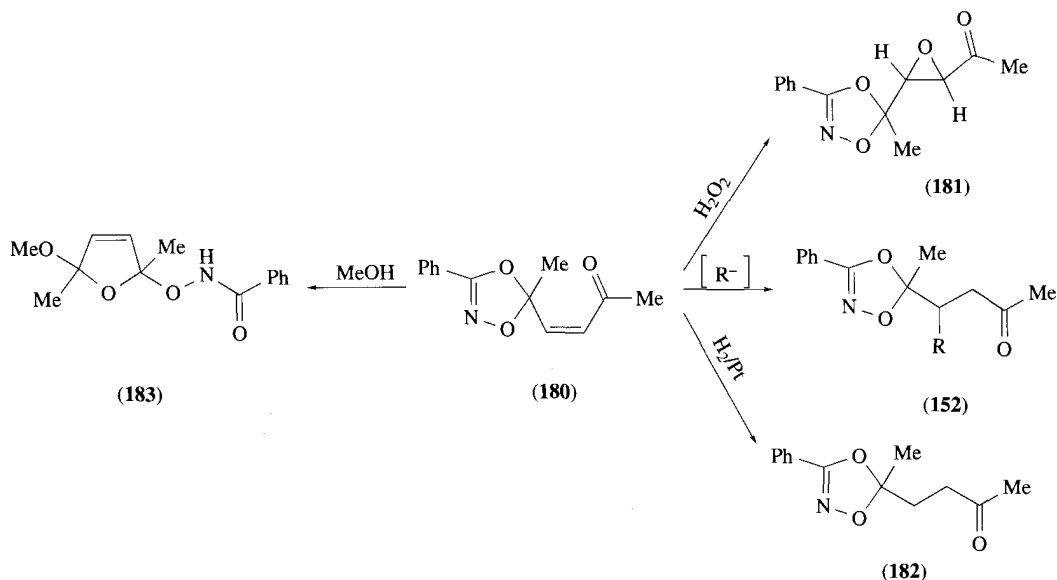
4.14.7.1 Alkyl Substituents

The 1,3,4-dioxazoline ring is stable enough to survive numerous transformations carried out on substituents at both C-2 and C-5. Polyfluorinated derivatives (177) ($X = H$, $R = CF_3$), especially those having an α -hydrogen at the C-5 substituent, are strong C—H acids and in protic solvents readily undergo reactions with various electrophiles. Examples include deuterium exchange with D_2O to give (177) ($X = D$), chlorination or bromination in the presence of NEt_3 to give (177) ($X = Cl$ or Br) and nitrosation by trifluoroacetyl nitrite to give (177) ($X = NO$) <84ZOR1498>. Facile dehydrofluorination of (177; $X = H$, $R = CF_3$) is accomplished by $NEt_3 \cdot BF_3$ to give (178) <84ZOR1498, 86MI 414-01> or by C_3F_7COCl/NEt_3 to yield (179) <84ZOR1498>, while for (177) ($R = CF_3$, CO_2Me), treatment with CF_3NO produced derivative (177) ($X = N(OH)CF_3$) <85MI 414-01>. The

alkenyl derivative (**178**), being a very electron-deficient dienophile, gives typical Diels–Alder reactions, e.g. with cyclopentadiene, and also addition reactions with various nucleophiles <84ZOR1983>. In all these reactions the ring remains unchanged.



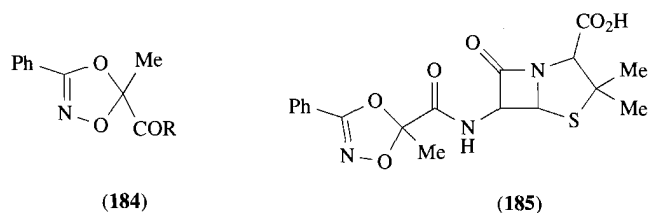
The dioxazoline ring in the *cis*-enone (**180**) operates principally as a protecting group of a half blocked *cis*-enedione, permitting various Michael type additions to the C=C bond and affording after deprotection (see Section 4.14.6.6), internally substituted diketone derivatives. In this respect, various nucleophiles have been employed to give diastereomeric mixtures of addition products (**152**) including the diastereomeric *trans*-epoxides (**181**) <86JOC2351>. Under carefully controlled hydrogenation conditions, compound (**182**) can also be obtained, in reasonable yields, without fragmentation of the dioxazoline ring, while with methanol the 2,5-dihydrofuranyl hydroxamate (**183**) is formed by ketalization of the second carbonyl group (Scheme 30) <80JCS(P1)2408>.



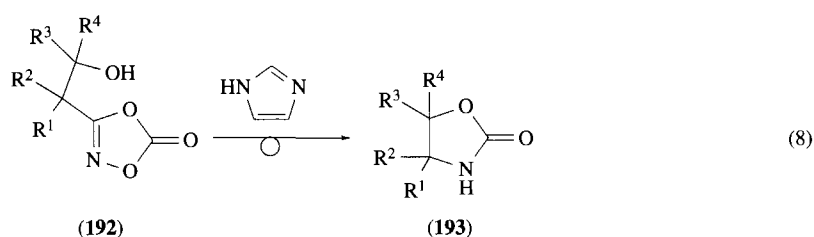
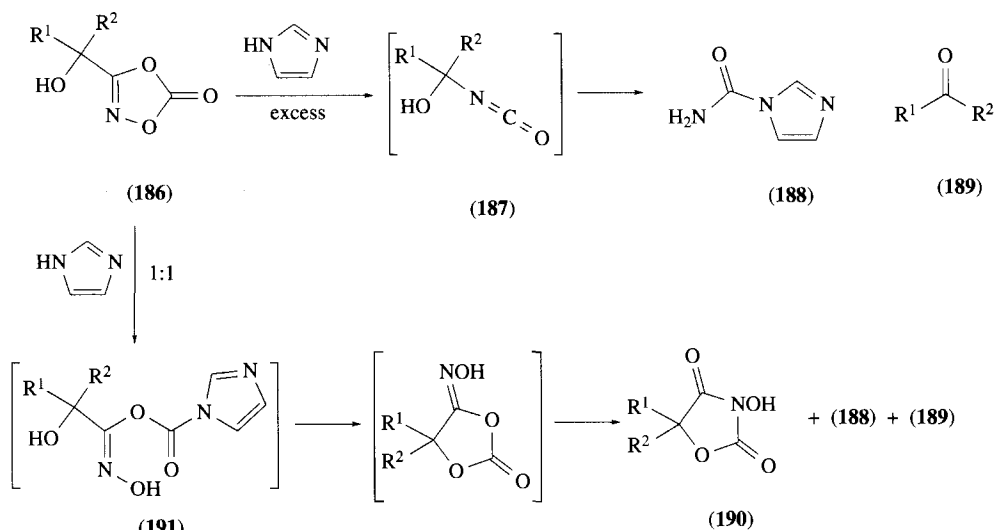
Scheme 30

In several transformations of 2-acyl or carboxyalkyl substituted dioxazoline derivatives the ring remains unchanged. Thus the methyl ketone (**184**; R = Me) yields, via haloform oxidation the corresponding carboxylic acid which is converted to its methyl ester (CH₂N₂) and then to the amide with NH₃ <72CB2805>. The ethyl ester (**184**; R = OEt) is transformed into the hydrazide with NH₂NH₂ and then to the azide with nitrous acid, or hydrolyzed to the carboxylic acid with 40% KOH and converted to the acyl chloride (R = Cl). The latter is further transformed into a highly effective penicillin derivative (**185**) <65USP3222360>.

Ring-cleavage reactions of some 1,3,4-dioxazol-2-one derivatives, having an α - or a β -hydroxyl

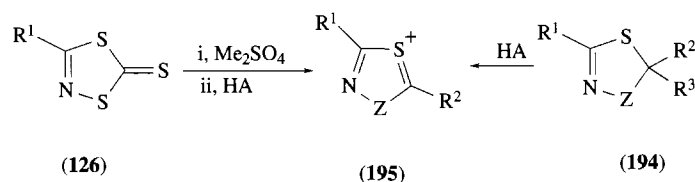


group on their C-5 substituent is usually accompanied by side reactions which involve these hydroxyl functionalities. Thus reactions of dioxazolone derivatives (**186**) with an excess of imidazole cause a rapid decomposition of the ring and afford the carbamoyl imidazole (**188**) and carbonyl compounds (**189**) probably through the isocyanate intermediate (**187**) (Scheme 31). With equimolar amounts of substrate and imidazole the oxazolidine derivative (**190**) is obtained together with (**188**) and (**189**) probably through the open-chain primary adduct (**191**) <82LA211>. An analogous reaction with dioxazolone (**192**) gives the oxazolidone (**193**) (Equation (8)) <82LA219>.



4.14.7.2 Other Substituents

Alkylamino, alkoxy or methylthio groups attached at C-5 position of dithiazolines (**194**) (Z = S) <91JCS(P1)183, 92JCS(P1)2065> or oxathiazolines (**194**) (Z = O) <91TL4329> are readily solvolized in strongly acidic media (HClO₄/Ac₂O or HBF₄-CF₃CO)₂O to give dithiazolium or oxathiazolium salts (**195**), in high yields, except for those obtained from the alkoxy group where the yields are low (Scheme 32) <91JCS(P1)183>. It should be noted that the parent dithiazolium salt has been prepared in this way.



Some reactions concerning the thione group of dithiazole thiones (**126**) have been discussed (see Section 4.14.5.7). As expected, the thione group is methylated with Me₂SO₄ affording, after treatment

with a strong acid (HClO_4 or HBF_4), the dithiazolium salts (**195**; $\text{R}^2 = \text{SMe}$) <85CC696, 92JCS(P1)2065>. The methylthio group of the dithiazoline derivative (**54**) (see Section 4.14.4) is subjected to aminolysis with Me_2NH <62AG(E)594> or HCONMe_2 <67USP3345374>.

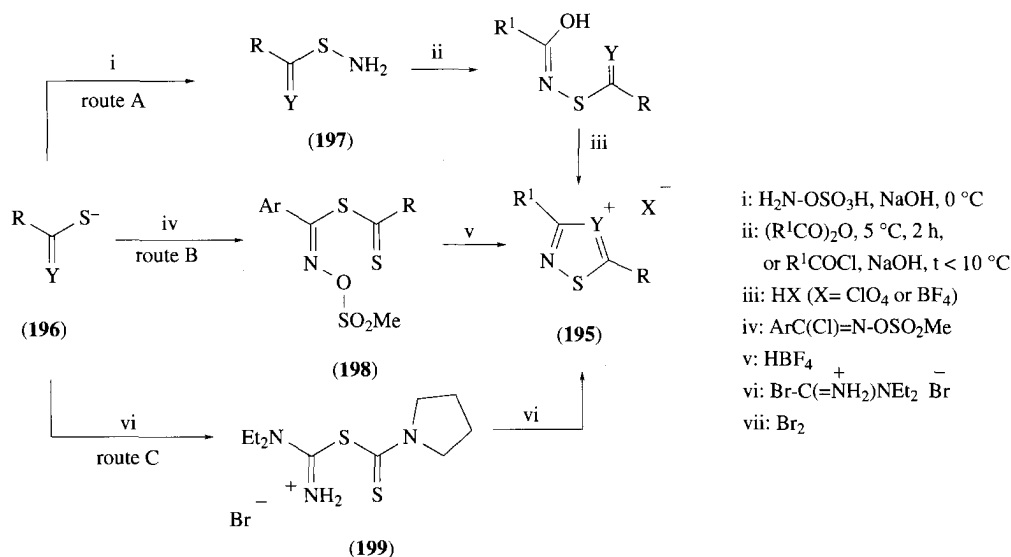
4.14.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

There are no reports concerning reactivity of substituents attached to ring heteroatoms. In fact, most 1,4-(oxa/thia)-2-azoles are unsubstituted at ring heteroatoms and the only data concerning dithia- or oxathiazolidine S,S-dioxides, or N-substituted derivatives is limited to their preparation and to the reactivity of the ring systems.

4.14.9 RING SYNTHESIS CLASSIFIED BY NUMBERS IN EACH COMPONENT

4.14.9.1 Formation of One Bond Adjacent to a Heteroatom

Of particular interest are some intramolecular cyclizations, which are used for the preparation of dithiazolium salts. There are three different routes all starting from sodium salts of dithiocarboxylic acids (**196**) (Scheme 33).

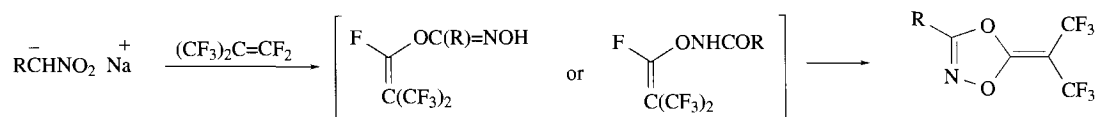


Scheme 33

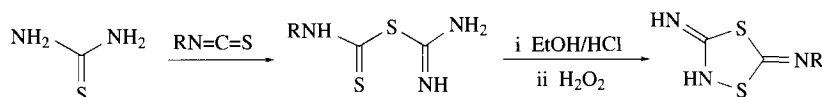
According to route (A) ($\text{Y} = \text{S}$), arylation or acylation of sulfenamides (**197**), is followed by dehydration in strong acidic media (HClO_4 or HBF_4) to give the dithiazolium salts (**195**) <86BCJ2017, 90BCJ2933, 90JCS(P1)2465, 92BCJ920>. This route has also been used for their industrial preparation <90JAP(K)0267275> as well as for the preparation of 1,3,4-oxathiazolium salts ($\text{Y} = \text{O}$) <90TL5935>. Route (B) involves reaction between sodium dithiocarbamates (**196**; $\text{R} = \text{NR}^1$) with α -chloro-oxime O-sulfonates to give the α -thiocarbamoyloxime O-sulfonate (**198**), which in turn is cyclized by HBF_4 to the salt (**195**) ($\text{Y} = \text{S}$) <85CC1641, 88JCS(P1)899>. Route (C) involves nucleophilic addition of sodium dithiocarbamate (**196**; $\text{R} = 1\text{-pyrrolidino}$) to the α -bromoiminium salts to give (**199**) followed by oxidative cyclization with bromine <88JCS(P1)899>.

Some intramolecular cyclizations of various open-chain precursors accompanied by eliminations are given in Schemes 34 to 37 and Equations (9) to (11): (Scheme 34 <69DOK(185)837, 70IZV2140>;

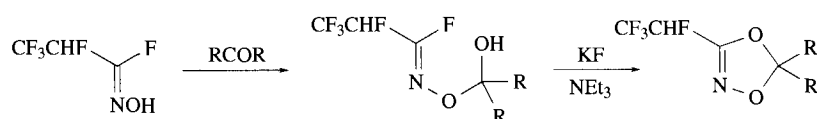
Scheme 35 <76AJC415>; Scheme 36 <80MI 414-01>; Equation (9) <84JOC919>; Scheme 37 <78JAP78127479>; Equation (10) <75LA1409>; Equation (11) <93TL3419>).



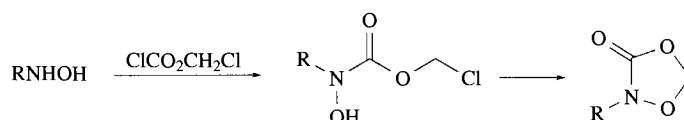
Scheme 34



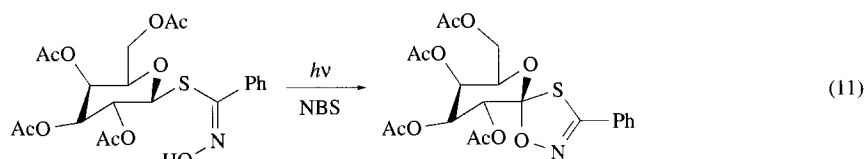
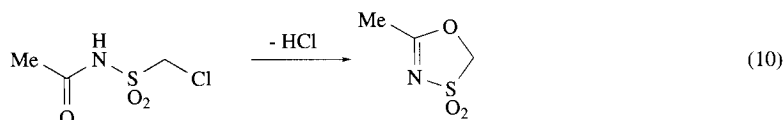
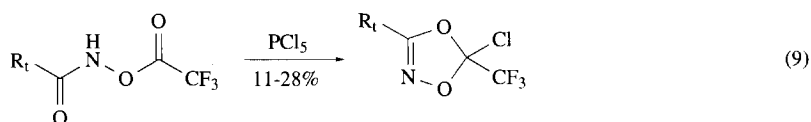
Scheme 35



Scheme 36



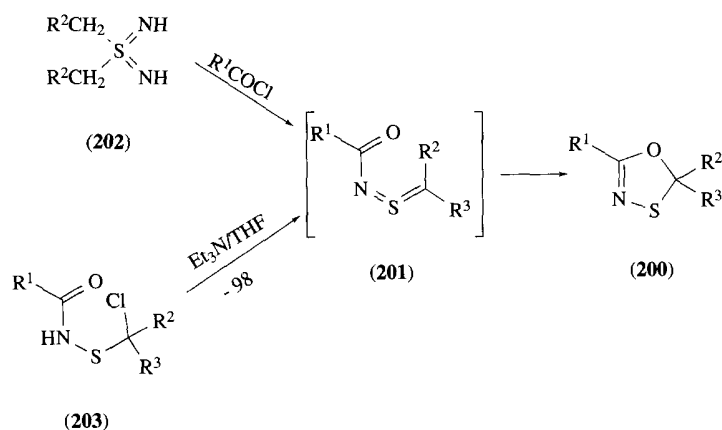
Scheme 37



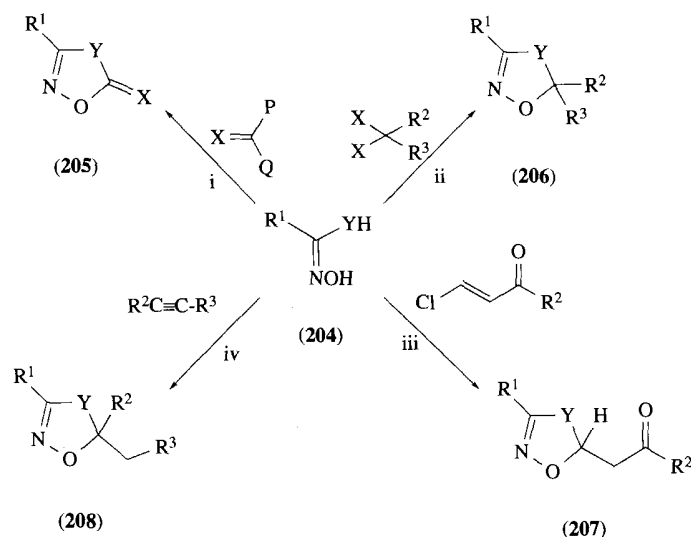
The oxathiazoline derivatives (**200**), are obtained by electrocyclization of the thione S-imide intermediates (**201**), which are formed either from the S,S-dibenzylsulfur diimides (**202**) and excess of aroyl chlorides ($\text{R}^2 = \text{Ar}$, $\text{R}^3 = \text{H}$) <74ZN(B)284>, or by base treatment of N-acyl chlorodiaryl methane sulfenamides (**203**; R^2 , $\text{R}^3 = \text{Ph}$ or fluorenyl residue) (Scheme 38) <74JOC2885>.

4.14.9.2 Formation of Two Bonds: Four-atom Fragment and Carbon

The cyclizations of hydroxamic acids (**204**) ($\text{Y} = \text{O}$ or S), with various reagents capable of undergoing nucleophilic attack twice at the same carbon atom, are very important routes for the synthesis of the ring systems in this chapter (Scheme 39).



Scheme 38

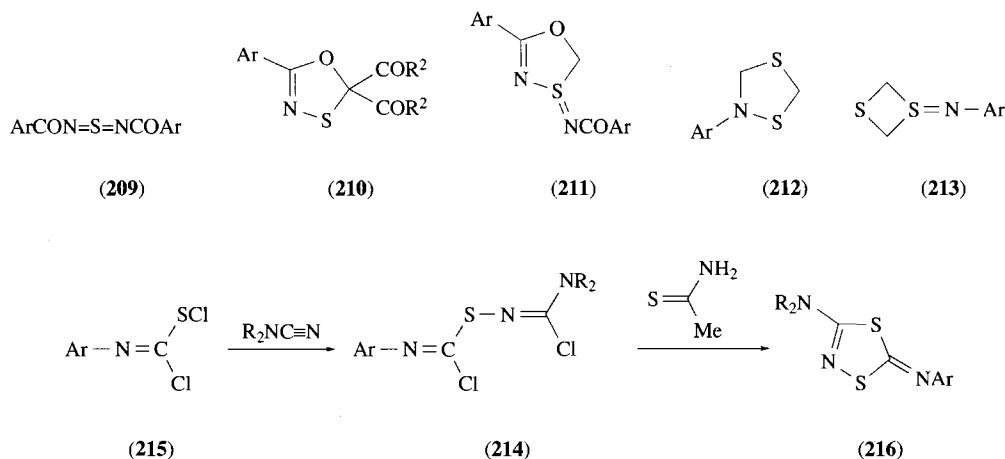


Scheme 39

Various electrophiles such as carbonyl, thiocarbonyl, imino [84CHEC-I(6)932], or iminium transfer reagents [85MI 414-02], react with hydroxamic acids (204) (route (i)) to give dioxazole or oxathiazole derivatives (205) with an exocyclic conjugation. A considerable amount of data concerning cyclization of hydroxamic acids (Y = O) and phosgene (P = Q = Cl, X = O) [67FRP1505468, 69USP3480595, 70BP1213668, 71USP3560518, 71USP3609163, 72GEP2059990, 73USP3737435, 74USP3825554, 78ZOB1465, 83JOC3845, 88JOC2674], thiohydroxamic acid (Y = S) and phosgene [63BEP632072, 72GEP2059990], hydroxamic acid and thiophosgene (P = Q = Cl, X = S) [72GEP2059990] and thiohydroxamic acid and thiophosgene (P = Q = Cl, X = Y = S) [72GEP2059990], has been reported mainly in the patent literature, obviously because of the commercial importance of the resulting oxathiazolones and dioxazolones. Imino and iminio transferring is performed by treatment of hydroxamic acids (Y = O, S) with N-dichloromethylene sulfonamides (P = Q = Cl; X = NSO₂Ar) [71AP(304)763] and N-dichloromethyleneiminium chlorides (P = Q = Cl; X = N⁺R² Cl⁻) [85MI 414-02], respectively. Other cyclocarbonylating reagents used are 1,1'-carbonyldiimidazole (P = Q = 1-imidazolyl; X = O) [79JHC1277, 82LA211, 82LA219] and ethyl chloroformate (P = Cl, Q = CO₂Et; X = O) [71RZC833].

According to route (ii) hydroxamic acids and ketals (R², R³ = alkyl or aryl, X = OEt) [56CLY779, 67BCJ664], or thiohydroxamic acid and benzophenone dichloride [72CB2815] afford compound (206), while following route (iii) alkali hydroxamates and various chloroenones yield the dioxazoline ketones (207) [74GEP107463, 78ZC57, 80ZOB1014]. Following route (iv) alkynic compounds and hydroxamic acids [73CJC1368, 77JPS772, 86JHC463] or thiohydroxamic acids [75H(3)563, 80OPP233] are cyclized via a double Michael addition to give dioxazoline or oxathiazoline derivatives (X = O, S) (208).

Other four-atom components which have been used in cyclocondensation reactions are the sulfur diimides (**209**) which with malonic acid derivatives <82ZOR2549> and diazomethane <74ZOR39> yield the oxathiazoline derivatives (**210**) and (**211**) respectively. The N-aryldithiazolidine derivative (**212**) is obtained from dithietan, *p*-chloroaniline, and *t*-butyl hypochlorite possibly via an unstable sulfimide intermediate (**213**) which rearranges to (**212**) by ring enlargement <85M1153>. Thioacetamide, as sulfur binucleophile and the carbimidoyl chloride (**214**), obtained from N-aryl-S-chloro-isothiocarbamoyl chloride (**215**) and cyanamide yield the 2-arylimino-dithiazole (**216**) (Scheme 40) <87CZ339>.

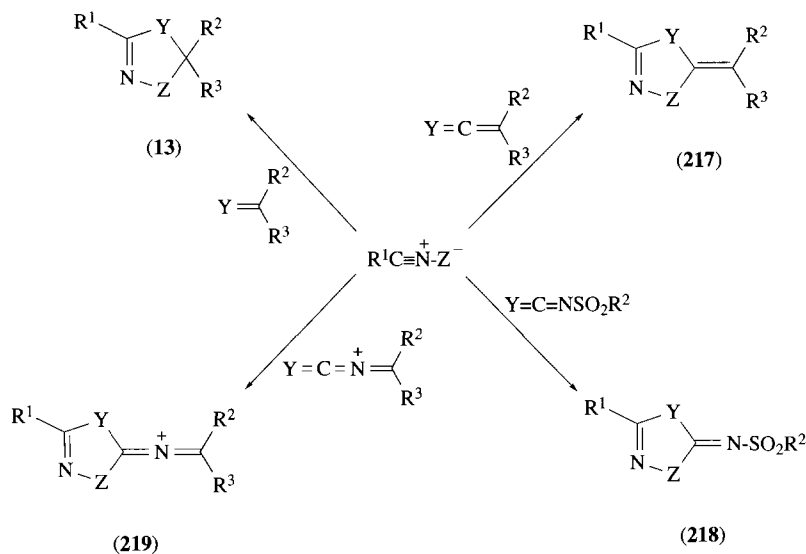


Scheme 40

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

1,3-Dipolar cycloaddition is one of the most important methods in assembling five-membered ring heterocycles. For the 1,4-(oxa/thia)-2-azole system, nitrile oxides, and nitrile sulfides have the correct sequence of atoms for the 4π 1,3-dipolar component and the 2π component can be either a $C=O$ or a $C=S$ heterodipolarophile (Scheme 41). Nitrile oxides, usually generated *in situ* from the corresponding hydroximoyl chlorides and a base, add to various types of $C=O$ bond affording 1,4,2-dioxazole derivatives.

Carbonyl compounds of sufficient dipolarophilic activity are aldehydes and ketones that have

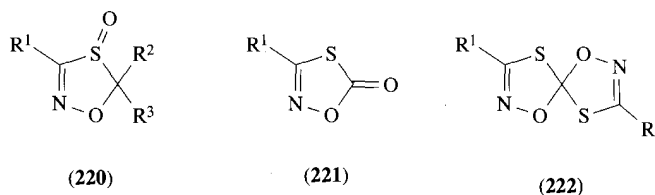


Scheme 41

been activated by an adjacent electron-withdrawing group affording 5H-1,4,2-dioxazole derivatives (**13**) ($Y = Z = O$) <72CB2805, 81MI 414-01, B-84MI 414-01, 85ZOR910, 91SL189>. However, in some instances as in the case of α -hydroxyiminophenyl acetonitrile oxide (**255**; $R = Ph$), cycloaddition takes place even with simple aliphatic aldehydes and ketones <89KGS1426> despite the fact that analogous reactions with benzonitrile oxide proceed only in the presence of BF_3 as catalyst <67TL331>. Other reactive carbonyls are part of cumulative unsaturated systems such as ketenes <70LZV2140>, isocyanates <91ZOR1262, 93UKZ48> or 1-oxa-3-azoniabutatriene salts <89T5825> which yield the fully conjugated dioxazole derivatives (**217**), (**218**), and (**219**) ($Y = Z = O$), respectively. In some cases reactive carbonyl groups are part of cyclic systems such as quinones and other heterocyclic rings <76TL83, 84BCJ1643, B-84MI 414-01, 86LA1863, 86MI 414-02, 90JHC1425> or substituents of other heterocyclic rings affording various 1,4,2-dioxazole derivatives <74JOC1221, 83JHC1505, 84JCR(S)362, 91JHC429>.

The 1,4,2-oxathiazole derivatives (**13**) ($Z = O$, $Y = S$) are easily obtained by cycloaddition of nitrile oxides with various thiocarbonyl compounds, which are usually more reactive than the corresponding carbonyl dipolarophiles. Thus many classes of thiocarbonyl compounds such as thioketones, dithiocarboxylic esters, thionocarboxylic esters, thioamides <72CB2815, 79CB1873, 91TL4329> and trithiocarbonates <76CB1069> are very good dipolarophiles. Moreover, unstable aliphatic thioaldehydes and thioketones can be trapped by cycloadditions with nitrile oxides <85TL5265, 88CB1159, 90JOC4200>. Fully conjugated 1,4,2-oxathiazole derivatives (**217**), (**218**), and (**219**) ($Z = O$, $Y = S$) are obtained from the very reactive $C=S$ bond of cumulated unsaturated systems of thioketenes <66AG(E)970, 70JOC3470, 84JCR(S)370>, sulfonyl isothiocyanates <75T1537>, or 1-thia-3-azoniabutatriene salts, a class of extremely electron-deficient isothiocyanates <91CB2537>.

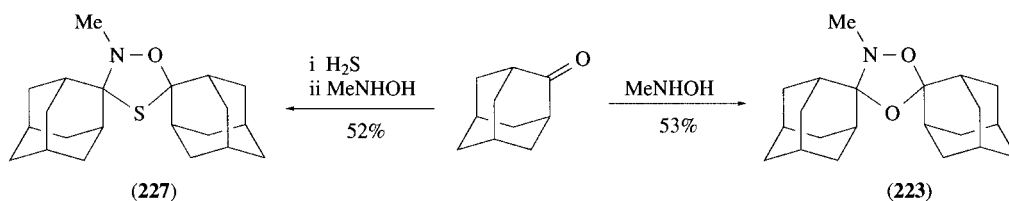
Also of interest are the cumulative systems of sulfoxes and of carbon disulfide which react with nitrile oxides to give 5H-1,4,2-oxathiazole S-oxide (**220**) <77JCS(P1)1468> and 1,4,2-oxathiazol-5-one derivatives (**221**), respectively <66JOC2417>. The latter is formed from the primary spiro bis adduct (**222**) by further decomposition (see also Section 4.14.5.6).



Cycloadditions of nitrile sulfides with $C=O$ or $C=S$ bonds results in the formation of 1,3,4-oxathiazole and 1,4,2-dithiazole rings (see also Section 4.14.5.6). The thermally unstable nitrile sulfides are generated *in situ* usually by decarboxylation of 1,3,4-oxathiazol-5-ones in the presence of an excess of dipolarophile <89CSR33>. Some typical electrophilic carbonyl compounds such as chloral, hexachloroacetone or α,α,α -trifluoromethyl acetophenone add to alkyl or aryl nitrile sulfides yielding 5H-1,4,3-oxathiazole derivatives (**13**) ($Y = O$, $Z = S$) <81JCS(P1)2991>. Reaction of nitrile sulfides with thioketones or thionoesters resulted in 5H-1,4,2-dithiazole derivatives (**13**) ($Y = Z = S$) <88CC852, 91JCS(P1)183>, a potentially general synthetic route to this class of compounds.

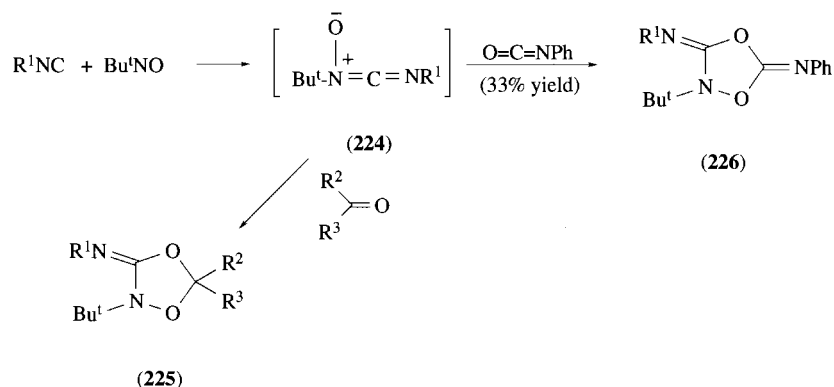
Nitrones and nitronate esters are a class of 1,3 dipoles which have the same sequence of atoms as nitrile oxides and can potentially be used for the synthesis of the tetrahydro derivatives of 1,4,-oxa/thia-2-azoles, by cycloaddition across the $C=O$ or $C=S$ bond. In fact there is only one report involving addition to the $C=O$ bond, that of pivalaldehyde with *C-t*-butyl-N-phenylnitrone (Equation (2), see Section 4.14.6.1.2) <80JCR(S)122>. However, reaction of adamantanone with methylhydroxylamine to give the tetrahydro derivative (**223**) obviously passed through a nitron intermediate (Scheme 42) <72CZ693>. The transient 1,3-dipole, carbodiimide N-oxide (**224**), is invoked to account for the formation of 3-imino-1,4,2-dioxazolidine derivative (**225**) from the reaction between 2-methyl-2-nitrosopropane, an isocyanide and an aldehyde or ketone <86JOC732>. This is analogous to the 'nitroso-isonitrile-isocyanate' reaction, where 3,5-diimino-1,4,2-diaxazolidines (**226**) are formed <69JOC2269, 75JOC3112>.

The $C=S$ double bond is very reactive towards nitrones, but in general, the resulting 1,4,2-oxathiazolidines are unstable and undergo further transformations (see Section 4.14.6.1) <75S205, B-84MI 414-01, 85CJC951, B-88MI 414-02>. Isolable 1,4,2-oxathiazolidine derivatives, respectively (**227**) <72CZ693>, (**228**) <75S205> and (**229**) (Scheme 43) <70JOC3470, 75S205> are obtained only from aliphatic thiocarbonyl compounds. In the same way benzaldoximes and thioketenes give the isolable, though unstable, oxathiazolidine (**229**; $R = H$) <70JOC3470>. Furthermore, 1-thia-3-azoniabutatriene salts and diphenyl-N-methyl nitron afford the oxathiazolidine (**230**) <91CB2537>, while unstable thioal-

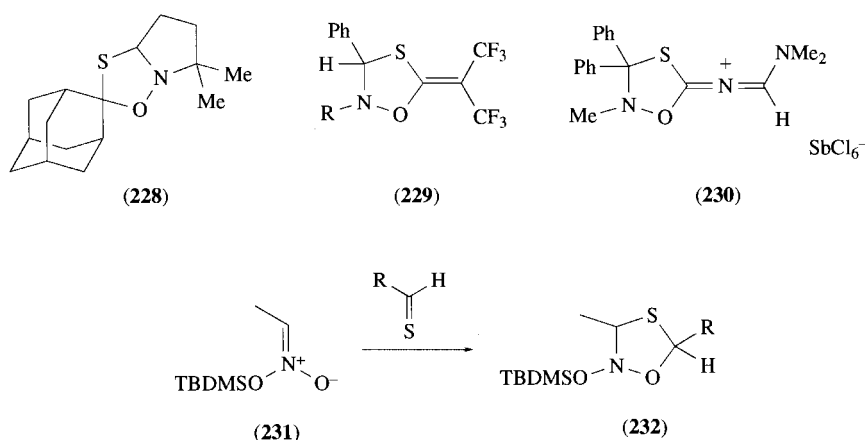


Scheme 42

dehydes are trapped by *t*-butyldimethylsilyl (TBDMS) nitronate esters (**231**) to give the rather stable oxathiazolidine derivative (**232**) (Equation (12)) <83JA1683, 83JA6999, 84JOC573>.



Scheme 43

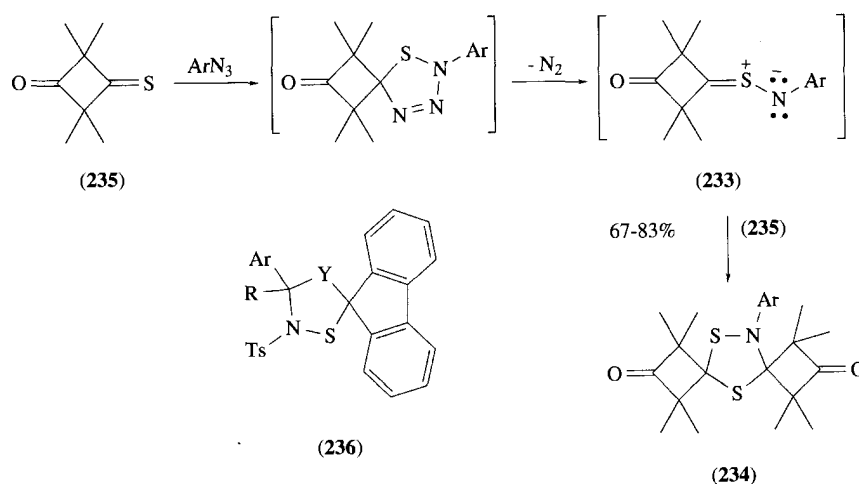


Closely related to the already mentioned electrocyclizations of N-acyl thione S-imide (see Section 4.14.9.2) are some intermolecular cycloadditions involving this unusual class of 1,3-dipoles. Thus, the thione-S-imide intermediate (**233**) is probably involved in the formation of spirodithiazoline derivative (**234**) from the thione (**235**) and aryl azides <93HCA2147>. Also fluorenone-S-*p*-tosylimide affords with carbonyl or thiocarbonyl compounds ($\text{R} \neq \text{H}$) the corresponding oxathia- or dithiazolidine derivatives (**236**) ($\text{Y} = \text{O}$ or S) <80BCJ1023> (Scheme 44) (see also Section 4.14.6.1).

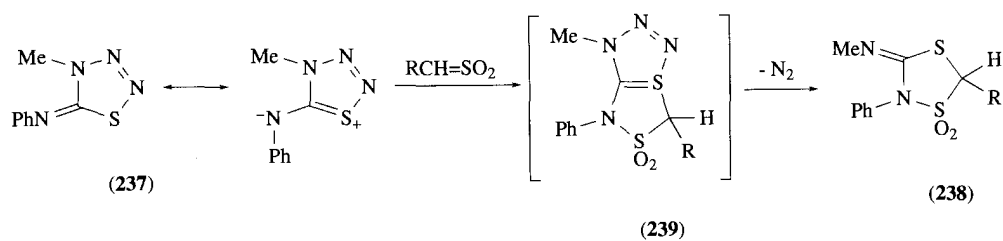
The thiatiazolines (**237**), which are obtained from isothiocyanates and alkyl azides are potentially masked 1,3-dipoles (see also Section 4.14.6.7) and react with sulfenes to give the sultams (**238**), probably through the thiapentalene-like transition state/intermediate (**239**) (Scheme 45) <78JOC4951>.

4.14.9.4 Formation of Two Bonds: [3 + 2] Atoms By Other Processes

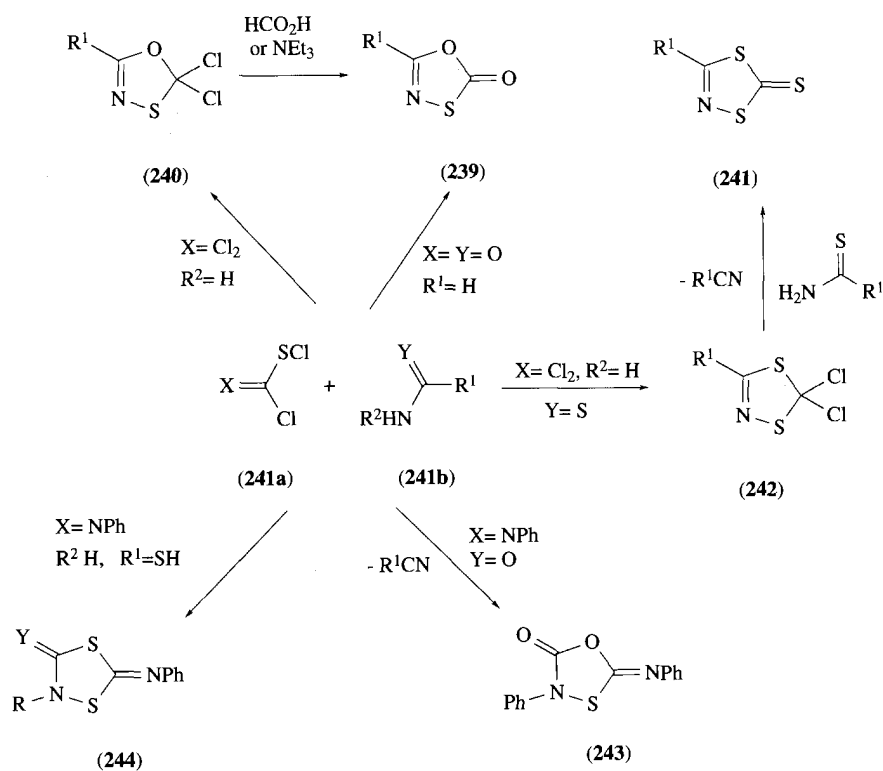
Oxathiazoles and dithiazoles with exocyclic conjugation have also been obtained from appropriately substituted sulfonyl chlorides and carboxamides as detailed in Scheme 46. Part of the chlorocarbonylsulfonyl chloride chemistry has been reviewed <70AG(E)54>.



Scheme 44



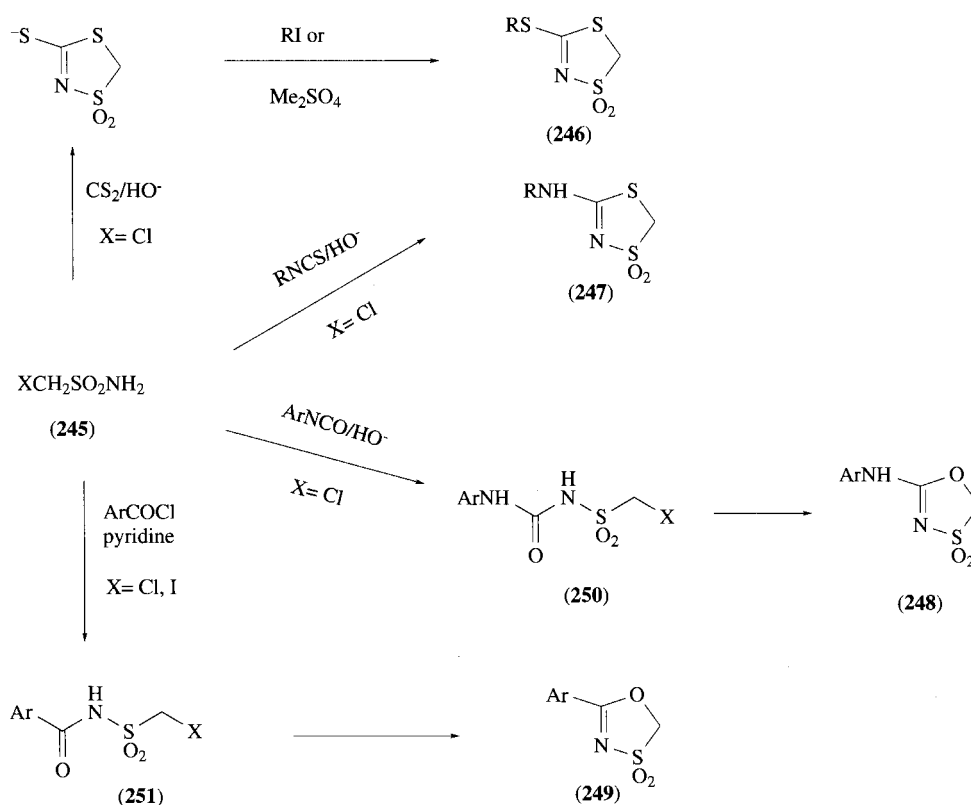
Scheme 45



Scheme 46

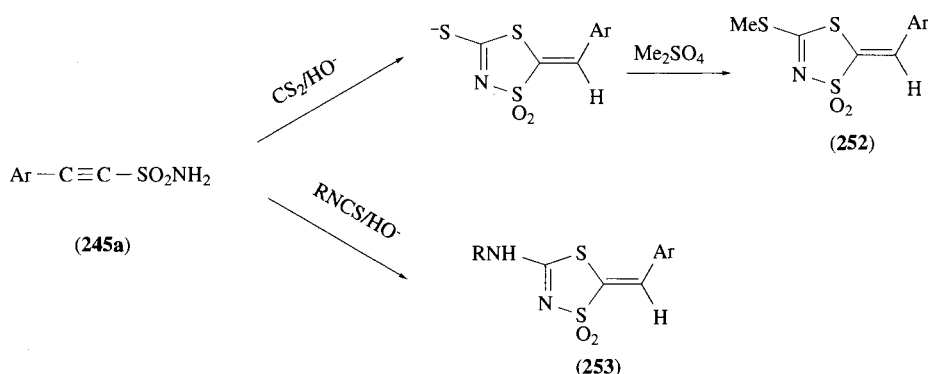
In particular, 1,3,4-oxathiazol-2-ones (**239**) are obtained from the corresponding carboxamides (**241b**) ($Y = O$, $R^3 = H$) either directly by treatment with chlorocarbonylsulfonyl chlorides (**241a**) ($X = O$), or with perchloromethylthiol (CCl_3SCl) where an intermediate dichlorooxathiazoline (**240**) is assumed $\langle 67ACS1871, 77JOC1813, 78JOC3736, 87JCS(P1)2339, 89CSR33 \rangle$. An analogous reaction between carboxamides and alkoxy carbonyl sulfonyl chlorides (BuO_2CSCl), has also been reported $\langle 85MI 414-02 \rangle$. Thioamides and perchloromethylthiol give the dithiazolethione (**241**) through the dithiazoline intermediate (**242**) $\langle 85JCS(P1)1205 \rangle$. Phenyliminomethanesulfonyl chloride (mustard oil chloride) (**241**) ($X = NPh$) and amides yield the imino oxathiazolinone derivative (**243**) $\langle 70AG(E)54 \rangle$, while with NEt_3 salts of thiono- ($Y = O$, $R^2 = SH$), or dithio- ($Y = S$, $R^2 = SH$) carbamic acids the iminodithiazolinone ($Y = O$) or the iminodithiazolinethione derivatives (**244**) are obtained $\langle 80JCB970 \rangle$. Closely related to these cyclizations is the formation, in low yield, of 1,4,2-dithiazolethiones (**241**) from thioamides with thiophosgene in carbon disulfide $\langle 67TL1013 \rangle$.

Another type of cyclization involves sulfonamides (**245**) as a three-atom component (Scheme 47). In particular, chloromethanesulfonamide reacts with various electrophilic multiple bonds ($C=O$ or $C=S$), mainly those of heterocumulenes (CS_2 , $RNCS$, $RNCO$, also $ArCOCl$ /pyridine) in basic media to give oxathiazoline or dithiazoline S,S -dioxides (**246**)–(**249**) $\langle 62AG(E)594, 67USP3345374 \rangle$. Under certain conditions the urea (**250**) and aroylsulfonamide (**251**) intermediates, are isolable $\langle 62AG(E)594, 64LA(671)135, 67USP3345374 \rangle$. In the same way, arylalkyne sulfonamides (**245a**), or β -bromostyrene sulfonamides and CS_2 or $RNCS$, afford in strong basic media the alkylidene derivatives (**252**) and (**253**) (Scheme 48) $\langle 78BCJ1805 \rangle$.

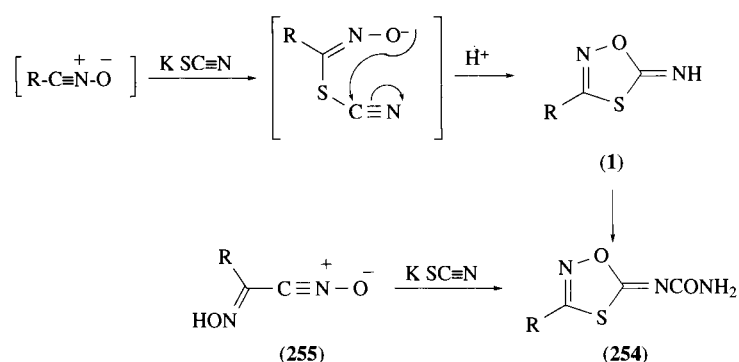


Scheme 47

For the Musante first preparation $\langle 38G331 \rangle$ of 5-imino-oxathiazoline (**1**), involving nitrile oxides and potassium thiocyanate a two-step mechanism is suggested (Scheme 49) $\langle 83JHC301 \rangle$. Other analogous reactions have also been described $\langle 92KGS687 \rangle$. In some instances, the imino compound is unstable and transformed into the carbamoyl derivative (**254**) $\langle 83JHC301 \rangle$, a type of compound which is also obtained from the α -hydroxyiminoacetonitrile oxide (**255**) and $KSCN$ $\langle 91IZV885 \rangle$.



Scheme 48



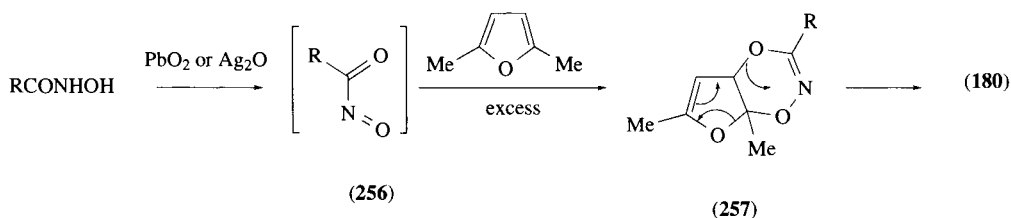
Scheme 49

4.14.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

In this section are included preparative approaches to oxa/thia-2-azole rings carried out by transformation of another heterocyclic ring which have not been reported in the previous sections. The classification of these reactions is in accordance with the ring size of the ring to be transformed.

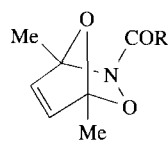
4.14.10.1 From Five-membered Rings

Cycloadditions of the transient acyl nitroso compound (256), obtained by oxidation of hydroxamic acids, with an excess of 2,5-dimethylfuran afford the unstable intermediates (257) which readily rearrange to the *cis*-enones (180). The intermediate (257) may be either the primary adduct, or be produced by a [3,3]-sigmatropic shift from the other possible primary adduct (258) (Scheme 50) <80JCS(P1)2408, 86JOC2351>.

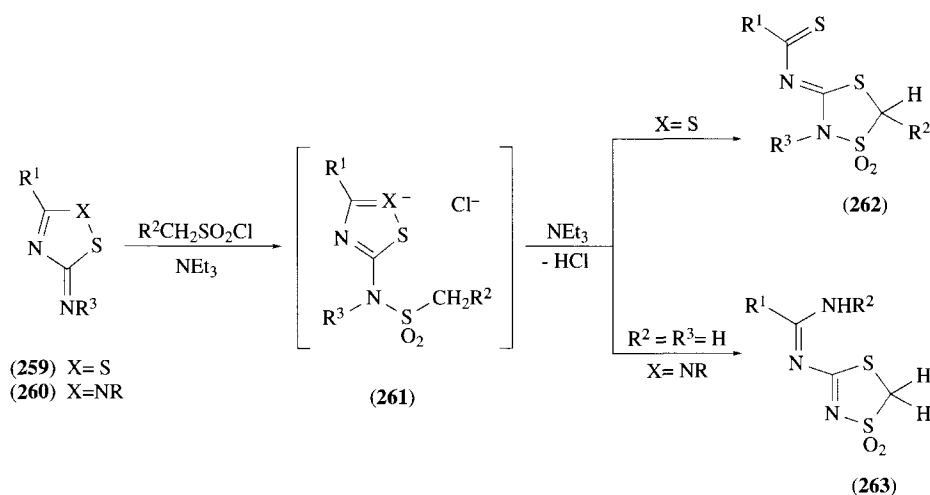


Scheme 50

The dithiazolimines (259) (X = S) or thiadiazolimines (260) (X = NR) are transformed to the sulfonamides (261), which in turn rearrange to the dithiazoline derivatives (262) <77TL1729> or (263) (Scheme 51) <81JHC1309>.

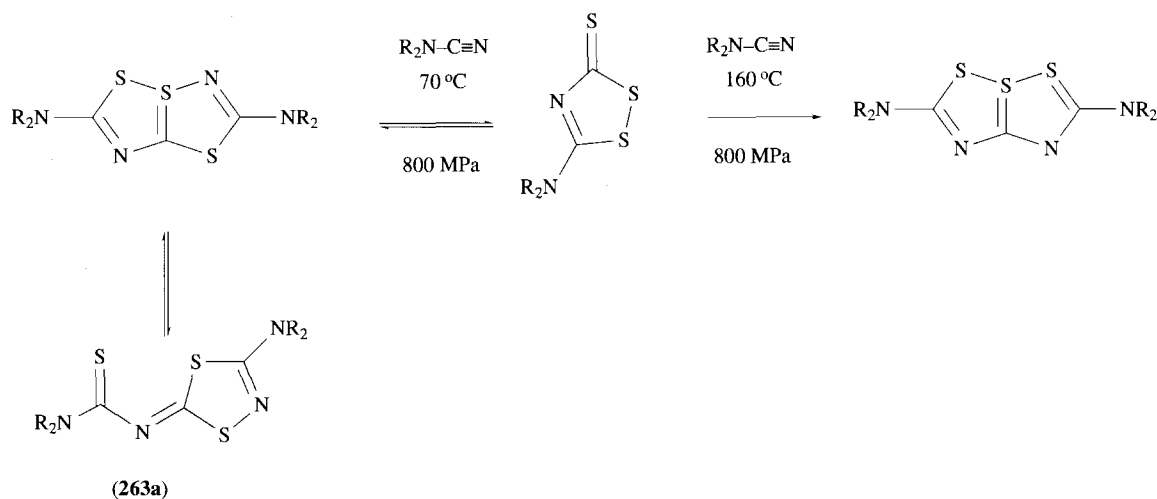


(258)



Scheme 51

Thermally labile 3-dialkylamino-5-dialkylthiocarbamoylimino-1,4,2-dithiazoles (**263a**) are obtained from 3-dialkylamino-1,2,4-dithiazole-5-thiones and dialkylcyanamides under high pressure (Scheme 52) <89CL1357>.

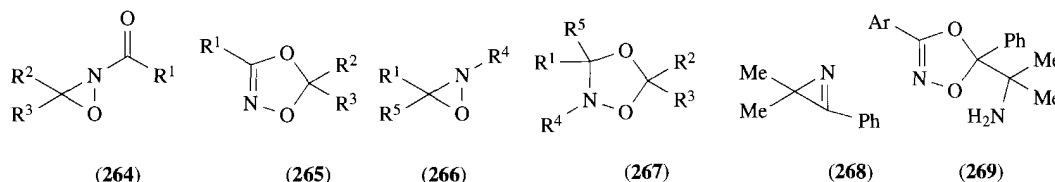


Scheme 52

4.14.10.2 From Three-membered Rings

Thermal rearrangement of N-aryloxaziridines (**264**) affords dioxazolidines (**265**) <65TL1857, 67CB2593, 76TL4325>. The N-perfluoroalkyl oxaziridine derivatives (**266**) are ring opened by ketones and recycled to dioxazolidine derivatives (**267**) <79IZV1788, 82JA4034, 86JOC4466>. It is believed that an oxaziridine intermediate and hexafluoroacetone are involved in the formation of dioxazolidine

derivative (**267**; $R^1, R^2, R^3, R^4, R^5 = CF_3$) <77AG(E)646> from trifluoronitrosomethane and bistrifluoromethyl diazomethane. The reaction of azirine (**268**) with arylhydroxamic acids which affords the dioxazoline derivatives (**269**) should also be noted <81KGS124>.



4.14.11 BEST SYNTHETIC METHODS

As it has been shown, there are many ways to assemble the 1,4-(oxa/thia)-2-azole ring. Most of them are performed by inter- or intramolecular cyclization of suitable acyclic precursors. Some of them are found to be suitable for the synthesis of various ring systems, by using readily available, and properly modified reactants. Of particular importance are the following: (a) the cyclizations of sulfenamides leading to (oxa/thia)azolium salts (Scheme 33); (b) the cyclization of hydroxamic acids (Scheme 39); (c) the dipolar cycloaddition methodology (Scheme 40); (d) the cyclizations of chlorosulphenyl chlorides (Scheme 46); and (e) the cyclizations of chloromethane sulfonamides (Schemes 47 and 48). Other cyclizations reported are preparative ways used mainly for the synthesis of specific compounds and the scope of these reactions has not been widely studied.

Relevant data is tabulated in Tables 8–13 in a similar way to that of CHEC-1. For convenience the arrangement follows the order of the general structures (**4**) to (**16**), taking into account the synthetic methods used in each case.

Table 8 Best synthetic methods for dithiazolium (**5**) and oxathiazolium salts^a (**6**) and (**7**).

Structure type	Ring system		Substituents		Yield (%)	Methods	Ref.
	Y	Z	R ¹	R ²			
(5)	S	S	H	H	50	4.14.7	92JCS(P1)2065
(5)	S	S	H, Alk, Ar	SMe	50–83	4.14.7	92JCS(P1)2065
(5)	S	S	H	1-piperidino	82	4.14.9.1	92JCS(P1)2065
(5)	S	S	Alk, Ar	NR ₂	41–93	4.14.9.1	92BCJ920
(5)	S	S	Alk, Ar	NR ₂	35–60	4.14.9.1	88JCS(P1)899
(5)	S	S	Ar	NR ₂	56–80	4.14.9.1	86BCJ2017
(5)	S	S	Ar	Ar	64–78	4.14.9.1	90BCJ2933
(5)	S	S	NEt ₂	1-pyrrolidino	77	4.14.9.1	88JCS(P1)899
(6)	S	O	Me, Aryl	Ar, SMe	81–99	4.14.7	91TL4329
(7)	O	S	H, Me, Ar	1-piperidino	17–90	4.14.9.1	90TL5935
(7)	O	S	H, Me, Ar	<i>p</i> -MeOPh	19–30	4.14.9	90TL5935

^a As perchlorates or fluoroborates.

4.14.12 APPLICATIONS

A considerable amount of data concerning actual or suggested applications of various types of oxa/thia-2-azoles has appeared mainly in the patent literature. This covers many areas, such as agrochemicals, pharmaceuticals, polymer, and photographic materials, etc. Some derivatives are commercially important with a variety of industrial uses. A brief account is given below.

Table 9 Best synthetic methods for azolinones (8) and azolinethiones (9).

Structure type	Ring system			Substituent, R ¹	Yields (%)	Methods	Ref.
	X	Y	Z				
(8)	O	O	O	Alk	90–92	4.14.9.2	88JOC2674
(8)	O	O	O	Fluoroalkyl	62–86	4.14.9.2	83JOC3845
(8)	O	O	O	1-Hydroxyalkyl	89–93	4.14.9.2	82LA211
(8)	O	O	O	2-Hydroxyalkyl	45–95	4.14.9.2	82LA219
(8)	O	O	O	Ar, Alk	51–90	4.14.9.2	68TL319
(8)	O	S	O	Ar		4.14.9.2	63BEP632072
(8)	O	S	O	Mes	31	4.14.9.3	66JOC2417
(8)	O	O	S	H	58	4.14.9.4	80CB1790
(8)	O	O	S	Alk, Ar	41–84	4.14.9.4	91JCS(P1)183
(8)	O	O	S	CF ₃	15	4.14.9.4	87JFC(36)429
(8)	O	O	S	NMe ₂	75	4.14.9.4	84T681
(8)	O	O	S	Alk	59–75	4.14.9.4	81JCS(P1)2991
(8)	O	O	S	Alk, Ar	30–86	4.14.9.4	78JOC3736 ^a
(8)	O	O	S	Ar	13–85	4.14.9.4	89JCS(P1)1679 ^b
(8)	O	O	S	Ar	72–78	4.14.9.4	87JCS(P1)2339
(8)	O	O	S	Ar		4.14.9.1	85ZOR2578
(8)	O	S	S	H	24	4.14.5.4.1	92JCS(P1)2065
(8)	O	S	S	Me	59	4.14.5.4.1	92JCS(P1)2065
(8)	O	S	S	Ar	45–75	4.14.5.6	67BSF2239
(9)	S	O	O	Ar	74–93	4.14.9.2	68TL319
(9)	S	O	O	Ar		4.14.9.2	72GEP2059990
(9)	S	S	S	H	76	4.14.5.4.2	92JCS(P1)2065
(9)	S	S	S	Me, Ar	76–77	4.14.5.4.2	92JCS(P1)2065
(9)	S	S	S	Ar	21–29	4.14.9.4	85JCS(P1)1205

^a23 examples. ^bVarious phenyl-alken-(yn)-oates.**Table 10** Best synthetic methods for azolinimines (10) and azonylenes (11).

Structure type	Ring system		Substituents on exocyclic N or C			Yield (%)	Methods	Ref.
	Y	Z	R ¹	R ²	R ³			
(10)	O	O	Ar	ArSO ₂		12–14	4.14.9.3	91ZOR1262
(10)	O	O	Ar	ClSO ₂		89	4.14.9.3	91ZOR1262
(10) ^a	O	O	Mes	R ₂ NC ⁺ H(Ph)		51–93	4.14.9.3	89T5825
(10)	S	O	Ar	H		42–93	4.14.9.4	83JHC301
(10)	S	O	Ar	CONH ₂		35–40	4.14.9.4	83JHC301
(10)	S	O	Ph	CONH ₂		64	4.14.9.4	91IZV885
(10)	S	O	2,4-Cl ₂ C ₆ H ₃	SO ₂ Me		78	4.14.9.4	77JAP77148076
(10) ^a	S	O	Ar	Me ₂ NC ⁺ H(Ph)		78–87	4.14.9.3	91CB2537
(10)	S	O	Various	Ts		34–98	4.14.9.3	75T1537
(10)	S	S	Ph	Ar		42–93	4.14.5.4.2	88BCJ4043
(10)	S	S	Ph	NHR		80–87	4.14.5.4.2	88BCJ4043
(10)	S	S	NR ₂	Ar		67–93	4.14.9.2	87CZ339
(11)	O	O	Ph	CF ₃	CF ₃	68	4.14.9.3	70IZV2140
(11)	S	O	Ph	CF ₃	CF ₃	68	4.14.9.3	70JOC3470
(11)	S	O	Ar	CN	CN, CO ₂ Me	56–87	4.14.9.3	66AG1023
(11)	S	O	Ar	H	Ph	33–38	4.14.9.3	84JCR(S)370
(11)	S	S	Ph	CN	Various	45–56	4.14.5.4.5	89BCJ1086
(11)	S	S	Ar	CO ₂ R	CO ₂ R	21–43	4.14.5.4.5	88JCS(P1)899
(11)	S	S	Ph	^b	^b	53	4.14.5.4.5	85CC696
(11)	S	S	Ph	^c	^c	89	4.14.5.4.5	85CC696
(11)	S	S	Ph	CN	CO ₂ Me	45	4.14.5.4.5	87JAP(K)62209069
(11)	S	SO ₂	SMe, RNH	H	Ar	7–63	4.14.4	78BCJ1805

^aAs SbCl₆ salts. ^bR², R³ = —COOC(Me)₂OCO—. ^cR², R³ = —CON(Me)CON(Me)CO—.

Table 11 Best synthetic methods for dioxazoles and dithiazoles (13).

Structure type	Ring system		Substituents			Yield (%)	Methods	Ref.
	Y	Z	R ¹	R ²	R ³			
(13)	O	O	Various	CF ₃	CF ₃	29–75	4.14.9.1	86MI 414-01
(13)	O	O	CF ₃ CH ₂	CF ₃ , CF ₂ Cl	CF ₃ CF ₂ Cl		4.14.9.1	81MI 414-01
(13)	O	O	Ph	Ph	Ph	93	4.14.2	56CLY779
(13)	O	O	Ar	Alk, Ar	Alk, Ar	28–75	4.14.2	67BCJ664
(13)	O	O	Alk, Ar	H	Alk, Ar	21–96	4.14.2	78ZCS7
(13)	O	O	Me, Ph	H, CH ₂ CO ₂ Me	CH ₂ R	15–65	4.14.2	73CJC1368
(13)	O	O	Ph	H	CH ₂ CO ₂ Et	64	4.14.2	86JHC463
(13)	O	O	Ar ₂ P(O)CH ₂	Me, Ph	H	47–75	4.14.9.2	80ZOB1014
(13)	O	O	Various	Ar	Various	41–91	4.14.9.3	72CB2805
(13)	O	O	Mes	^a	^a	5–25	4.14.9.3	76TL83, 86MI 414-02
(13)	O	O	RCO ^c	CF ₃	CF ₃	78–80	4.14.9.3	81JOC316
(13)	O	O	Me, Ph	H	^c	46–78	4.14.9.3	83JHC1505
(13)	O	O	Mes	Ph	^c	49	4.14.9.3	84JCR(S)362
(13)	O	O	Ar	CCl ₃	—NCO	60–80	4.14.9.3	85ZOR910
(13)	O	O	PhC(=NOH)	H, Alk	H, Alk		4.14.9.3	89KGS1426
(13)	O	O	Ar	Ph	^c	9–50	4.14.9.3	91JHC429
(13)	O	O	Ph	Me	Various	11–94	4.14.10	86JOC2351
(13)	O	O	Ar	Ph	CMe ₂ NH ₂	75–78	4.14.10	81KGS124
(13)	O	O	Ar	^d	^d	65–70	4.14.10	65TL1857
(13)	O	O	Ar, Me	Ph	H	48–81	4.14.10	67CB2593
(13)	S	S	Various	H, Ph, O Et	Various	41–83	4.14.5.4.2	90JCS(P1)2465
(13)	S	S	Ph	Ph	Ar, Alk	33–93	4.14.5.4.2	90BCJ2933
(13)	S	S	Aryl	Ar, Alk	Ph, Alk, OEt	10–75	4.14.9.3	91JCS(P1)183
(13)	S	SO ₂ ^e		H	H	20–47	4.14.10	81JHC1309

^aR², R³ = —C(R')=C(R'')CO—. ^bVarious cyclohexyl or adamantyl or dicyclo[2,2,1] substituents. ^c4-(substituted)5H-isoxazolyl. ^dR², R³ = —(CH₂)₅—. ^eR¹ = N⁺=C(R')NHR'.

Table 12 Best synthetic methods for oxathiazoles (13).

Structure type	Ring system		Substituents			Yield (%)	Methods	Ref.
	X	Y	R ¹	R ²	R ³			
(13)	O	S	Ph	Ph	Ph	31	4.14.9.1	74JOC2885
(13)	O	S	Ph	^a	^a	46	4.14.9.1	74JOC2885
(13)	O	S	Alk, Ar	Ph, CCl ₃	H, CCl ₃	18–76	4.14.9.3	81JCS(P1)2991
(13)	O	SO ₂	NHPh	H	H		4.14.9.1	62AG(E)594
(13)	O	SO ₂	Ar	H	H	49–93	4.14.9.1	64LA(671)135
(13)	O	SO ₂	Me	H	H	80	4.14.9.1	75LA1409
(13)	S	O	Ar	Ar	Ar	80	4.14.9.3	71S378
(13)	S	O	Ar	Ar, SR, OR	Ar, SR, OR	31–97	4.14.9.3	72CB2815
(13)	S	O	Ph	SMe	CH=CHAr	45–90	4.14.9.3	73BSF1973
(13)	S	O	Mes	SPh	Ts	Quant.	4.14.9.3	76CB1069
(13)	S	O	Ph	Ph	SiMe ₃	60	4.14.9.3	81CC822
(13)	S	O	Various	^b	^b	78–95	4.14.9.3	84JCS(P1)2641
(13)	S	O	Ph, Alk	OMe	C(S)OMe	42–46	4.14.9.3	86CZ338
(13)	S	O	Mes	H, Alk, Ph	H	27–65	4.14.9.3	85TL5265
(13)	S	O	Mes	Alk	Alk, Ar	32–95	4.14.9.3	88CB1159
(13)	S	O	Mes	CHO, Ph	Ph, PhCO	85–95	4.14.9.3	90JOC4200
(13)	S	O	Ar	Ph	SiMe ₃	81–95	4.14.9.3	90H(31)47
(13)	S	O	Ar, Me	SMe	Ar, SMe	40–94	4.14.9.3	91TL4329
(13)	SO	O	Ph	Ph	Ph		4.14.6.2	72CB2815
(13)	SO	O	Ar	^b	^b	81–87	4.14.6.2	84JCS(P1)2641
(13)	SO	O	Ph	Ar	Ar	50–88	4.14.9.3	77JCS(P1)1468

^aR¹, R² = 2,2'-biphenylene. ^bR¹, R² = adamantanyl residue.

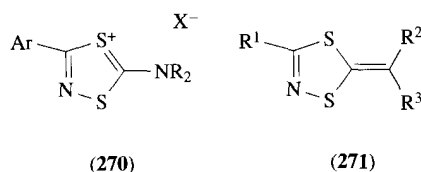
Table 13 Best synthetic methods for various azolidine derivatives (12), (14), (15), and (16).

Structure type	Ring system				Substituents					Yield (%)	Methods	Ref.
	X	Y	Z	W	R ¹	R ²	R ³	R ⁴	R ⁵			
(12)	NPh	O	O	NBu ^t					Bu ^t	33	4.14.9.3	69JOC2269
(12)	NPh	O	S	O					Ph	—	4.14.9.4	70AG(E)54
(14)		O	O	NR ^a		H, Me	Ph, Alk	Bu ^t		26–75	4.14.9.3	86JOC732
(14)		S	S	C(CN)COR		H	COR	Ar		39–57	4.14.9.3 ^f	80JPR(322)407
(14)		O	O	O		H	H	Ph		46	4.14.9.1	78JAP78127479
(15)	C(CF ₃) ₂	S	O		Ar			Me	H	31–90	4.14.9.3	70JOC3470
(15)	^b	S	O		Ph			Me	Ph	22	4.14.9.3	91CB2537
(16)		O	O		^c	^d	^d	Me	^c	53	4.14.9.3	72CZ693
(16)		O	O		F	Me	Alk	CF ₃	F	35–75	4.14.10	86JOC4466
(16)		O	O		CF ₃	Ph	Ph	C(CF ₃) ₃	CF ₃	87	4.14.10	79IZV1788
(16)		O	O		CF ₃	CF ₃	CF ₃	CF ₃	CF ₃	25	4.14.10	77AG(E)646
(16)		S	O		Me	^e		OTBS	H	90	4.14.9.3	84JOC573
(16)		S	O		Me	H	Alk	OTBS	H	73–93	4.14.9.3	83JA6999

^aR = Alkyl or aryl group. ^bX = N⁺ = C(Ph)NMe₂. ^{c,d}R¹, R⁵ and R², R³ = spiroadamantyl residue. ^eR², R³ = (CH₂)₁₁. ^fUnique method.

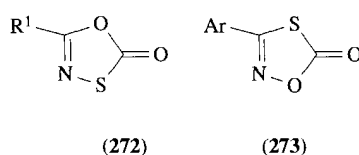
4.14.12.1 Agrochemicals

A number of 1,4-(oxa/thia)-2-azoles like 5-alkylamino-3-aryl-1,4,2-dithiazolium salts (**270**) <86JAP(K)6168480> and dithiazolylene derivatives (**271**) <87JAP(K)62209069> have been patented as useful agrochemicals. For others their suggested applications or activity are specified as detailed below.



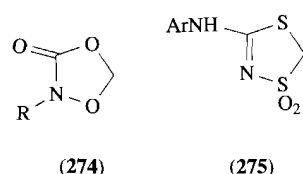
4.14.12.1.1 Fungicides and herbicides

The 1,3,4-oxathiazolones (**272**) have been found to have fungicidal activity <67BRP1079348> and the isomeric 1,4,2-oxathiazolone (**273**) (Ar = Ph) is an effective growth inhibitor against various fungi, e.g. *Corticium rolfsii*, *Phytophthora cactorum* and *Fusarium* species <72GEP2059990>, while the closely related compound (**273**) (Ar = 2,6-Cl₂C₆H₃) shows effective pre-emergent herbicide selectivity controlling raddish, oats, and mustard without damage to cotton wheat and millet <63BEP632072>. Compounds claimed to have the structure (**44**) are reported to have low pre- and post-emergent herbicidal and fungicidal activity <77CCC2680>.



4.14.12.1.2 Insecticides

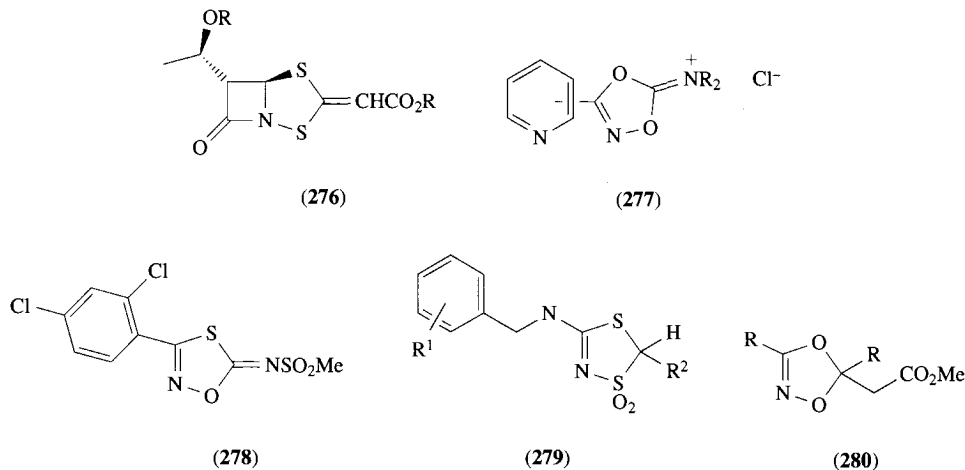
Insecticidal properties are reported for dioxazolidinones (**274**) against *Plutella maculipennis*, *Myzus persicae*, *Nilaparvata lugens*, and *Trivolum confuzum* <78JAP78127479> and for the dithiazolidine S,S-dioxides (**275**) <76GEP2608488> is claimed to control plant-eating insects.



4.14.12.2 Pharmaceuticals

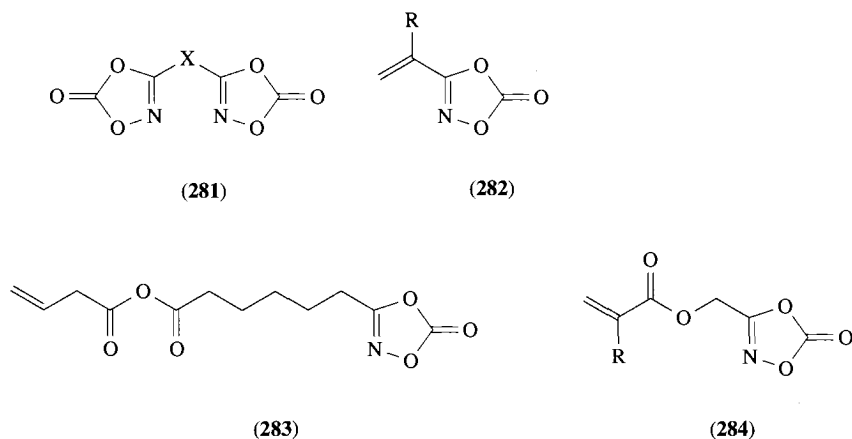
The synthetic penicillins (**185**) are highly effective antibiotics <65USP3222360>. The β -lactams (**276**) are potent inhibitors of human leukocyte elastase (HLE) although devoid of antibacterial activity <91TL3771>. Analgesic effects have been claimed for the dioxazole derivatives (**277**) <85MI 414-02>. The 5-alkylamino-1,4,2-dithiazolium salts (**270**) and the dithiazolylene derivatives (**271**) have been patented as useful pharmaceuticals (no data) <87JAP(K)62209069>, while compound (**278**) is reported to be a useful agricultural antibacterial against *Rhizoctonia solani* and *Venturia inaequalis*.

<77JAP77148076>. Some other oxathiazoline derivatives (**279**) have central nervous system (CNS) activity, as tranquilizers and ataraxics with low toxicity <68SAP6804299> and some dioxazoline derivatives (**280**) have a modest CNS depressant activity <77JPS772>.



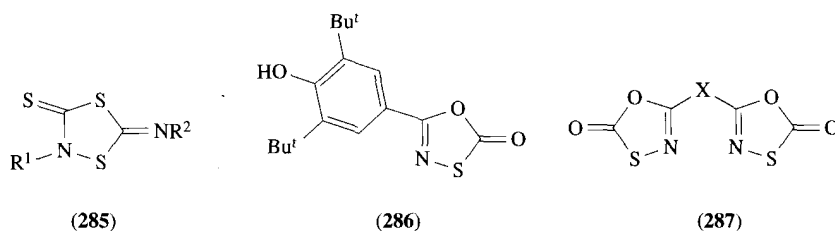
4.14.12.3 Polymer Chemicals

1,3,4-Dioxazol-2-one derivatives, also referred to in the patent literature as nitrile carbonates, are probably the most versatile class of compounds covered in this chapter. They behave as masked isocyanates since on thermolysis lose CO_2 to give various isocyanates (see also Section 4.14.5) which are important industrial polyurethane precursors. An extensive patent literature appeared mainly during the 1970s and focused on preparation (see Section 4.14.9.2), manufacturing and suggested or specified applications. Of particular importance are the bis(dioxazolone) derivatives (**281**) which are widely used monomers for polyurethane industry. Especially the so-called adipodinitrile carbonate (**281**) ($\text{X} = (\text{CH}_2)_4$) <73MI 414-01> has been patented for many applications, e.g. polyurethane coatings <72GEP2220806, 74USP3813365, 74GEP2411258, 75USP3897397, 78USP4075181>, polyurethane foams <74USP3813365, 77USP4021378, 78USP4072634>, thermoplastic polyurethanes <74USP3953387, 76USP306668>, light transparent polyurethane films <74GEP2423191>, epoxy <73MI 414-01>, and crosslinking acrylic resins <74MI 414-01, 76USP306668>, etc. Moreover, analogous suggested applications have been claimed for other bis(dioxazole) derivatives ($\text{X} = \text{various aromatic residues}$) <68FRP1543700, 70GEP1959203, 76USP3946014>. Other particularly interesting dioxazolone derivatives are those having an alkenyl moiety on C-5 (**283**) <84JAP(K)59174672>, (**282**) <79USP4133813> and (**284**) <76GEP2447370>, which may be either homo- or copolymerized to give interesting classes of polymer materials.



4.14.12.4 Other Applications

The 5-alkylamino substituted dithiazolium salts are claimed to be useful cationic dyes and electroconducting materials (no data given) <86JAP(K)6168480, 86JAP(K)6168481> and they have also been patented as anti-fogging agents for color photographic films <89JAP(K)01225940>. The thiones (**126**) and the dithiazolidine (**285**; R^1 , R^2 , R^3 = alkyl, aryl or aralkyl) are also claimed to be highly effective fog inhibitors for high-temperature development of both normal color photographic films and thermally developed photographic materials <88JAP(K)63294555>. The 5-hydroxyaryl-substituted 1,3,4-oxathiazol-2-one derivative (**286**) is suggested as light stabilizer and antioxidant for polypropylenes <88USP4724246> and the bis(oxathiazolone) (**287**) <77GEP2638029> is used in the vulcanization of rubbers.



4.15

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

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4.15.1 INTRODUCTION

The six possible saturated parent five-membered rings containing three oxygen or sulfur atoms in the 1,2,3-positions are shown in Figure 1. 1,2,3-Trioxolane (**1**) is the parent compound of the so-called primary ozonides, the initial products of the reaction of ozone with alkenes. 1,2,3-Trioxolanes are generally extremely unstable, and rearrange to the more stable 1,2,4-trioxolanes (a key step in the ozonolysis reaction), though a handful of compounds, including the parent (**1**), have been detected and characterized at low temperatures (cf. Sections 4.15.3.2, 4.15.3.3 and 4.15.3.5). Simple 1,2,3-trithiolanes have been isolated, though some of these tend to undergo slow decomposition at room temperature. S-Oxides of 1,2,3-trithiolanes are also known. In the case of saturated heterocycles of the mixed types, that is, dioxathiolanes and oxadithiolanes, derivatives of 1,2,3-dioxathiolane (**3**) are unknown, and the others are known only in the form of oxidized derivatives, primarily S-oxides and S,S-dioxides, though S-thiono and S-imino derivatives are also known in the 1,3,2-dioxathiolane series. Of these, the largest group comprises the S-oxides and S,S-dioxides of derivatives of 1,3,2-dioxathiolane, that is, the cyclic sulfite and sulfate esters of 1,2-diols, respectively.

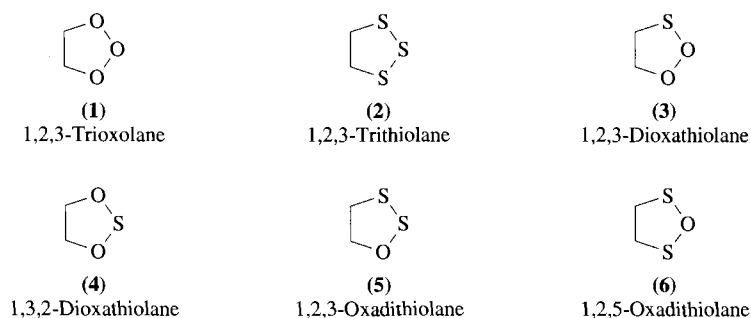


Figure 1 Saturated heterocycles containing oxygen or sulfur atoms in the 1,2,3-positions.

The ring systems covered in this chapter generally cannot form a conjugated aromatic π -electron system; desaturation across the C—C bond of each of the saturated systems (**1**)–(**6**) gives rise to compounds which, if fully conjugated, contain a formally antiaromatic 8π -electron system. Monocyclic and benzo derivatives of 1,2,3-trithiole, 1,3,2-dioxathiole, 1,2,3-oxadithiole and 1,2,5-oxadithiole have been prepared, examples in the mixed series again only being known as S-oxides or related oxidized derivatives. These compounds tend to adopt nonplanar conformations, in keeping with their formal antiaromatic character. Oxidation of these sulfur-containing unsaturated compounds to S,S-dioxides or related compounds removes the possibility for conjugation.

The chemistry of 1,2,3-trioxolanes has been summarized in some recent comprehensive review articles on the ozonolysis reaction <B-84MI 415-01, 92CSR79, B-93MI 415-01>. The chemistry of 1,3,2-dioxathiolane 2-oxides <63CRV557, 66HC(21-1)1, 76CRV747> and the 2,2-dioxides <66HC(21-1)1, B-77MI 415-01> has also been reviewed, though mostly in a wider context.

Significant advances in the chemistry of these ring systems over the past 10 years include the first unambiguous detection, and characterization by microwave spectroscopy as 1,2,3-trioxolane, of the primary ozonide from ethene and ozone (cf. Section 4.15.3.2), and the introduction of 1,3,2-dioxathiolane 2,2-dioxides as epoxide equivalents in organic synthesis (cf. Section 4.15.5.3). Advances have also been made in the synthesis and characterization of the chemistry of 1,2,3-trithiolanes and 1,2,3-trithioles.

The chemistry of the ring systems covered in this chapter tends to be dominated by the three-heteroatom array, rather than by the degree of unsaturation. For this reason the sections on reactivity of conjugated and nonconjugated rings have been combined, in order that the reactivities of the 1,2,3-triheteroatom function can be compared more easily. Also, the methods of synthesis of some of the sulfur-containing compounds are fairly diverse, and many have not been widely exemplified. The sections on synthesis from acyclic precursors and from other heterocyclic rings have therefore been combined, in order that the methods available for the synthesis of specific types of heterocycles be treated together. Tables are provided for the reader who wishes to identify those methods utilizing only acyclic or heterocyclic precursors.

Within each of the following sections, the structural types are discussed in the order in which they are arranged in Figure 1; in each case the heterocycles are treated in the order saturated rings (nonoxidized), saturated rings (oxidized), unsaturated rings (nonoxidized) and unsaturated rings (oxidized).

4.15.2 THEORETICAL METHODS

Theoretical studies on the structure of five-membered rings containing three oxygen or sulfur atoms in the 1,2,3-positions deal primarily with the likely preferred conformations of the various classes of compounds. 1,2,3-Trioxolane (**1**) has received the most study. Like cyclopentane, this compound is treated as undergoing conformational changes by pseudorotation. However, unlike cyclopentane, which does not adopt a single well-defined conformation but undergoes a continuous interconversion by pseudorotation, the introduction of three adjacent oxygen atoms is expected to have a significant effect on the overall energy of the molecule, increasing the likelihood of preferred conformations being adopted by compound (**1**).

Figure 2 shows the possible conformations of 1,2,3-trioxolane (**1**). A recent *ab initio* MP2 study using the 6-31G(d,p) basis set calculated the O-2 envelope form (**1d**), with a folding angle (i.e., the angle between the planes defined by O(3)C(4)C(5)O(1) and O(1)O(2)O(3)) of 52.9°, to be the most stable <89JA2497>; this is in excellent agreement with the conformation recently determined experimentally by microwave studies (cf. Section 4.15.3.2). These MP2 results are consistent with those obtained from earlier *ab initio* calculations, which were obtained using a basis set containing extensive polarization functions <79JCP(70)1898, 79JCP(70)1911>. Such functions are now known to be critical to the success of *ab initio* studies on compounds like 1,2,3-trioxolanes, which contain a linear array of three heteroatoms <89JA2497>; a study using a basis set without polarization functions predicted the half-chair conformer (**1g**) to be the most stable <80CPL489>. Recent semiempirical AM1 calculations also indicate that conformation (**1d**) is the preferred conformation adopted by 1,2,3-trioxolane, and by the *cis* and *trans* isomers of 4,5-dimethyl-1,2,3-trioxolane <91JA735>.

A conformational analysis of the unknown 1,2,3-dioxathiole (**7**) has been carried out using MNDO calculations <91NJC533>. The results indicate that the molecule is likely to adopt a conformation which has O-2, S-3, C-4 and C-5 in a planar arrangement, with the following bond lengths and angles: O-2—S-3, 1.665 Å; S-3—C-4, 1.685 Å; C-4—C-5, 1.369 Å; C-5—O-1, 1.384 Å; O-2—S-3—C-4, 92.8°; S-3—C-4—C-5, 108.5°; C-4—C-5—O-1, 113.5°.

An *ab initio* conformational study of 1,3,2-dioxathiolane 2-oxide (ethylene sulfite) (**8**) using the STO-3G basis set suggests that the molecule adopts a twisted S-2 envelope conformation with the exocyclic oxygen atom of the cyclic sulfite moiety in a pseudoaxial arrangement <81CCC400>. The dihedral angle O(3)C(4)—C(5)O(1) was calculated to be 18°, and the angle between the plane defined by O-1, O-3 and S-2 and the sulfur oxygen substituent was calculated to be 112°. Calculations using semiempirical CNDO/2 techniques gave a similar conformation, with the angle between the plane defined by O-1, O-3 and S-2 and the oxygen substituent on sulfur being calculated as 116° <81CCC400>.

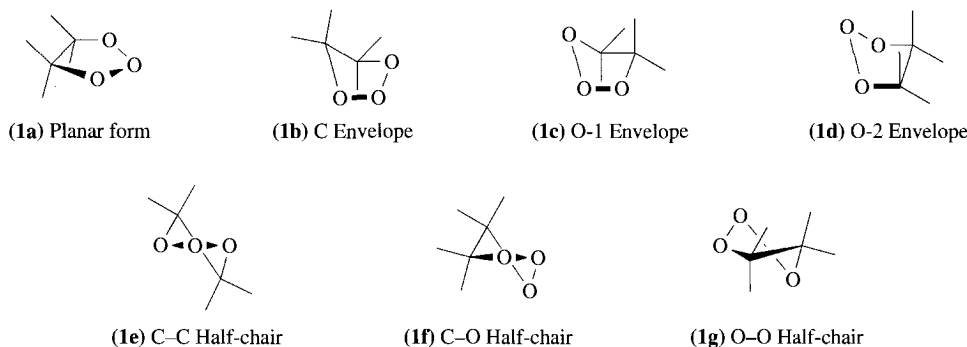
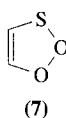
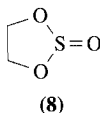


Figure 2 Possible conformations of 1,2,3-trioxolane (1).



and 113.5° $\langle 83\text{MI } 415\text{-}01 \rangle$. These results are compared to the experimentally determined conformations of some simple 1,3,2-dioxathiolanes in Section 4.15.4.2. The charge distribution around the $-\text{O}-\text{SO}-\text{O}-$ moiety of 1,3,2-trioxolane 2-oxide (8) has been calculated by *ab initio* (STO-3G) methods to be 0.98 at S-2, -0.34 at O-1 and O-3 and -0.56 at the $\text{S}=\text{O}$ oxygen atom $\langle 81\text{CCC}400 \rangle$. The corresponding figures from two CNDO/2 studies are 0.75, -0.27 and -0.46 $\langle 81\text{CCC}400 \rangle$, and 0.35, -0.18 and -0.24 $\langle 83\text{MI } 415\text{-}01 \rangle$; reasons for the discrepancies between these sets of results have not been reported. The $\text{S}=\text{O}$ stretching force constant of 1,3,2-dioxathiolane (8) has been calculated to be $11.07 \text{ mdyne}\text{\AA}^{-1}$ (MNDO) and $8.63 \text{ mdyne}\text{\AA}^{-1}$ (PM3) $\langle 92\text{MI } 415\text{-}01 \rangle$.



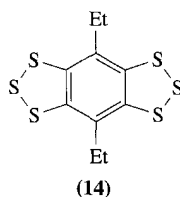
Other theoretical calculations, which have been carried out in association with experimental investigations, are described in the relevant sections below.

4.15.3 EXPERIMENTAL STRUCTURAL METHODS

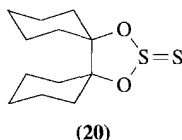
4.15.3.1 X-ray and Electron Diffraction

Bond lengths and bond angles which have been determined for some derivatives of 1,2,3-trithiolane, 1,2,3-trithiole, 1,3,2-dioxathiolane, 1,3,2-dioxathiole and 1,2,5-oxadithiole by x-ray or electron diffraction techniques are summarized in Table 1. X-ray diffraction studies showed that the conformationally restricted *exo* trithiolanes (9) and (10) adopt an S-2 envelope conformation, with dihedral angles $\text{S}(3)\text{C}(4)-\text{C}(5)\text{S}(1)$ of -0.1° and -0.6° , and folding angles of 53.6° and 56.6° , respectively $\langle 79\text{AX}(\text{B})2119, 86\text{AX}(\text{C})332 \rangle$. The related 1,2,3-trithiolane 2-oxide (11), in which the oxide, the central sulfur atom S-2 and the trithiolane ring are all *exo*, is twisted away from the envelope conformation with a dihedral angle $\text{S}(3)\text{C}(4)-\text{C}(5)\text{S}(1)$ of 15.9° $\langle 92\text{AX}(\text{C})2092 \rangle$. The 2-methyl-1,2,3-trithiolanium cation (12) adopts a markedly puckered conformation, with dihedral angles $\text{S}(3)\text{C}(4)-\text{C}(5)\text{S}(1)$, $\text{C}(4)\text{C}(5)-\text{S}(1)\text{S}(2)$ and $\text{C}(5)\text{S}(1)-\text{S}(2)\text{S}(3)$ of -48° , 16.5° and -14.4° , respectively $\langle 90\text{ZAAC}(591)150 \rangle$. In the case of trithioles, x-ray diffraction studies showed that the benzo-trithiole (13) adopts an S-2 envelope conformation with dihedral angles $\text{S}(3)\text{C}(4)-\text{C}(5)\text{S}(1)$ and $\text{C}(4)\text{C}(5)-\text{S}(1)\text{S}(2)$ of -0.6° and -28.4° , respectively $\langle 85\text{JA}3871 \rangle$. Similarly, the benzene bis(trithiole) (14) was shown to adopt a C_2 -symmetrical double S-2 envelope conformation $\langle 89\text{TL}3453 \rangle$. In

contrast, the 7 π -electron 4,5-bis(trifluoromethyl)-1,2,3-trithiolium radical cation (**15**) was shown to be planar $\langle 91CC358 \rangle$.



Gas-phase electron diffraction studies indicated that 1,3,2-dioxathiolane 2-oxide (**8**) adopts a planar, or close to planar, conformation with a pyramidal sulfite moiety $\langle 70DOK(195)1333 \rangle$, whereas the 4,5-dimethyl-1,3,2-dioxathiolane (**16**) adopts a puckered conformation, with dihedral angles $O(3)C(4)-C(5)O(1)$, $C(4)C(5)-O(1)S(2)$ and $C(5)O(1)-S(2)O(3)$ of 41.2° , 34.6° and 14.0° , respectively $\langle 75BSB775 \rangle$. The 1,3,2-dioxathiolane 2-oxides (**17**)–(**19**) have been shown to adopt half-chair conformations, which have the $S=O$ oxygen substituent in a pseudoaxial position, by x-ray diffraction $\langle 84CC262, 90AX(C)1912 \rangle$; increasing stereochemical constraints observed on moving across this series are reflected in the increasing dihedral angles $O(3)C(4)-C(5)O(1)$, 25° , 35° and 39.4° , respectively. Likewise, the 1,3,2-dioxathiolane 2-thioxide (**20**) also adopts a half-chair conformation in which the dihedral angle $O(3)C(4)-C(5)O(1)$ is 37.8° , the $S=S$ sulfur substituent is in a pseudoaxial position and the $S=S$ bond length is $1.901 \text{ \AA}$ $\langle 80CC825 \rangle$.



1,3,2-Dioxathiolane 2,2-dioxide (ethylene sulfate) (**21**) has been shown to adopt a puckered conformation by x-ray diffraction $\langle 68JA2970 \rangle$. Its unsaturated counterpart, 1,3,2-dioxathiole 2,2-dioxide (**22**) (vinylene sulfate), is planar within experimental error $\langle 68JA2970 \rangle$, though the corresponding benzo derivative (catechol sulfate) adopts an S-2 envelope conformation, with the sulfur atom $0.249 \text{ \AA}$ above the plane defined by the aromatic ring and the two oxygen atoms $\langle 69JA6604 \rangle$. X-ray studies showed that the benzannelated 1,2,5-oxadithiole 2,2,5,5-tetroxide (**23**) takes up an O-1 envelope conformation, with a folding angle of 20.4° $\langle 82CSC1643 \rangle$.

4.15.3.2 Microwave Spectroscopy

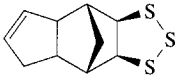
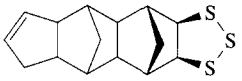
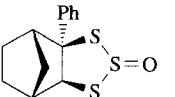
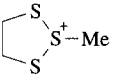
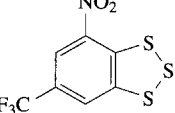
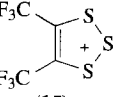
The only heterocycle within the scope of this chapter to have been studied by microwave spectroscopy is 1,2,3-trioxolane (**1**). In the gas phase at -100°C , this compound was shown to adopt an O-2 envelope conformation (**1d**) (Figure 2) with C_s symmetry $\langle 87CPL(139)64 \rangle$, with a folding angle of 50.85° $\langle 88JA7991 \rangle$. This is in excellent agreement with the O-2 envelope conformation with a folding angle of 52.9° , predicted by *ab initio* calculations (cf. Section 4.15.2). Rotational constants, bond lengths and bond angles for 1,2,3-trioxolane (**1**) are summarized in Table 2. The microwave spectra of a series of ^2H , ^{13}C and ^{18}O isotopomers of 1,2,3-trioxolane have also been reported $\langle 88JA7991 \rangle$.

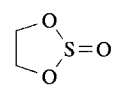
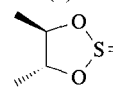
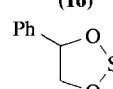
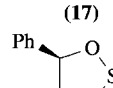
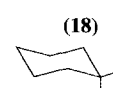
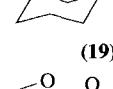
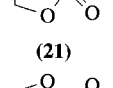
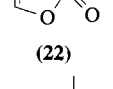
4.15.3.3 NMR Spectroscopy

4.15.3.3.1 Proton NMR spectroscopy

The low-temperature ^1H NMR spectra of symmetrical 4,5-dialkyl-1,2,3-trioxolanes show only one signal for the two vicinal ring protons, with the signal for the *cis* isomer resonating at lower field than that of the *trans* isomer. Thus, in dichlorodifluoromethane solution at -130°C , the ring protons of *cis* 4,5-dimethyl- and *cis* 4,5-diethyl-1,2,3-trioxolane resonate at $\delta 4.52$ and $\delta 4.53$, respectively, whereas the ring protons of the corresponding *trans* isomers resonate at $\delta 4.12$ and $\delta 4.07$, respectively, under the same conditions $\langle 68JOC1629 \rangle$. The spectra of the *cis* and *trans* isomers

Table 1 Structural parameters of derivatives of 1,2,3-trithiolane, 1,3,2-dioxathiolane and 1,2,5-oxadithiolane and some unsaturated counterparts, obtained by x-ray or electron diffraction.

Compound	Bond lengths (Å)					Bond angles (°)					Method ^a	Ref.
	a	b	c	d	e	α	β	γ	δ	ε		
 (9)	2.041	2.049	1.827	1.559	1.833	95.1	93.7	95.2	112.8	113.0	X	86AX(C)332
 (10)	2.046	2.047	1.839	1.572	1.833	94.2	93.4	94.3	112.4	112.6	X	79AX(B)2119
 (11)	2.088	2.090	1.857	1.566	1.810	102.3	92.7	105.8	110.6	115.0	X	92AX(C)2092
 (12)	2.069	2.049	1.798	1.520	1.830	99.7	98.6	94.5	110.7	110.6	X	90ZAAC(591)150
 (13)	2.065	2.071	1.762	1.406	1.777	94.1	95.3	94.3	118.1	117.5	X	85JA3871
 (15)	2.026	2.026	1.710	1.340	1.710	98.8	100.2	98.8	121.0	121.0	X	91CC358

 (8)	1.629	1.629	1.438	1.535	1.438	^b	102.0	^b	^b	^b	E	70DOK(195)1333
 (16)	1.624	1.624	1.434	1.535	1.434	112.3	93.5	112.3	102.4	102.4	E	75BSB775
 (17)	1.634	1.600	1.472	1.510	1.406	113.8	93.6	111.2	103.2	107.8	X	84CC262
 (18)	1.614	1.632	1.451	1.545	1.461	108.6	93.2	113.8	103.5	102.3	X	84CC262
 (19)	1.615	1.616	1.473	1.549	1.483	112.5	94.2	113.4	102.5	101.2	X	90AX(C)1912
 (21)	1.533	1.533	1.459	1.483	1.459	111.5	98.4	111.5	103.7	103.7	X	68JA2970
 (22)	1.616	1.616	1.341	1.305	1.341	110.2	93.6	110.2	113.0	113.0	X	68JA2970
 (23)	1.633	1.613	1.754	1.383	1.747	95.9	117.6	96.2	113.4	113.5	X	82CSC1643

^aX = x-ray diffraction, E = electron diffraction. ^bNot reported.

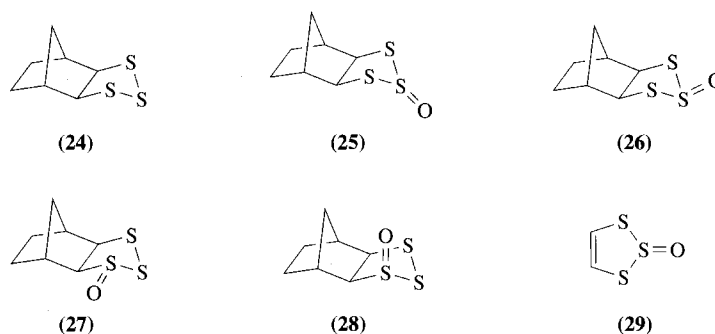
Table 2 Rotational constants, bond lengths and bond angles of 1,2,3-trioxolane, obtained by microwave spectroscopy.

Rotational constants (MHz) ^a		Bond lengths (Å) ^b		Bond angles (°) ^b	
<i>A</i>	8190.22	O—O	1.453	OOO	100.1
<i>B</i>	7541.42	C—O	1.417	COO	102.1
<i>C</i>	4402.31	C—C	1.546	CCO	103.9

^a<87CPL64>. ^b<88JA7991>.

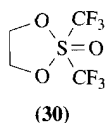
of 4-ethyl-5-methyl-1,2,3-trioxolane are complicated by the lack of symmetry in the molecules, though again the ring protons of the *cis* isomer are observed at lower field (overlapping signals centred at δ 4.35) than the *trans* isomer (overlapping signals centred at δ 4.08) <68JOC1629>.

The simplest 1,2,3-trithiolane for which ¹H NMR data are available is 4-methyl-1,2,3-trithiolane, the ring protons of which resonate at δ 3.30 <88JA7813>. The effects of oxidation on the chemical shifts of 1,2,3-trithiolane ring protons have been studied in the series of norbornane trithiolanes (**24**)–(**28**) <88JA7499>; in CDCl₃ solution the ring protons of the symmetrical parent compound (**24**) and the *endo* and *exo* 2-oxides (**25**) and (**26**) resonate at δ 3.60, δ 4.70 and δ 4.80, respectively, whereas the 4- and 5-protons of the unsymmetrical *endo* and *exo* 1-oxides (**27**) and (**28**) are observed at δ 3.25 and δ 3.95, and δ 3.39 and δ 3.75, respectively. The ¹H NMR spectrum of 1,2,3-trithiole 2-oxide (**29**) consists of a singlet at δ 6.13 in hexadeuterobenzene solution <88RTC440>.



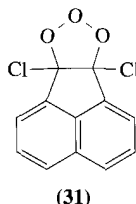
The ¹H NMR spectrum of 1,3,2-dioxathiolane 2-oxide shows two signals at δ 4.45 and δ 4.81 in tetrachloromethane solution <73JCS(P2)243, 75JCS(P2)190, 76CJC1428>. This is due to the compound undergoing a rapid pseudorotation between twist-envelope forms, resulting in the *cis* vicinal ring protons (*H_A*, *H_C*) and the *trans* vicinal ring protons (*H_B*, *H_D*) each becoming magnetically equivalent (Figure 3). Monosubstituted derivatives of 1,3,2-dioxathiolane 2-oxide preferentially adopt the conformation in which the substituent is in an equatorial position. 1,3,2-Dioxathiolane 2,2-dioxide also undergoes a rapid conformational equilibrium analogous to that shown in Figure 3 for 1,3,2-dioxathiolane 2-oxide, though in this case the two conformers form a degenerate pair. Consequently, all the ring protons are magnetically equivalent, and only one sharp line is observed in the ¹H NMR spectrum (CCl₄ solution) at δ 4.68 <61JA2105>. The ¹H NMR spectrum (CDCl₃ solution) of 2,2-bis(trifluoromethyl)-1,3,2-dioxathiolane 2-oxide (**30**) shows a single sharp line at δ 4.25 <93IC3205>. The ¹H NMR spectrum of 1,2,3-oxadithiolane 2-oxide has been interpreted, though no definite conclusions about its geometry in solution could be made <75ACS(A)414>.

**Figure 3** Twist-envelope conformations (Newman projection down C—C bond) for 1,3,2-dioxathiolane 2-oxide (**8**).

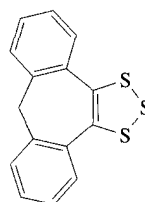
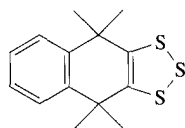
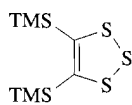


4.15.3.3.2 Carbon-13 NMR spectroscopy

Very little ^{13}C NMR spectroscopic work has been carried out on 1,2,3-trioxolanes due to their extreme instability. The unusually stable example (31) shows a resonance at $\delta 116.39$ (CDCl_3) assigned to the trioxolane ring carbon atoms $\langle 80\text{AG(E)474} \rangle$. In the 1,2,3-trithiolane series, the effects of oxidation on the chemical shifts of trithiolane ring carbon atoms have been investigated in the series of norbornane trithiolanes (24)–(28) $\langle 88\text{JA7499} \rangle$; the ring carbon resonances (CDCl_3 solution) of the symmetrical derivatives (24), (25) and (26) are observed at $\delta 69.70$, $\delta 71.32$ and $\delta 79.70$, respectively, and the 4- and 5-carbons of the unsymmetrical 1-oxides (27) and (28) are observed at $\delta 70.97$ and $\delta 87.10$, and $\delta 59.94$ and $\delta 87.36$, respectively.



The ^{13}C NMR spectrum (CDCl_3) of 4,5-bis(trimethylsilyl)-1,2,3-trithiole (32) shows a singlet at $\delta 145.08$, assigned to the ring carbon atoms $\langle 93\text{BCJ623} \rangle$. The spectra (CDCl_3) of the 1,2,3-trithioles (33) and (34) have not been fully interpreted, though each shows two singlets in the range $\delta 134$ – 142 , one of which can be assigned to the ring carbon atoms of the symmetrical trithiole moiety $\langle 88\text{CL657, 90TL5323} \rangle$. The chemical shifts of the ring carbon atoms of 1,3,2-dioxathiolane 2-oxide (8) and 1,3,2-dioxathiolane 2,2-dioxide are observed at $\delta 67.6$ and $\delta 68.68$, respectively $\langle 88\text{MRC671} \rangle$. Derivatives of (8) monosubstituted at the 4-position or disubstituted at the 4- and 5-positions with methyl or phenyl groups show resonances due to the ring carbon atoms in the range $\delta 70.9$ – 91.0 , whereas the analogous derivatives of 1,3,2-dioxathiolane 2,2-dioxide show corresponding resonances between $\delta 63.86$ and $\delta 95.33$.



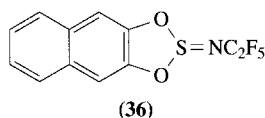
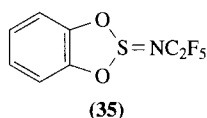
4.15.3.3.3 Oxygen-17 NMR spectroscopy

The oxygen shifts for 1,3,2-dioxathiolane 2-oxides (cyclic sulfites) are deshielded relative to those of the corresponding 2,2-dioxides (cyclic sulfates) due to the large differences in electron density around each of the oxygen atoms in each system. Thus, the ring oxygens (O-1 and O-3) and the exocyclic oxygen ($\text{S}=\text{O}$) of 1,3,2-dioxathiolane 2-oxide resonate at $\delta 155.5$ and $\delta 213.2$, respectively, whereas the corresponding resonances for 1,3,2-dioxathiolane 2,2-dioxide are observed at $\delta 120.5$ and $\delta 155.9$ $\langle 88\text{MRC671} \rangle$. Only one signal is observed for the exocyclic oxygen atoms of simple, conformationally flexible 1,3,2-dioxathiolane 2,2-dioxides, though for more hindered compounds (e.g., *cis*-4,5-dimethyl- and *cis*-4,5-diphenyl-1,3,2-dioxathiolane 2,2-dioxides) two signals are observed, since in these cases complete ring inversion by pseudorotation is not possible.

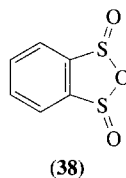
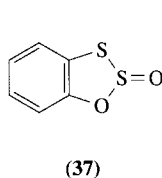
4.15.3.4 Mass Spectrometry

The mass spectral fragmentation patterns of 1,2,3-trithiolanes and 1,2,3-trithioles have not been studied in detail, though loss of S_n units seems to be a common pathway. Thus, 4-methyl-1,2,3-trithiolane gives peaks due to $[S_3]^+$ and $[M-S_3]^+$ ions <88JA7813>, 4,5-bis(trimethylsilyl)-1,2,3-trithiole (32) gives a peak due to a $[M-S_2]^+$ ion <93BCJ623> and the trithiole (34) gives peaks due to $[M-S]^+$, $[M-S_2]^+$ and $[M-S_3]^+$ ions <90TL5323>. Benzotrithioles containing a nitro group at a position adjacent to the trithiole ring show a strong peak for $[M-SO]^+$ fragment ions <80JOC4806>.

In the case of 1,3,2-dioxathiolane 2-oxides, the following fragmentation pathways appear to operate: (i) loss of $C_nH_{2n}O$ units; (ii) a process involving loss of SO_2 which produces daughter ions related to the corresponding epoxide parent ions; (iii) a rearrangement similar to the pinacol rearrangement resulting in the expulsion of SO_2 and formation of a ketone or aldehyde radical ion; (iv) formation of $[M-HSO_2]^+$ species <B-84CHEC-I(4)851>. Pathways (i) and (ii) are typical for simple alkyl and aryl derivatives, respectively. The mass spectra of the 1,3,2-benzodioxathiole 2-*N*-pentafluorethyl imines (35) and (36) show strong peaks for $[M-CF_3]^+$ and $[M-SNC_2F_5]^+$ ions <81JFC(18)357>. 1,3,2-Dioxathiolane 2,2-dioxides fragment differently to 1,3,2-dioxathiolane 2-oxides, their mode of fragmentation depending in a nonspecific way on the substitution pattern <77AJC569>.



The mass spectra of 1,2,3-oxadithiolan-5-one 2-oxide and its 4,4-dimethyl derivative show no trace of a molecular ion <77MI 415-02>. In contrast, 1,2,3-benzoxadithiole 2-oxide (37) shows a strong molecular ion; the principal fragmentation route for this compound is formation of a $[C_5H_4S]^+$ ion, with SO_2 cleavage only taking place to a minor extent <81AG(E)570>. The benzannelated 1,2,5-oxadithiole 2,5-dioxide (38) fragments with loss of SO_2 <83JOC2943>.

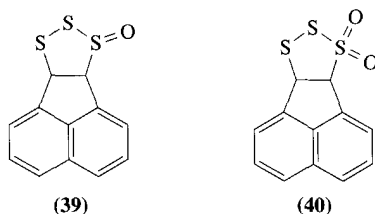


4.15.3.5 IR and Raman Spectroscopy

The IR spectroscopic properties of 1,2,3-trioxolanes can only be studied at very low temperatures due to their extreme instability. By means of isotopic substitution (^{16}O , ^{18}O , ^{13}C , ^2H), the following major bands in the spectrum of the parent compound, 1,2,3-trioxolane (1), obtained in a xenon matrix, were assigned: 409 cm^{-1} (O_3 bend), 647 cm^{-1} (O_3 asymmetric stretch), 727 cm^{-1} (COO bend and CO stretch), 846 cm^{-1} (O_3 symmetric stretch), 927 cm^{-1} (CO stretch), 983 cm^{-1} (CO stretch and CH_2 deformation) and 1214 cm^{-1} (CH_2 deformation) <81JA2578>. While the CO stretching vibrations at 927 cm^{-1} and 983 cm^{-1} are reasonable for single bonds, the symmetric and asymmetric O_3 stretching modes at 647 cm^{-1} and 846 cm^{-1} , respectively, are unusually low for single bonds, consistent with the decomposition of 1,2,3-trioxolane by $O-O$ bond rupture (cf. Section 4.15.4.1). The low-temperature IR spectra of a number of alkyl-substituted 1,2,3-trioxolanes show bands consistent with the assignment of the spectrum of (1) <72JA4856, 79JCS(P2)1644>.

The IR spectrum of the 1,2,3-trithiolane 1-oxide (39) shows an absorption at 1075 cm^{-1} , and the corresponding 1,1-dioxide (40) shows absorptions at 1320 cm^{-1} and 1120 cm^{-1} , assigned to the $-S-SO-$ and $-S-SO_2-$ groups, respectively <92BCJ1188>. The Raman spectrum of liquid 1,3,2-dioxathiolane 2-oxide and its solid-state IR spectrum show all 24 vibrations anticipated for a symmetrical envelope conformation <62CB2333>. The $S=O$ stretching vibration of substituted monocyclic 1,3,2-dioxathiolane 2-oxides (cyclic sulfites) appears in the region $1200-1230\text{ cm}^{-1}$, depending on the nature of the substituents <56JA454, 56JCS1813> and, to a lesser extent, on the solvent and concentration <73JCS(P2)243, 73JCS(P2)1966>. The $S=N$ stretching vibrations of the 1,3,2-benzo-

dioxathiole 2-imines (**35**) and (**36**) appear at 1386 cm^{-1} and 1388 cm^{-1} , respectively $\langle 81\text{JFC}(18)357 \rangle$. Substituted monocyclic 1,3,2-dioxathiolane 2,2-dioxides (cyclic sulfates) show two IR absorption bands due to the $\text{—SO}_2\text{—}$ group in the ranges $1190\text{--}1230\text{ cm}^{-1}$ and $1365\text{--}1401\text{ cm}^{-1}$ $\langle 60\text{JCS}201, 88\text{MRC}671 \rangle$, with the latter absorption occurring at a higher wavenumber ($1416\text{--}1428\text{ cm}^{-1}$) in strained bicyclic 1,3,2-dioxathiolane 2,2-dioxides $\langle 79\text{JA}7510, 82\text{LA}1982 \rangle$.



The benzannulated 1,2,5-oxadithiole 2,5-dioxide (**38**) shows strong S=O stretching absorptions at 1120 cm^{-1} and 1140 cm^{-1} $\langle 81\text{JOC}2691 \rangle$. The related 2,2,5,5-tetroxide (**23**) displays bands at 1390 cm^{-1} (SO_2 asymmetric stretch), 1180 cm^{-1} and 1170 cm^{-1} (both SO_2 symmetric stretch) $\langle 82\text{MI}415-01 \rangle$. The IR spectrum of the latter compound also shows bands at 800 cm^{-1} and 730 cm^{-1} , attributed to ring SOS asymmetric and symmetric stretching vibrations, respectively.

4.15.3.6 UV Spectroscopy

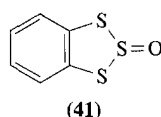
The following UV absorption bands are observed for 4,5-bis(trimethylsilyl)-1,2,3-trithiole (**32**): 249 nm (ϵ , 1960), 279 nm (1937), 363 nm (185) and 492 nm (197) $\langle 93\text{BCJ}623 \rangle$. Similar bands at 255 nm (ϵ , 15600), 305 nm (8600), 372 nm (430) and 477 nm (720) have also been described for the more conjugated fused trithiole (**34**) $\langle 90\text{TL}5323 \rangle$, whereas only a single absorption at 378 nm (ϵ , 110) was reported for the trithiole (**33**) $\langle 88\text{CL}657 \rangle$. 1,2,3-Benzotrithiole 2-oxides show a strong UV absorption band in the range $245\text{--}285\text{ nm}$ ($\epsilon \sim 8000$), assigned to a $\pi \rightarrow \pi^*$ transition of the fused benzenoid ring $\langle 93\text{TL}673 \rangle$.

Alkyl-substituted 1,3,2-dioxathiolane 2-oxides show a weak UV absorption at $213\text{--}218\text{ nm}$, attributed to an $n \rightarrow \pi^*$ transition $\langle 74\text{JOC}2073 \rangle$. In derivatives in which the sulfur atom becomes an asymmetric center, the S=O group possesses chiroptical properties which can be used to gain information about the conformations adopted by these compounds in solution; for example, the CD spectra of both stereoisomers of 4-methyl-1,3,2-dioxathiolane 2-oxide are consistent with each compound adopting a twist-envelope conformation in which the S=O substituent is axial and the methyl group is equatorial $\langle 74\text{JOC}2073 \rangle$. The 1,3,2-dioxathiole 2-oxide chromophore has been reported to show an absorption maximum at 260 nm $\langle 63\text{JOC}1075 \rangle$. A single UV absorption at 272 nm (ϵ , 1600) was observed for the benzannulated 1,2,5-oxadithiole 2,5-dioxide (**38**) $\langle 81\text{JOC}2691 \rangle$.

4.15.3.7 PE Spectroscopy

The vertical ionization potentials of molecules containing adjacent heteroatoms depend strongly on the torsion angles of the neighboring orbitals, thus allowing the conformations of saturated heterocycles containing such groups to be investigated by PE spectroscopy. The PE spectrum of 1,3,2-dioxathiolane 2-oxide (**8**) shows the first band at 10.93 eV to be doubled in intensity, indicating that the first and second ionization potentials are equal in energy $\langle 74\text{CB}2299 \rangle$. This is consistent with an envelope-like conformation, with the S=O substituent axial $\langle 72\text{AG}436 \rangle$.

The PE spectra of 1,2,3-benzotrithiole 2-oxide (**41**) and the related 1,2,3-oxadithiole 2-oxide (**37**) show vertical ionization potentials at 8.73 eV (π), 9.07 eV (π) and 9.90 eV (π , S=O) $\langle 82\text{JOC}1979 \rangle$, and 8.77 eV (π), 9.48 eV (π), 10.14 eV and 10.97 eV $\langle 81\text{AG(E)}570 \rangle$, respectively.



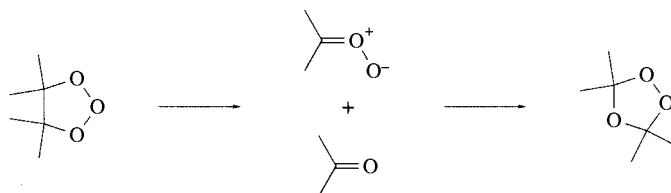
4.15.3.8 Dipole Moments

The gas-phase dipole moment of 1,2,3-trioxolane was determined to be 3.43 D from microwave spectroscopic studies $\langle 88JA7991 \rangle$. This compares with calculated values of 3.90 D and 4.03 D using SCF and MP2 methods, respectively $\langle 89JA2497 \rangle$. The dipole moment of 1,3,2-dioxathiolane 2-oxide has been measured as 3.65 D $\langle 49DOK(69)41 \rangle$ and 3.74 D $\langle 61JA2105 \rangle$ (both in benzene), and that of 1,3,2-dioxathiolane 2,2-dioxide has been determined to be 5.64 D (in dioxane) $\langle 68JHC289 \rangle$. These results are consistent with the compounds adopting nonplanar conformations.

4.15.4 THERMODYNAMIC ASPECTS

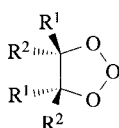
4.15.4.1 Stability

1,2,3-Trioxolanes are generally highly unstable species which fragment rapidly at low temperatures to give a zwitterionic carbonyl oxide and a carbonyl compound; these then recombine to form the more stable 1,2,4-trioxolanes (Scheme 1). This overall conversion is an important step in the mechanism of the ozonolysis reaction, which is discussed in more detail in Chapter 4.16 and has been the subject of some detailed reviews $\langle B-84M1\ 415-01, B-93M1\ 415-01 \rangle$. For unsymmetrically substituted 1,2,3-trioxolanes, two modes of fragmentation are possible, giving rise to different carbonyl oxides. Furthermore, if the carbonyl oxide bears different substituents, then *syn* and *anti* stereoisomers may be formed. Thus, fragmentation of a 1,2,3-trioxolane can lead to the formation of up to four carbonyl oxides and two carbonyl compounds. The low-temperature decomposition of 1,2,3-trioxolanes has been studied by IR $\langle 79JCS(P2)1644 \rangle$ and ^1H NMR $\langle 84JOC4465 \rangle$ spectroscopy; rate constants for the decomposition of some symmetrical 1,2,3-trioxolanes are summarized in Table 3. The only 1,2,3-trioxolane stable enough to be isolated at room temperature is the fused derivative, (31) $\langle 80AG(E)474 \rangle$, though the *cis* and *trans* isomers of 4,5-bis(chloromethyl)-1,2,3-trioxolane have also been reported to be relatively stable $\langle 83JCS(P1)1319 \rangle$.



Scheme 1

Table 3 Rate constants for the decomposition of 1,2,3-trioxolanes, determined by IR and NMR spectroscopy.

						
R^1	R^2	Solvent	Temperature (°C)	Method ^a	k (s ⁻¹)	Ref.
Et	H	CS ₂	-99.6	I	1.58×10^{-4}	79JCS(P2)1644
Pr ⁱ	H	CS ₂	-99.1	I	6.02×10^{-5}	79JCS(P2)1644
Bu ^t	H	CS ₂	-82.6	I	1.00×10^{-5}	79JCS(P2)1644
Me	Me	CD ₂ Cl ₂	-101.8	N	0.217	84JOC4465

^aI = IR spectroscopy, N = ^1H NMR spectroscopy.

The mechanism of the dissociation of 1,2,3-trioxolanes to carbonyl oxides and carbonyl compounds has been studied by theoretical methods. Earlier *ab initio* calculations concluded that a biradical pathway and a concerted pathway were equally probable $\langle 81JA3619, 81JA3627 \rangle$, though it has been suggested that the transition state was not sufficiently characterized in these calculations to enable firm conclusions to be drawn from this work $\langle 91JA735 \rangle$. More recent semiempirical AM1

calculations indicated that the reaction proceeds by a concerted [3 + 2] cycloreversion pathway <91JA735>.

Simple 1,2,3-trithiolanes are unstable (though not sufficiently so to preclude their isolation and characterization) but their mode of decomposition seems to vary depending on the substitution pattern. Thus, 4-methyl-1,2,3-trithiolane decomposes to a compound having a molecular weight of 212 at temperatures above 0°C <88JA7813>, whereas 4-ethyl-1,2,3-trithiolane polymerizes at room temperature to compounds having molecular weights of 300 000 or more <77MM718>. Bicyclic 1,2,3-trithiolanes such as **(9)** and **(24)** are more stable, though they readily polymerize upon heating <80PS(9)227> or on treatment with nucleophiles, such as sodium benzenethiolate <84MI 415-01>.

4.15.4.2 Conformational Analysis

With the exception of 1,3,2-dioxathiolane derivatives, the conformations of heterocycles within the scope of this chapter have been investigated by a single method, and the results have already been summarized in Section 4.15.3. The experimentally determined conformations for examples of the following heterocycles are discussed in the sections indicated: 1,2,3-trioxolane (Section 4.15.3.2), 1,2,3-trithiolane (Section 4.15.3.1), 1,2,3-trithiole (Section 4.15.3.1), 1,3,2-dioxathiole (Section 4.15.3.1) and 1,2,5-oxadithiole (Section 4.15.3.1). In the case of 1,2,3-trioxolane, the experimentally determined O-2 envelope conformation was found to be in excellent agreement with that calculated using *ab initio* and AM1 methods (Section 4.15.2). *Ab initio* calculations indicate that the barrier to pseudorotation of the O-2 envelope conformation (**1d**) (Figure 2) of 1,2,3-trioxolane is ca. 3.6 kcal K⁻¹ mol⁻¹, with a higher barrier of 7.7 kcal K⁻¹ mol⁻¹ to inversion through the planar form (**1a**) (Figure 2) <79JCP(70)1898, 83IJ72>.

The conformations of 1,3,2-dioxathiolane 2-oxide (ethylene sulfite) (**8**) and substituted derivatives have been studied by various techniques. In the solid state, the IR spectrum of (**8**) indicates that the compound adopts a symmetrical S-2 envelope conformation (Section 4.15.3.5). The Raman spectrum of this compound in the liquid phase is also indicative of a symmetrical S-2 envelope conformation (Section 4.15.3.5). In solution, however, the ¹H NMR spectra of 1,3,2-dioxathiolane 2-oxide and its alkyl substituted derivatives are consistent with the compounds undergoing a rapid pseudorotation between twist-envelope forms (Section 4.15.3.3.1); the solution-phase UV spectra of alkyl-substituted 1,3,2-dioxathiolane 2-oxides also indicate twist-envelope conformations in which the S=O substituent is axial (Section 4.15.3.6). In agreement with these solution phase findings, the dipole moment of 1,3,2-dioxathiolane 2-oxide is consistent with a nonplanar conformation (Section 4.15.3.8). In the gas phase, electron diffraction studies indicated that 1,3,2-dioxathiolane 2-oxide (**8**) is planar, or close to planar, whereas the 4,5-dimethyl-1,3,2-dioxathiolane (**16**) adopts a puckered conformation (Section 4.15.3.1). Overall, these experimental results suggest that 1,3,2-dioxathiolane 2-oxide and its derivatives are conformationally mobile, with the conformation adopted being dependent on the physical state of the sample, and, for substituted compounds, on the level and nature of substitution. The lowest energy conformation of 1,3,2-dioxathiolane 2-oxide calculated by *ab initio* methods is a twisted S-2 envelope with the S=O substituent pseudoaxial and a dihedral angle C(3)O(4)—C(5)O(1) of 18° (Section 4.15.2). However, the calculated energy difference between this conformation and the symmetrical S-2 envelope (with a dihedral angle C(3)O(4)—C(5)O(1) of 0°) is only 2.4 kcal mol⁻¹ <81CCC400>, and thus these theoretical results are largely consistent with the experimentally observed conformational effects. For 1,3,2-dioxathiolane 2-oxide (**8**), the barrier to inversion at sulfur has been calculated to be ca. 43 kcal mol⁻¹ <81CCC400>.

1,3,2-Dioxathiolane 2,2-dioxide (**21**) adopts a puckered conformation in the solid state, as shown by x-ray diffraction (Section 4.15.3.1). In solution, the ¹H NMR spectrum of (**21**) indicates that the compound undergoes a rapid pseudorotation between twist-envelope forms (Section 4.15.3.3.1); the ¹⁷O NMR spectra of simple derivatives also indicate a rapid conformational equilibrium by pseudorotation, although substitution may act as a barrier to complete ring inversion (Section 4.15.3.3.3). The solution-phase dipole moment of 1,3,2-dioxathiolane 2,2-dioxide is consistent with a nonplanar conformation (Section 4.15.3.8).

4.15.4.3 Thermodynamic Properties

The enthalpy of formation of 1,2,3-trioxolane at 25°C has been estimated to be -23.9 kcal mol⁻¹ by comparison of the enthalpies of formation for cyclopentane, tetrahydrofuran, and 1,2-dioxolane

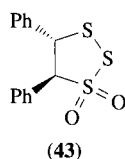
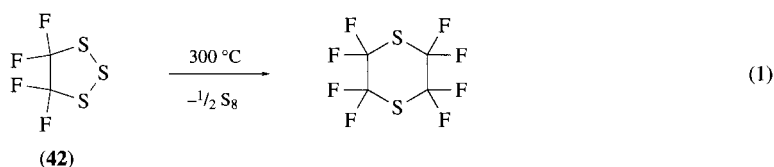
with those for related aliphatic compounds <92MI 415-02>. Some estimated values for the ideal gas thermodynamic properties for 1,2,3-trioxolane at different temperatures have been reported <92MI 415-02>.

4.15.5 REACTIVITY OF RINGS (CONJUGATED AND NONCONJUGATED)

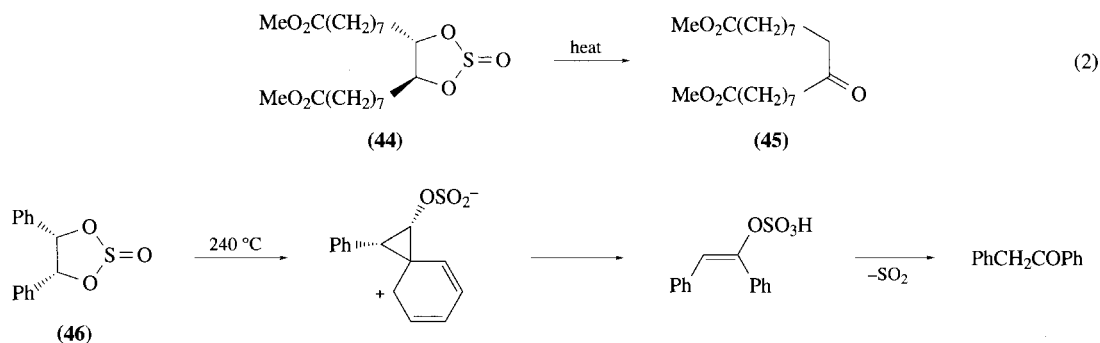
4.15.5.1 Thermal and Photochemical Reactions Formally Involving No Other Species

4.15.5.1.1 Thermolysis

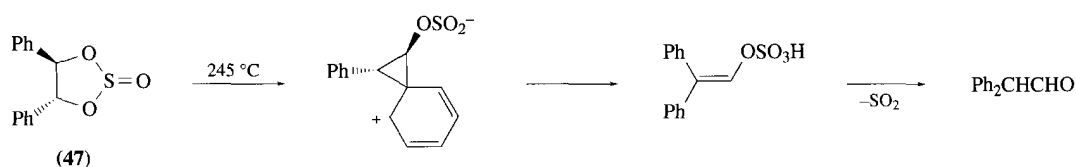
The dissociation of 1,2,3-trioxolanes to carbonyl oxides and carbonyl compounds (and hence to 1,2,4-trioxolanes) has been discussed in Section 4.15.4.1. 1,2,3-Trithiolanes do not undergo a similar thermal rearrangement to 1,2,3-trioxolanes, simple examples tending to decompose or polymerize at ambient temperatures (cf. Section 4.15.4.1). At elevated temperatures they decompose with loss of sulfur; for example, tetrafluoro-1,2,3-trithiolane (**42**) afforded octafluoro-1,4-dithiane upon heating (Equation (1)) <62JOC3995>, and *trans*-4,5-diphenyl-1,2,3-trithiolane 1,1-dioxide (**43**) decomposed on melting with loss of sulfur and sulfur dioxide to afford stilbene <68JCS(C)1612>. Thermolysis of benzotrithiole 2-oxide (**41**) proceeded with extrusion of sulfur monoxide to afford the transient species, benzodithiete, which was detected by PE spectroscopy <82JOC1979>.



The thermolysis of 1,3,2-dioxathiolane 2-oxides is characterized by the elimination of sulfur dioxide. Thus, when heated at 275 °C on calcium oxide, 4,5-dimethyl-1,3,2-dioxathiolane 2-oxide (a mixture of *cis* and *trans* isomers) afforded a mixture of 2-butanone and 2,3-dimethyloxirane <B-66MI 415-01>. Since thermolysis of the related *trans*-1,3,2-dioxathiolane 2-oxide (**44**) only produced the product (**45**) arising from a pinacol-like rearrangement (Equation (2)) <83AQ52>, it may be that in the thermolysis of 4,5-dimethyl-1,3,2-dioxathiolane 2-oxide the *trans* isomer produced 2-butanone, whereas the *cis* isomer gave 2,3-dimethyloxirane. Thermolysis of isomeric 4,5-diphenyl-1,3,2-dioxathiolane 2-oxides (**46**) and (**47**) also gives rise to different products, which have been rationalized on the basis of the involvement of bridged phenonium intermediates (Schemes 2 and 3) <66HC(21-1)1>. Thermolysis of tetraphenyl-1,3,2-dioxathiolane 2-oxide afforded tetraphenyloxirane in virtually quantitative yield <72JOC2589>.

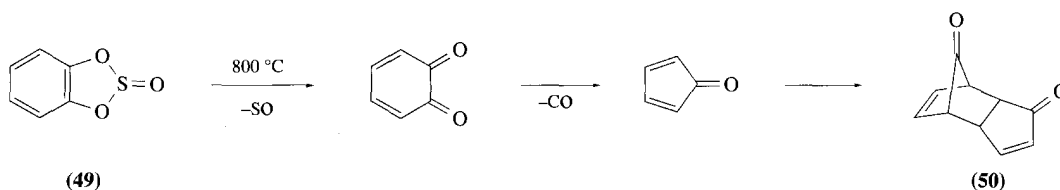
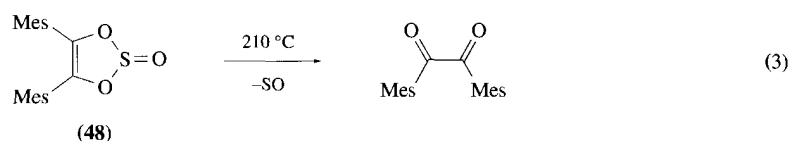


Scheme 2

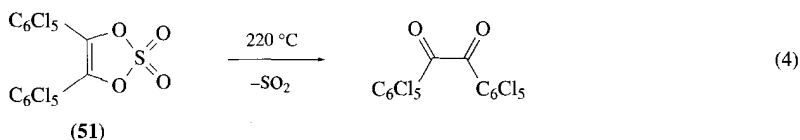


Scheme 3

Thermolysis of the 1,3,2-dioxathiolane 2-oxide (**48**; Mes = 2,4,6-trimethylphenyl) proceeded with loss of sulfur monoxide, affording the 1,2-diketone (Equation (3)) <63JOC1075>. Similarly, 1,3,2-benzodioxathiolane 2-oxide (**49**) underwent an initial loss of sulfur monoxide on thermolysis, in a process which ultimately affords the dimeric product (**50**) (Scheme 4) <67TL271>. The perchlorodiphenyl-1,3,2-dioxathiolane 2,2-dioxide (**51**) underwent loss of sulfur dioxide on thermolysis, affording perchlorobenzil (Equation (4)) <86JOC1100>.



Scheme 4



Flash vacuum thermolysis of 1,2,3-oxadithiolane 2-oxide has been reported to proceed via the intermediacy of 1,2-oxathietan <82JCS(P2)279>. The gas-phase thermolysis of 1,2,3-benzoxadithiole 2-oxide (**37**) proceeds in an analogous manner to the thermolysis of 1,3,2-benzodioxathiolane 2-oxide (**49**), affording cyclopentadienethione <81AG(E)570>.

4.15.5.1.2 Photolysis

Three types of photoextrusion reactions have been identified in the irradiation of aryl-substituted 1,3,2-dioxathiolane 2-oxides: [5 → 1 + 2 + 2] cycloelimination to produce a carbonyl compound, a carbene and sulfur dioxide; extrusion of sulfur dioxide accompanied by a pinacol-like rearrangement to yield an aldehyde or ketone; and extrusion of sulfur trioxide to give an alkene <72JOC2589>. Sensitization and quenching experiments indicate that a singlet state is responsible for the cycloelimination reaction, whereas the rearrangement and sulfur trioxide extrusion reactions arise from a triplet state <82JCR(S)175>.

4.15.5.1.3 Polymerization

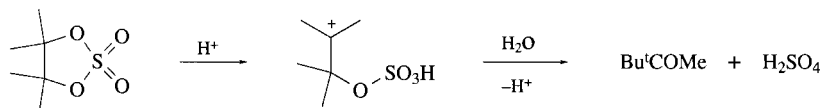
It has been suggested that the oligomers and polymers formed in the ozonolysis reactions of some alkenes arise from the reactive 1,2,3-trioxolane intermediates or their fragmentation products (cf. Section 4.15.4.1) <B-84CHEC-I(4)851>, though relatively little is known about the mode of formation of many of these polymeric species. The tendency of simple 1,2,3-trithiolanes to polymerize has

been described in Section 4.15.4.1. 1,3,2-Dioxathiolane 2-oxides polymerize in the presence of catalytic amounts of bases, such as dialkylanilines or pyridines, though at elevated temperatures these polymers depolymerize back to the corresponding monomers <57USP2798877, 61ZOB1332>.

4.15.5.2 Reactions with Electrophiles

4.15.5.2.1 Reactions involving protons or Lewis acids

Bridged bicyclic 1,2,3-trithiolanes such as (9), (10), and (24) react with K_2PtCl_4 or $trans-[(PhCN)_2PdCl_2]$ to afford the complexes $trans-[(trithiolane)_2PtCl_2]$ and $[(trithiolane)PdCl_2]_2$, respectively, in which the trithiolane moieties are attached to the metal through the sulfur-containing ring <79JCR(S)251>. Photochemical reaction of 1,3,2-dioxathiolane 2-oxide with $MnCp(CO)_3$ or $Cr(CO)_6$ gave metal complexes in which the heterocycle replaces one carbon monoxide unit, with the sulfur atom functioning as the electron donor <65CB2248>. On heating in aqueous acid, tetramethyl-1,3,2-dioxathiolane 2,2-dioxide afforded pinacolone (Scheme 5) <74JOC3415>.

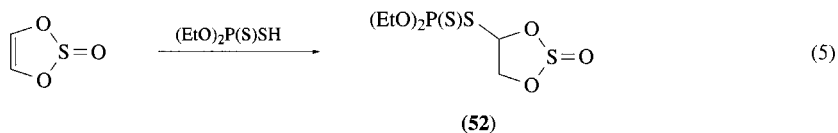


Scheme 5

Acid catalyzed reactions with nucleophiles will be dealt with in Section 4.15.5.3.

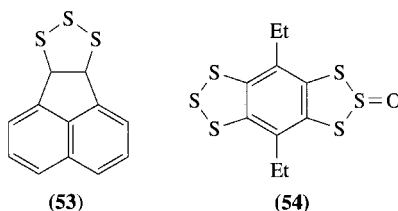
4.15.5.2.2 Electrophilic addition at double bonds

Electrophilic addition of *O,O*-diethyl dithiophosphate to the double bond of 1,3,2-dioxathiole 2-oxide afforded the dithiophosphate (52) (Equation (5)) <62USP3053852>.



4.15.5.2.3 Oxidation without ring cleavage

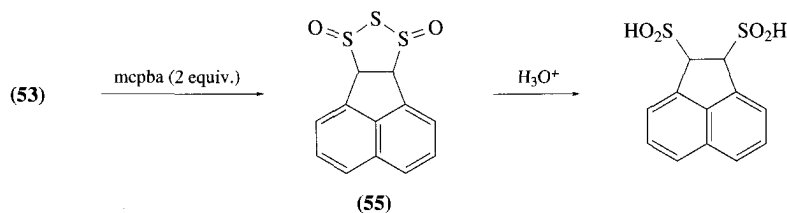
The products arising from oxidation of 1,2,3-trithiolanes are dependent on the oxidant used and on the substrate. Thus, oxidation of norbornane trithiolane (24) with 1 equivalent of *m*-chloroperoxybenzoic acid afforded a mixture of the monoxides (25), (27) and (28), in which the symmetrical 2-oxide (25) was predominant <88JA7499>, whereas oxidation of the 1,2,3-trithiolane (53) using the same reagent gave only the 1-oxide (39) <92BCJ1188>. Oxidation of the trithiolane (53) or its 1-oxide (39) with *N*-bromosuccinimide/water yielded the 1,1-dioxide (40) <92BCJ1188>. The use of ozone as an oxidant in the case of the trithiolane (24) resulted in the formation of the *endo* and *exo* 2-oxides, (25) and (26), respectively <88JA7499>. The oxidation of the benzobis(trithiole) (14) using *m*-chloroperoxybenzoic acid afforded the mono 2-oxide (54) <93TL673>.



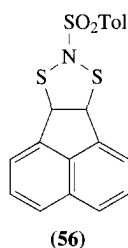
The most widely used method for the oxidation of 1,3,2-dioxathiolane 2-oxides to the corresponding 2,2-dioxides is the recently developed ruthenium tetroxide oxidation, which is normally carried out using a catalytic amount of ruthenium trichloride with sodium periodate as the reoxidant <88JA7538, 93ACS307>. This method is favored due to the wide range of substituents which are tolerated under the mild reaction conditions <89TL655>, though the transformation may also be effected using other oxidants, for example calcium permanganate <63CRV557>, potassium permanganate <90JOC1211> or oxone <92JMC2113>. Oxidation of diastereomeric 1,3,2-dioxathiolane 2-oxides with ^{17}O -labeled ruthenium tetroxide showed that the oxidation proceeds with retention of configuration at sulfur <83CC1392>.

4.15.5.2.4 Oxidation with ring cleavage

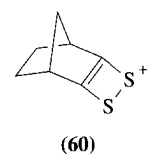
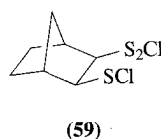
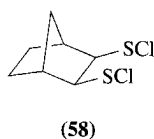
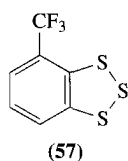
Treatment of the 1,2,3-trithiolane (**53**) with 2 equivalents of *m*-chloroperoxybenzoic acid afforded 1,2-acenaphthalenedisulfinic acid; the same product was obtained from the *m*-chloroperoxybenzoic acid oxidation of the corresponding 1-oxide (**39**) <92BCJ1188>. The formation of this product is rationalized as proceeding through the 1,2,3-trithiolane 1,3-dioxide intermediate (**55**), itself formed by reaction of the most electron-rich sulfur atom S-3 of the trithiolane 1-oxide (**39**) with the strongly electrophilic oxidant (Scheme 6). Oxidation of trithiolane (**53**) with chloramine-T afforded a low yield of the 1,3,2-dithiazolidine (**56**), the reaction being presumed to proceed via the intermediacy of a 1,2,3-trithiolane sulfilimine <92BCJ1188>. Treatment of norbornane 1,2,3-trithiolane with elemental sulfur sets up an equilibration reaction with the corresponding pentathiepane (Scheme 7) <87JOC4937>; a similar equilibrium reaction has also been reported for the 1,2,3-benzotrithiole (**57**) <85JA3871>. Chlorination of norbornane 1,2,3-trithiolane afforded the bis(sulfonyl) chlorides (**58**) and (**59**) <91PS(62)127>. Solvolysis of norbornane 1,2,3-trithiolane in sulfuric acid afforded a solution in which the dithiete radical cation (**60**) was reportedly detected by ESR spectroscopy <85JA4175>, although it has been suggested that the structure of this product may actually be a 1,2,3-trithiolium radical cation <91CC358>.



Scheme 6



Scheme 7

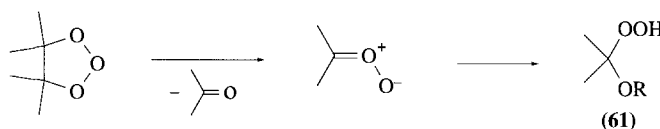


Electrophilic chlorination of 1,3,2-dioxathiolane 2-oxides gives rise to ring-opened products; for example, chlorination of 1,3,2-dioxathiolane 2-oxide afforded 2-chloroethyl chlorosulfate $\langle 67\text{JCS}(C)314 \rangle$.

4.15.5.3 Reactions with Nucleophiles

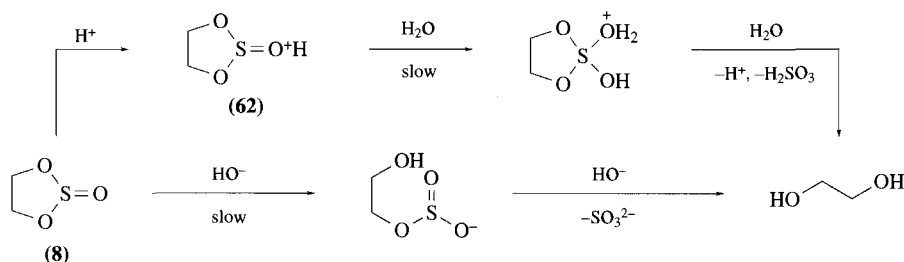
4.15.5.3.1 O-Nucleophiles

Generation of a 1,2,3-trioxolane (by reaction of an alkene with ozone) in the presence of an alcohol leads to the formation of an α -alkoxyalkyl hydroperoxide (**61**), the product arising by reaction of the alcohol with the carbonyl oxide formed by cycloreversion of the 1,2,3-trioxolane (Scheme 8) (cf. Section 4.15.4.1) $\langle 75\text{AG}765 \rangle$. Analogous products have been obtained from the addition of acetic acid or hydrogen peroxide to the carbonyl oxide $\langle 75\text{AG}765 \rangle$, whereas addition of water leads to unstable α -hydroxyalkyl hydroperoxides which decompose either to carboxylic acids and water, or to carbonyl compounds and hydrogen peroxide $\langle \text{B-}72\text{MI } 415\text{-}01 \rangle$.



Scheme 8

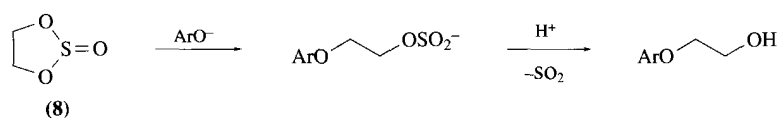
Hydrolysis of 1,3,2-dioxathiolane 2-oxides normally occurs by nucleophilic attack at sulfur followed by S—O bond cleavage, giving rise to 1,2-diols with retention of configuration $\langle 63\text{CRV}557, 76\text{CRV}747 \rangle$. The mechanism of hydrolysis of 1,3,2-dioxathiolane 2-oxide (**8**) has been studied in detail; the rate-determining step of the perchloric acid catalyzed hydrolysis is the addition of water to the conjugate acid (**62**) to give a tetracoordinate intermediate which undergoes rapid ring cleavage, whereas the rate-determining step of the alkaline hydrolysis involves attack of hydroxide ion at sulfur, which is accompanied by ring cleavage (Scheme 9) $\langle 76\text{CRV}747 \rangle$.



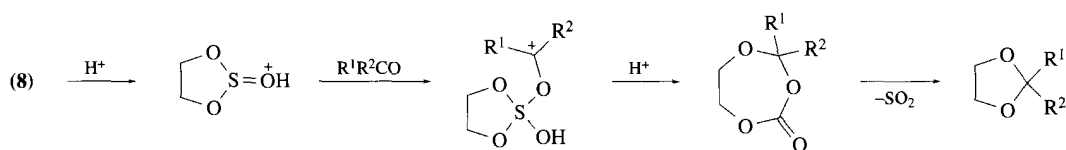
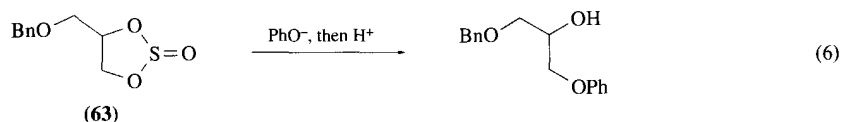
Scheme 9

Reaction of 1,3,2-dioxathiolane 2-oxides with sodium alkoxides occurs exclusively by nucleophilic attack at sulfur. Reaction of sodium methoxide with (**8**) afforded, among other products, oxirane and sodium methyl sulfite $\langle 76\text{CRV}747 \rangle$, whereas reaction with the substituted derivative (**44**) yielded the corresponding 1,2-diol with retention of configuration $\langle 83\text{AQ}52 \rangle$. In contrast, phenolates react with (**8**) predominantly at carbon to give aryloxyethyl sulfites, which are easily converted to aryl 2-hydroxyethyl ethers (Scheme 10) $\langle 63\text{CRV}557 \rangle$. In the case of the substituted 1,3,2-dioxathiolane 2-oxide (**63**), nucleophilic attack by phenoxide ion occurred exclusively at the less hindered carbon atom (Equation (6)) $\langle 93\text{ACS}617 \rangle$. 1,3,2-Dioxathiolane 2-oxide (**8**) undergoes an acid-catalyzed reaction with carbonyl compounds, which can formally be regarded as a nucleophilic attack at the sulfur atom of the conjugate acid of (**8**) by the oxygen atom of the carbonyl compound, to give 1,3-dioxolanes $\langle 66\text{HC}(21\text{-}1)1 \rangle$. A mechanism involving a seven-membered intermediate has been postulated (Scheme 11), although in the presence of trace amounts of water, the intermediate formation

of 1,2-dihydroxyethane and subsequent reaction with the carbonyl compound cannot be ruled out <66BCJ1785>.

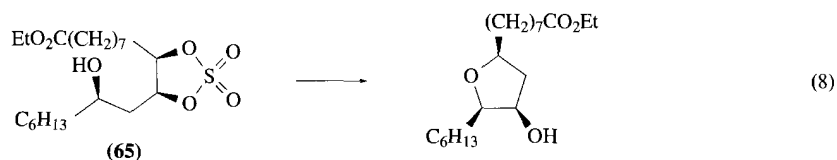
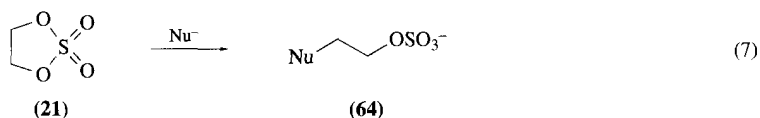


Scheme 10

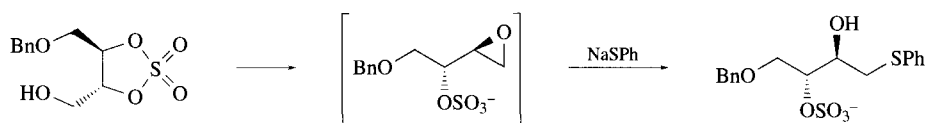


Scheme 11

In contrast to 1,3,2-dioxathiolane 2-oxides, the hydrolysis of 1,3,2-dioxathiolane 2,2-dioxides proceeds predominantly by nucleophilic attack at carbon, except under strongly alkaline conditions when a small amount of S—O bond fission is also observed <B-77MI 415-01>. 1,3,2-Dioxathiolane 2,2-dioxides are powerful alkylating agents towards nucleophiles <88JA7538, 89TL655>; reaction of 1,3,2-dioxathiolane 2,2-dioxide (**21**) with carboxylates, phenolates, or pyridine *N*-oxide afforded the corresponding 2-substituted ethyl sulfates (**64**; Nu = RCO₂, ArO and C₅H₅N⁺O, respectively) (Equation (7)) <72JHC891>. Reaction of unsymmetrical alkyl-substituted 1,3,2-dioxathiolane 2,2-dioxides with benzoate ion takes place primarily at the less hindered carbon atom, and proceeds with inversion of configuration <90TL3813, 92S989>, whereas for compounds substituted with an alkoxycarbonyl group, reaction occurs exclusively at the position adjacent to that group <88JA7538, 89TL655>. Dioxathiolane dioxides bearing 2-hydroxyalkyl substituents, for example, (**65**), cyclize exclusively by attack at the distal carbon with inversion of configuration, affording tetrahydrofurans (Equation (8)) <93ACS307>, whereas those bearing hydroxymethyl substituents cyclize by attack at the proximal carbon, resulting in a Payne-type rearrangement (Scheme 12) <93TL4675>. The sulfate esters formed in these reactions are readily hydrolyzed to the parent alcohol, and thus the reaction of *O*-nucleophiles with 1,3,2-dioxathiolane 2,2-dioxides can be regarded as being analogous to their reactions with oxiranes <88JA7538>.

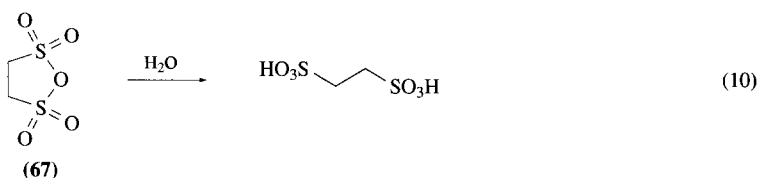
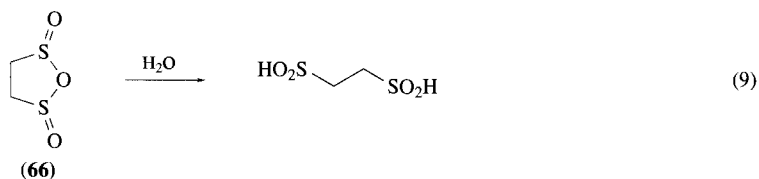


Both 1,3,2-benzodioxathiole 2-oxide and the corresponding 2,2-dioxide hydrolyze by nucleophilic attack of hydroxide ion at sulfur; in each case, the rate of hydrolysis is much faster than observed for the saturated counterparts, 1,3,2-dioxathiolane 2-oxide <76CRV747> and 1,3,2-dioxathiolane 2,2-dioxide <B-77MI 415-01>, respectively. 1,2,5-Dioxathiolane 2,5-dioxide (**66**) undergoes rapid hydrolysis to ethane 1,2-disulfonic acid in boiling water (Equation (9)) <76CRV747>. Similarly, 1,2,5-dioxathiolane 2,2,5,5-tetroxide (**67**) undergoes hydrolysis to ethane-1,2-disulfonic acid (Equation (10)) <66HC(21-1)1>. In an analogous manner, the unsaturated benzo-fused derivatives of (**66**) and



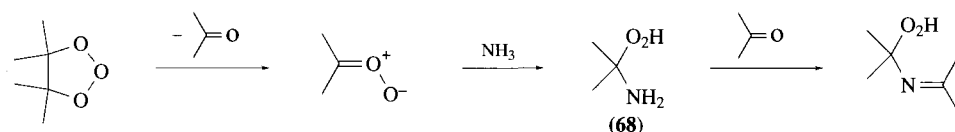
Scheme 12

(67) are readily hydrolyzed to benzene-1,2-disulfonic and -disulfonic acids, respectively <66HC(21-1)1, 81JOC2691>.

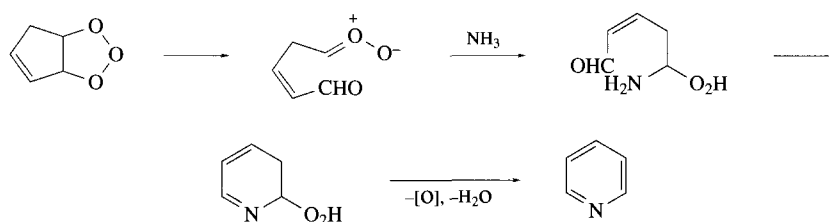


4.15.5.3.2 N-Nucleophiles

Generation of 1,2,3-trioxolanes (by ozonolysis of alkenes) in liquid ammonia or in aqueous ammonia solutions leads to the formation of α -aminoalkyl hydroperoxides (68), which arise by reaction of ammonia with the carbonyl oxides formed by cycloreversion of the 1,2,3-trioxolanes (cf. Section 4.15.4.1). These products, unlike the analogous α -alkoxyalkyl hydroperoxides (cf. Section 4.15.5.3.1), tend to be unstable under the reaction conditions, and condense with the carbonyl component of the 1,2,3-trioxolane decomposition to give imines (Scheme 13). In the case of cycloalkenes, this condensation step represents a ring-expanding recyclization to afford nitrogen-containing heterocycles which may undergo further reactions, for example, aromatization; thus, ozonolysis of cyclopentadiene in the presence of ammonia afforded pyridine in 18% yield (Scheme 14), and indene was transformed into isoquinoline in 62% yield <64JOC2240>. Alternatively, some α -aminoalkyl hydroperoxides may cyclize to form oxaziridines <66CB3233>.



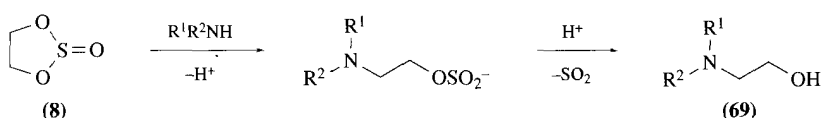
Scheme 13



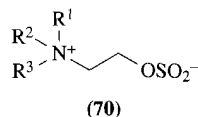
Scheme 14

In contrast to their reactions with water and simple alcohols (cf. Section 4.15.5.3.1), 1,3,2-dioxathiolane 2-oxides react with *N*-nucleophiles exclusively at carbon. Thus, treatment of 1,3,2-

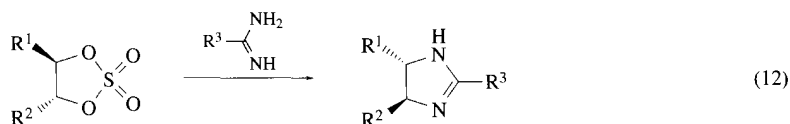
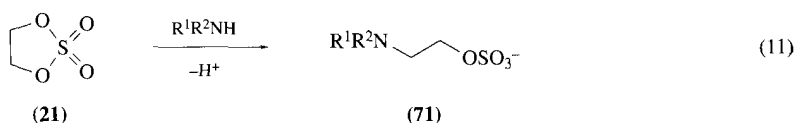
dioxathiolane 2-oxide (**8**) with primary and secondary amines afforded 2-aminoethyl sulfites, or, following mild acid hydrolysis, the corresponding 2-aminoethanols (**69**) (Scheme 15) <66HC(21-1)1>. Reaction of primary and secondary amines with unsymmetrical alkyl-substituted 1,3,2-dioxathiolane 2-oxides takes place at the less hindered carbon atom <81JAP(K)56152461, 82JAP(K)57002246>, and proceeds with inversion of configuration <90TL7591, 91TL1775>. Treatment of (**8**) with tertiary amines yielded sulfitebetaines (**70**) <71BRP1257851>. 1,3,2-Dioxathiolane 2-oxides undergo nucleophilic substitution by azide ion at elevated temperatures to afford, after hydrolysis, 2-azidoethyl alcohols <90TL4317, 91CC95, 93T901>. The regiochemistry of these reactions, which proceed with inversion of stereochemistry, show a marked dependence on the substituents present on the dioxathiolane 2-oxide; for alkyl-substituted compounds, attack occurs at the least hindered position, whereas for unsymmetrical phenyl-substituted compounds, attack occurs at the position adjacent to the phenyl group <91CC95>.



Scheme 15



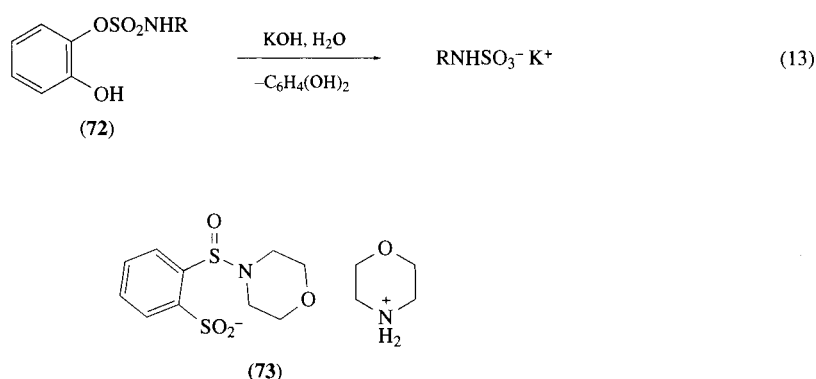
1,3,2-Dioxathiolane 2,2-dioxide (**21**) reacts with ammonia and primary and secondary amines to give 2-aminoethyl sulfates (**71**) (Equation (11)) <72JHC891>. Reaction of the same amines with unsymmetrical alkyl-substituted 1,3,2-dioxathiolane 2,2-dioxides occurs at the less hindered carbon <89TL2623>, and proceeds with inversion of configuration <90TL7591, 91TL1775>. The sulfate esters obtained from these reactions are readily hydrolyzed to the corresponding alcohol using aqueous acid <71BRP1257851, 89TL2623>, whereas treatment with base promotes a second nucleophilic substitution reaction of the sulfate group leading to the formation of aziridines <89TL2623>. Treatment of 1,3,2-dioxathiolane 2,2-dioxides with bidentate amidine nucleophiles also results in a double displacement reaction, each step of which proceeds with inversion of stereochemistry, affording imidazolines (Equation (12)) <91TL999>. Reaction of 1,3,2-dioxathiolane 2,2-dioxide (**21**) with tertiary amines gave sulfatobetaines analogous to (**70**) <75JPR943>.



Reaction of 1,3,2-dioxathiolane 2,2-dioxides with azide ion takes place with inversion of configuration, giving rise to 2-azidoethyl sulfates <88JA7538, 89TL655>. The regiochemistry of these reactions is dependent on the substituents present on the dioxathiolane 2,2-dioxide; for unsymmetrical alkyl-substituted compounds, attack occurs at the less hindered position <88JA7538, 93H(35)577>, whereas compounds bearing an alkoxy carbonyl substituent undergo reaction at the position adjacent to the alkoxy carbonyl group <88JA7538, 89TL655>. For fused-bicyclic 1,3,2-dioxathiolane 2,2-dioxides, it has been reported that there is a preference for the axial C—O bond to act as the leaving group <93TL3625>.

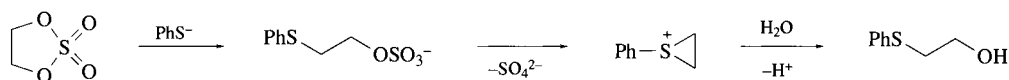
Primary amines react with 1,3,2-benzodioxathiole 2,2-dioxide affording sulfonylamines (**72**), which themselves are readily hydrolyzed to sulfamic acid salts (Equation (13)) <80JOC5371>; this two-step procedure represents a mild, high yielding method for the sulfamoylation of primary

amines. The benzannelated 1,2,5-oxadithiole 2,5-dioxide (**38**) reacts with 2 equivalents of morpholine to form the salt (**73**) in high yield <83JOC2943>.

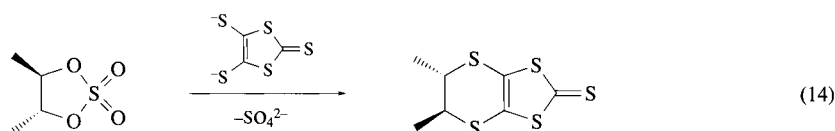


4.15.5.3.3 S- and Se-Nucleophiles

The sodium benzenethiolate catalyzed polymerization of certain 1,2,3-trithiolanes has been described in Section 4.15.4.1. Both 1,3,2-dioxathiolane 2-oxide and 1,3,2-dioxathiolane 2,2-dioxide react with arenethiolates in the same manner as they react with phenolates (cf. Section 4.15.5.3.1). In the case of 1,3,2-dioxathiolane 2,2-dioxide, the intermediate 2-phenylthioethyl sulfates are not stable in aqueous solution, hydrolyzing readily to the corresponding alcohols via a neighboring group participation involving the arylthio group (Scheme 16) <72JHC891>. Reaction of alkyl-substituted 1,3,2-dioxathiolane 2,2-dioxides with bidentate S-nucleophiles results in a double displacement reaction, each step of which proceeds with inversion of configuration (Equation (14)) <86HCA69>. A fused bicyclic 1,3,2-dioxathiolane 2,2-dioxide was reported to react with phenylselenide ion to afford, after acid hydrolysis, a cyclic 2-phenylselenoalcohol <93CC995>.

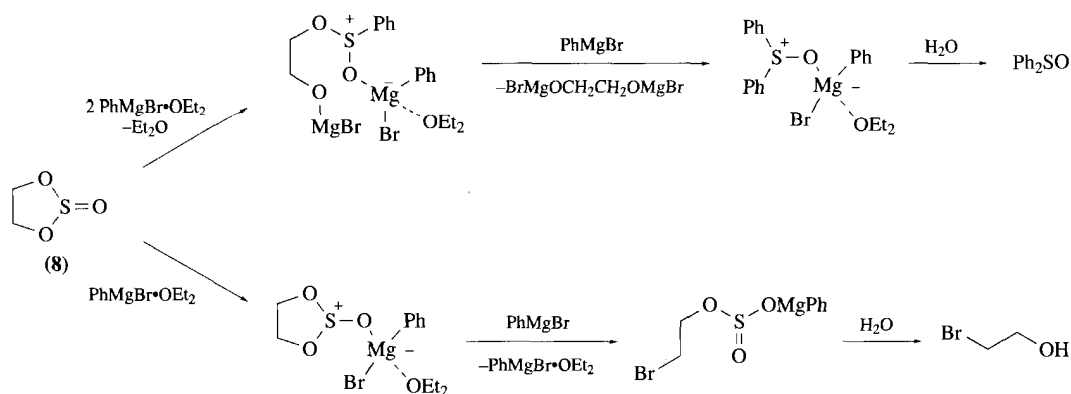


Scheme 16

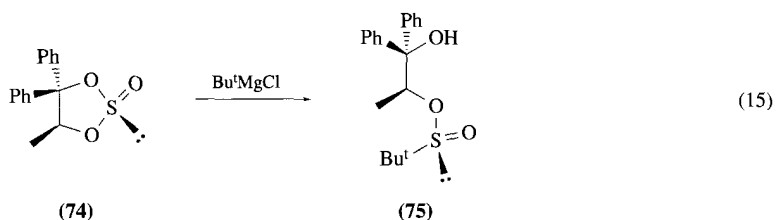


4.15.5.3.4 C-Nucleophiles

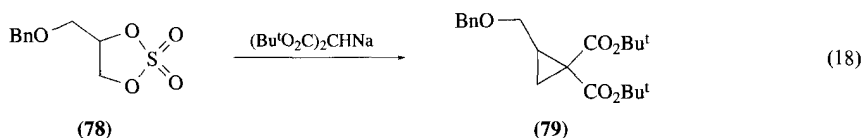
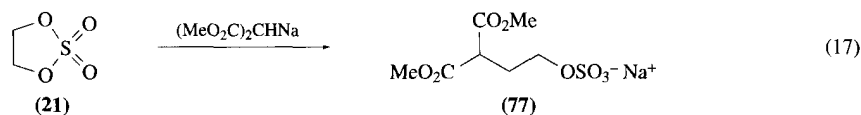
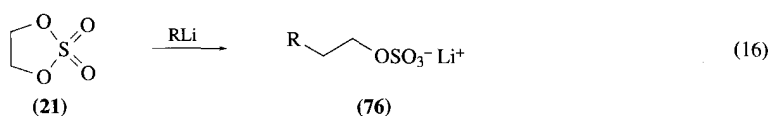
1,2,3-Trioxolanes undergo reductive ring cleavage on reaction with Grignard reagents (see Section 4.15.5.4). The reaction of 1,3,2-dioxathiolane 2-oxide (**8**) with phenylmagnesium bromide afforded varying yields of diphenyl sulfoxide and 2-bromoethanol, depending on the reaction conditions <56JA454>. The sulfoxide is formed by repeated attack of the Grignard reagent at sulfur, whereas the bromoethanol arises from a nucleophilic displacement at carbon by bromide ion, presumably as outlined in Scheme 17. On treatment with *t*-butylmagnesium chloride, the sterically hindered chiral 1,3,2-dioxathiolane 2-oxide (**74**) underwent nucleophilic attack at sulfur with inversion of configuration to afford the sulfinate (**75**) (Equation (15)) <93AG(E)568>.



Scheme 17

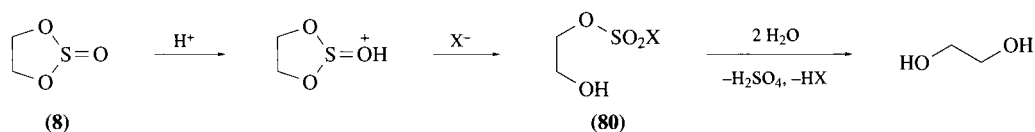


The reaction of 1,3,2-dioxathiolane 2,2-dioxide (**21**) with organometallic compounds which do not bear α -hydrogen atoms, such as phenyl lithium or lithium phenylacetylide, proceeds by nucleophilic attack at carbon, affording 2-substituted ethyl sulfates ((**76**), $\text{R} = \text{Ph}$, $\text{C}\equiv\text{CPh}$) (Equation (16)) <72JHC891>. Reaction of 4-alkyl-1,3,2-dioxathiolane 2,2-dioxides with lithium acetylides furnished analogous products arising from attack at the less hindered carbon atom <91T9929>. The reactions of 1,3,2-dioxathiolane 2,2-dioxides with carbanionic species bearing weakly acidic α -hydrogen atoms, for example, α -anions derived from simple esters, amides and sulfones, also afford related products arising from nucleophilic addition at the less hindered carbon atom <94JOC520>. In the case of reaction with carbanions bearing more acidic α -hydrogen atoms, the analogous addition products are formed initially, but then in some cases the reaction may proceed further by deprotonation and cyclization onto the adjacent sulfate intermediate to form cyclopropanes <88JA7538>. Thus, treatment of 1,3,2-dioxathiolane 2,2-dioxide (**21**) with the sodium salt of diethyl malonate afforded the addition product (**77**) (Equation (17)) <72JHC891>, whereas reaction of the substituted 1,3,2-dioxathiolane 2,2-dioxide (**78**) with the sodium salt of di-*t*-butyl malonate afforded the cyclopropane (**79**) (Equation (18)) <93JOC3767>. Reaction of 4-decyl-1,3,2-dioxathiolane 2,2-dioxide with lithiated dimethyl methylphosphonate afforded mainly the addition product (82%) accompanied by a small amount (7%) of the corresponding cyclopropane double-displacement product <94JOC520>.

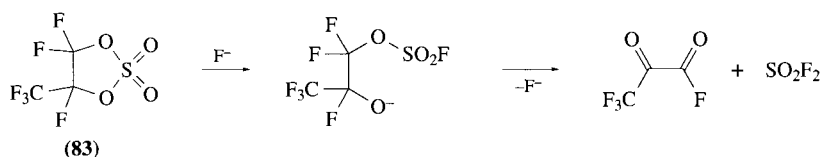
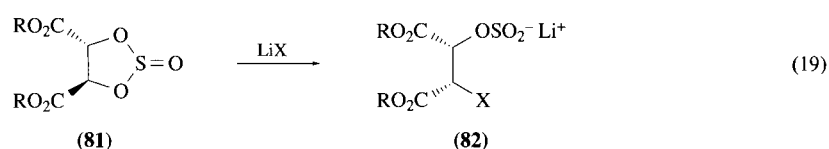


4.15.5.3.5 Halide ions

The hydrohalic acid catalyzed hydrolysis of 1,3,2-dioxathiolane 2-oxide (**8**) is considered to occur, at least partly, via a halosulfite intermediate, for example, ((**80**), X = Cl) (Scheme 18) <76CRV747>. A similar nucleophilic catalysis has been suggested to explain the dramatic acceleration of the aqueous hydrolysis of 1,3,2-benzodioxathiole 2-oxide by fluoride ion <76CRV747>. Under anhydrous conditions, the substituted 1,3,2-dioxathiolane 2-oxides ((**81**), R = Me, Et, Prⁱ) undergo nucleophilic attack at carbon by halide ion (LiBr or LiCl) with inversion of configuration to afford the halo sulfites ((**82**), R = Me, Et, Prⁱ, X = Br, Cl) (Equation (19)) <91TL3155>. Similarly, 1,3,2-dioxathiolane 2,2-dioxides undergo an analogous reaction with fluoride ion (R₄N⁺ F⁻) under anhydrous conditions to afford fluorosulfates <88JA7538, 89CL1689, 90JOC1211>. In contrast, the perfluorinated dioxathiolane 2,2-dioxide (**83**) afforded trifluoro-2-oxopropionyl fluoride and sulfonyl fluoride on treatment with caesium fluoride under anhydrous conditions, the reaction presumably proceeding via attack at sulfur by fluoride ion (Scheme 19) <73IZV2725>.



Scheme 18

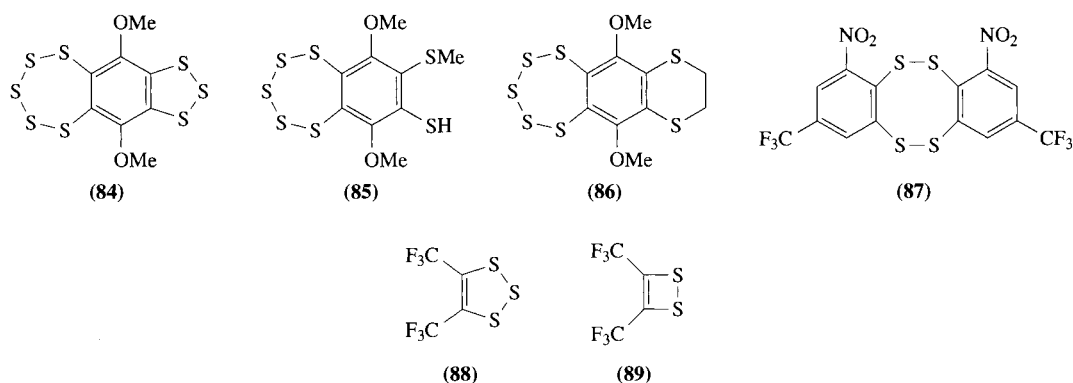


Scheme 19

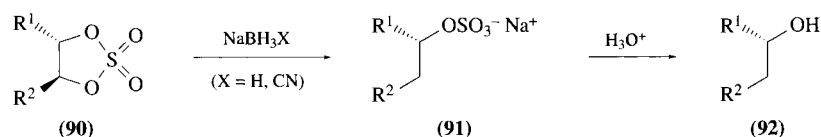
4.15.5.4 Reduction

1,2,3-Trioxolanes undergo reductive ring cleavage upon reaction with isopropylmagnesium halides at low temperature, affording 1,2-diols <60CB689, 63JOC1159>; these reactions provided the early chemical evidence that the C—C linkage was retained in the initial product from the reaction of ozone with alkenes. The reduction of benzotrithioles has been studied briefly; reaction of the benzotrithiole (**84**) with 0.5 equivalents of sodium borohydride, followed by quenching with methyl iodide or 1,2-dibromoethane afforded the reduced alkylated products (**85**) and (**86**), respectively <88TL6291>, and reduction of the nitrobenzotrithiole (**13**) with triethyl phosphite yielded the dibenzotetrathiocin (**87**) and triethyl thiophosphate <80JOC4806>. The detailed mechanisms of these desulfurization reactions have not been discussed. Reduction of the antimony hexafluoride salt of cation (**15**) with sulfur dioxide and potassium iodide afforded a mixture of products, tentatively assigned as trithiole (**88**) and dithiete (**89**) <92JCS(D)1563>.

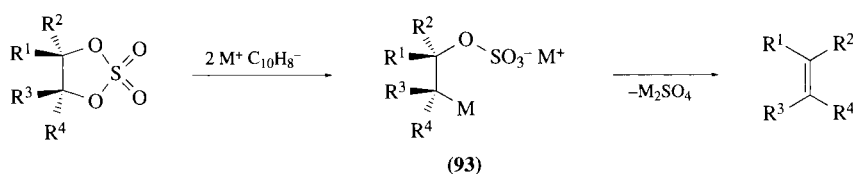
Reduction of 1,3,2-dioxathiolane 2,2-dioxides (**90**) by hydride-donating reagents, such as borohydride and cyanoborohydride, affords, after hydrolysis of the initially formed sulfate (**91**), secondary alcohols (**92**) (Scheme 20). Thus, reduction of (**90**) (R¹ = R² = CO₂Prⁱ) with sodium cyanoborohydride followed by hydrolysis gave (**92**) (R¹ = R² = CO₂Prⁱ), and similar treatment of (**90**) (R¹ = C₁₅H₃₁, R² = CO₂Me), but using sodium borohydride, afforded (**92**) (R¹ = C₁₅H₃₁, R² = CO₂Me) <88JA7538>. 1,3,2-Dioxathiolane 2,2-dioxides are reduced to alkenes on treatment with sodium or lithium naphthalenide. Two equivalents of the naphthalenide are required for complete reduction <90SL479>, the reaction being thought to proceed via a β-metallo sulfate intermediate



(93) (Scheme 21) <92TL5597>. In cases where *E/Z* isomers of the product alkene are possible, the thermodynamically preferred isomer predominates <90SL479>. Electrochemical reduction of certain 1,3,2-dioxathiolane 2,2-dioxides also affords alkenes <84BCJ3160>. Reduction of the *cis* and *trans* isomers of 4,5-dimethyl-1,3,2-dioxathiolane 2-thione using Raney nickel afforded *meso*- and ($\pm$)-2,3-butanediol, respectively <65JOC2696>.



Scheme 20

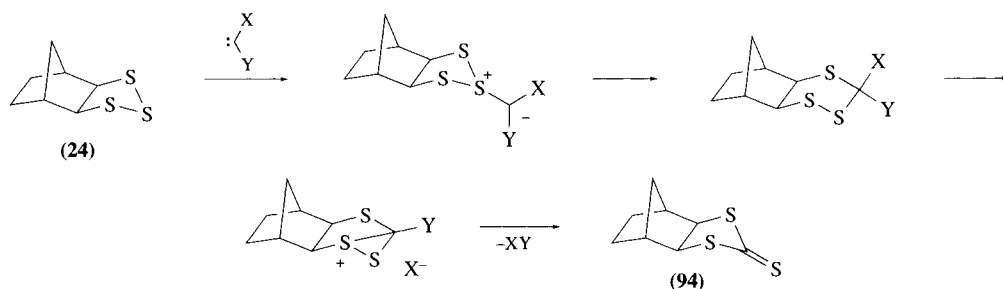


Scheme 21

4.15.5.5 Reactions with Radicals and Carbenes

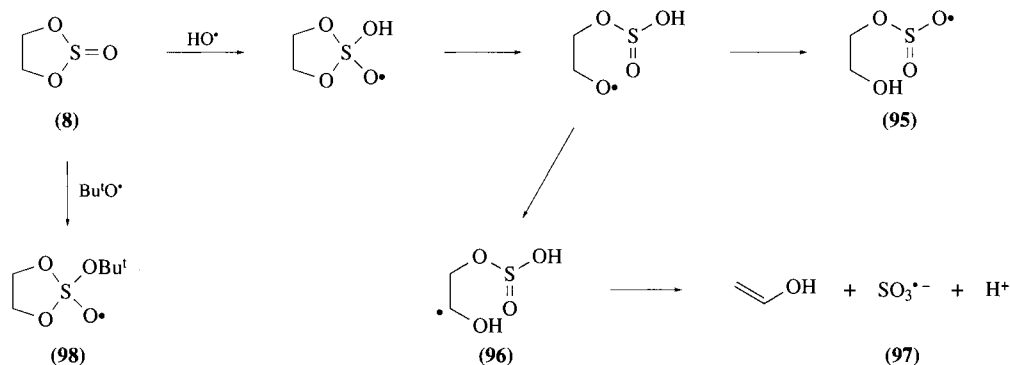
Reaction of norbornane trithiolane (24) with both dichloro- and dibromocarbene afforded the trithiocarbonate (94), which upon further reaction with the dihalocarbene yielded the corresponding dithiocarbonate <90JOC1146>. The mechanism of formation of (94) from (24) is postulated to proceed by addition of the carbene to S-2 of the trithiolane, followed by a ring-expansion reduction sequence as outlined in Scheme 22.

Reaction of 1,3,2-dioxathiolane 2-oxide (8) with hydroxyl radicals gave rise to the radicals (95),



Scheme 22

(96), and (97), which were trapped and detected by ESR methods (Scheme 23) <76JCS(P2)1040>. The *t*-butoxyl radical reacted similarly with (8) at sulfur to afford the radical (98) <77JMR(27)509>. The radical chlorination of 1,3,2-dioxathiolane 2,2-dioxide afforded a mixture of the *cis* and *trans* isomers of 4,5-dichloro-1,3,2-dioxathiolane 2,2-dioxide <68JA2970>.

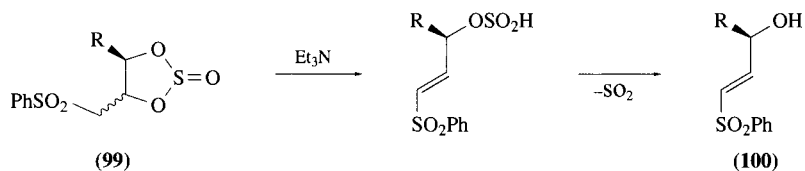


Scheme 23

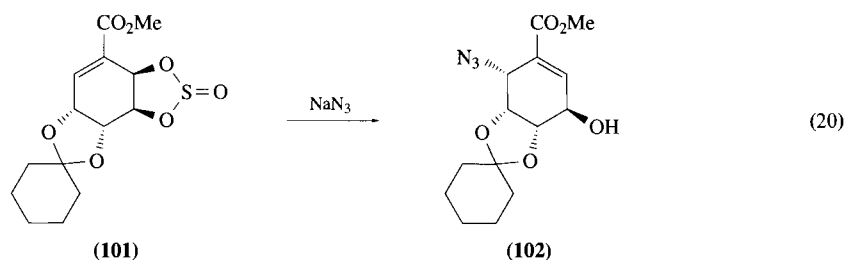
4.15.6 REACTIVITY OF RING SUBSTITUENTS

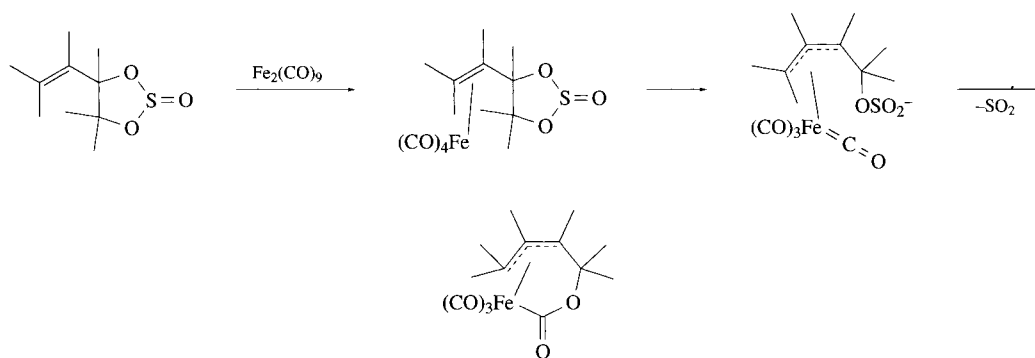
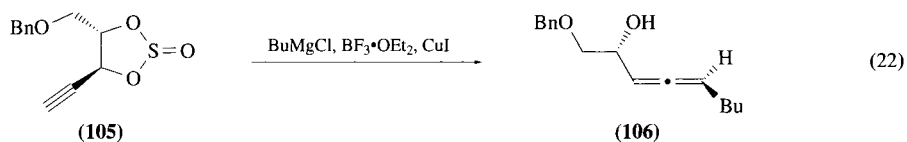
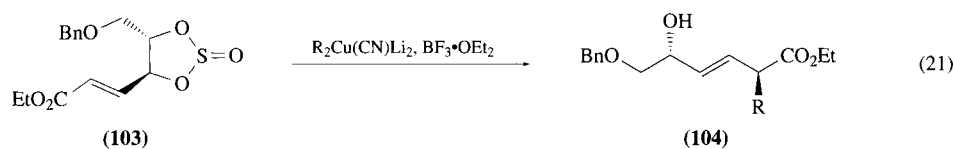
4.15.6.1 Substituents Attached to Ring Carbon Atoms

Generation of 4-alkyl-5-sulfonomethyl-1,3,2-dioxathiolane 2-oxides (99) in the presence of triethylamine results in an elimination reaction, followed by loss of SO₂, affording hydroxyalkenes (100) (Scheme 24) <92JCS(P1)405>. The stereochemistry at the 4-position of (99) is retained in the product, whereas the *E*-alkene is produced regardless of the stereochemistry at the 5-position. 1,3,2-Dioxathiolane 2-oxides bearing alkenyl substituents may undergo a diastereoselective S_N2' reaction with nucleophiles, followed by loss of SO₂, leading to the formation of hydroxyalkenes. Thus, the low-temperature reaction of the dioxathiolane 2-oxide (101) with azide gave the azidoalcohol (102) (Equation (20)) <93CC464>, and the boron trifluoride etherate promoted reaction of methyl- or butylcuprate reagents with the 1,3,2-dioxathiolane 2-oxide (103) afforded hydroxyalkenes ((104), R = Me) and (104: R = Bu), respectively (Equation (21)) <92TA705>. In an analogous manner, the alkynyl-substituted 1,3,2-dioxathiolane 2-oxide (105) underwent a copper iodide/boron trifluoride etherate promoted reaction with *n*-butylmagnesium chloride to afford the allene (106) (Equation (22)) <92TA1509>. The dioxathiolane 2-oxide (103) underwent reductive elimination on treatment with samarium diiodide, yielding the hydroxyalkene ((104), R = H) <93JCS(P1)9>. Alkenyl-1,3,2-dioxathiolane 2-oxides react with diiron nonacarbonyl to give allyltricarbonyliron lactone complexes (Scheme 25) <90SL224>.



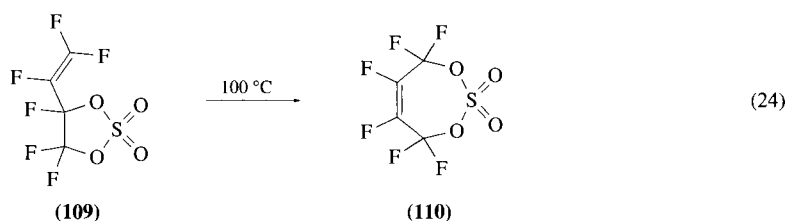
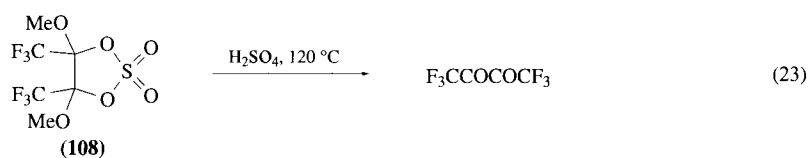
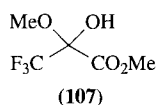
Scheme 24





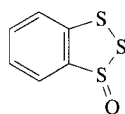
Scheme 25

Halogen atoms or alkoxy groups attached to the ring carbon atoms of 1,3,2-dioxathiolane 2-oxides may undergo nucleophilic displacement; examples are methanolysis of the perfluoro derivative (83) to the carboxylic ester (107) <73IZV2725>, and the acid catalyzed cleavage of (108) to hexafluorobiacetyl (Equation (23)) <77JA1214>. The perfluorinated alkenyl derivative (109) underwent a thermal rearrangement, involving insertion of the alkenyl group into the 1,3,2-dioxathiolane 2,2-dioxide ring, affording the seven-membered cyclic sulfate (110) (Equation (24)) <79IZV118>.



4.15.6.2 Substituents Attached to Ring Heteroatoms

Irradiation of the 1,2,3-benzotrithiole 2-oxide (41) with a high-pressure mercury lamp afforded the corresponding 1-oxide (111) <93TL673>. This rearrangement, which was also observed for a number of related benzotrithiole 2-oxides, was shown to be an intramolecular process by cross-over experiments using ^{18}O -labeled materials.



(111)

4.15.7 RING SYNTHESIS

4.15.7.1 General Survey

The syntheses of five-membered heterocycles containing three oxygen or sulfur atoms in the 1,2,3-positions can be classified into three groups: (i) one-component syntheses, in which a suitable acyclic molecule is cyclized by linkage of two heteroatoms; (ii) two-component syntheses, in which the ring is built up either by a [3 + 2] process or a [4 + 1] process; and (iii) synthesis by transformation of another heterocyclic ring.

The various possibilities for the first two types of syntheses are listed schematically in Table 4, and the possibilities for synthesis from other heterocycles are listed in Table 5. In each case the method is discussed in more detail in the following sections; Tables 4 and 5 indicate the section(s) in which a particular reaction is described. In the case of sulfur-containing heterocycles, *S*-oxides and *S,S*-dioxides are treated alongside the basic parent structures, since for 1,3,2-dioxathiolane, 1,2,3-oxadithiolane, and 1,2,5-oxadithiolane the unoxidized rings are unknown.

Table 4 Ring syntheses of five-membered heterocycles containing three oxygen or sulfur atoms from non-heterocyclic components.

Type of synthesis	Arrangement of heteroatoms in the starting systems	Starting components utilized	Heterocyclic ring skeleton obtained ^a	Section in which the reaction type is illustrated
One-component syntheses (formation of one bond)		HO—SO _n —C—C—SO _n —OH	1,2,5-[C ₂ O ₂ S]	4.15.7.2.1
		HO—SO _n —C=C—SO _n —OH	1,2,5-[C ₂ O ₂ S]	4.15.7.2.2
Two-component syntheses (formation of two bonds)		HS—C—C—SH + SO _n X ₂	1,2,3-[C ₂ S ₃]	4.15.7.2.3
		HS—C=C—SH + SOCl ₂	1,2,3-[C ₂ S ₃]	4.15.7.2.2
		HO—C—C—OH + SO _n X ₂	1,3,2-[C ₂ O ₂ S]	4.15.7.2.1
				4.15.7.2.3
				4.15.7.2.5
		HO—C—C—OH + F ₂ S=NC ₂ F ₅	1,3,2-[C ₂ O ₂ S]	4.15.7.2.4
		HO—C—C—OH + S ₂ Cl ₂	1,3,2-[C ₂ O ₂ S]	4.15.7.2.7
		HO—C=C—OH + SO _n X ₂	1,3,2-[C ₂ O ₂ S]	4.15.7.2.2
		HO—C=C—OH + F ₂ S=NC ₂ F ₅	1,3,2-[C ₂ O ₂ S]	4.15.7.2.4
		O=C—C=O + SO ₂	1,3,2-[C ₂ O ₂ S]	4.15.7.2.2
		ClOS—C—C—SOCl + H ₂ O	1,2,5-[C ₂ OS ₂]	4.15.7.2.1
		HS—C—C—OH + SOCl ₂	1,2,3-[C ₂ OS ₂]	4.15.7.2.1
				4.15.7.2.3
		HS—C=C—OH + SOCl ₂	1,2,3-[C ₂ OS ₂]	4.15.7.2.2
		C=C + O ₃	1,2,3-[C ₂ O ₃]	4.15.7.2.1
				4.15.7.2.3
		C=C + S ₈	1,2,3-[C ₂ S ₃]	4.15.7.2.3
		C≡C + S ₈	1,2,3-[C ₂ S ₃]	4.15.7.2.6
				4.15.7.2.3
				4.15.7.2.7
		Br—C—C—Br + Na ₂ S ₄	1,2,3-[C ₂ S ₃]	4.15.7.2.3
		Br—C=C—Br + S ₈	1,2,3-[C ₂ S ₃]	4.15.7.2.2
		C=C + SO ₃	1,3,2-[C ₂ O ₂ S]	4.15.7.2.6
		C=C + peroxydisulfite	1,3,2-[C ₂ O ₂ S]	4.15.7.2.3
		C≡C + S ₈ /AsF ₆	1,3,2-[C ₂ O ₂ S]	4.15.7.2.3
		Br—C—C—Br + Ag ₂ SO ₄	1,3,2-[C ₂ O ₂ S]	4.15.7.2.1
		O=C—C—OH + F ₂ NH + H ₂ SO ₄	1,3,2-[C ₂ O ₂ S]	4.15.7.2.4

^a[C₂O₃] trioxolane, [C₂S₃] trithiolane or trithiole, [C₂O₂S] dioxathiolane or dioxathiole, [C₂OS₂] oxadithiolane or oxadithiole.

Table 5 Syntheses of five-membered heterocycles containing three oxygen or sulfur atoms by ring inter-conversion.

Type of ring transformation	Starting systems		Heterocyclic ring skeleton obtained ^a	Section in which the reaction type is illustrated
Insertion of an —SO ₂ — or an —SO ₃ — moiety		SO _n (n = 2 or 3), or H ₂ SO ₄	1,3,2-[C ₂ O ₂ S]	4.15.7.2.1 4.15.7.2.3 4.15.7.2.6
Displacement of a ring heteroatom		SOCl ₂	1,2,3-[C ₂ S ₃] 1,3,2-[C ₂ O ₂ S]	4.15.7.2.1 4.15.7.2.1
		SCl ₂	1,2,3-[C ₂ S ₃]	4.15.7.2.7
Ring cleavage and displacement of C=X by S		S ₈ (X = S) or NaSH (X = O)	1,2,3-[C ₂ S ₃]	4.15.7.2.2
Thermal decomposition and reaction of intermediate with sulfur		S ₈ , heat	1,2,3-[C ₂ S ₃]	4.15.7.2.3
Elimination of nitrogen		heat -N ₂	1,2,3-[C ₂ S ₃]	4.15.7.2.2
Oxidative transfer of —OSO ₃ — moiety to alkene			1,3,2-[C ₂ O ₂ S]	4.15.7.2.1 4.15.7.2.3

^a[C₂S₃] trithiolane or trithiole, [C₂O₂S] dioxathiolane or dioxathiole, [C₂OS₂] oxadithiolane or oxadithiole.

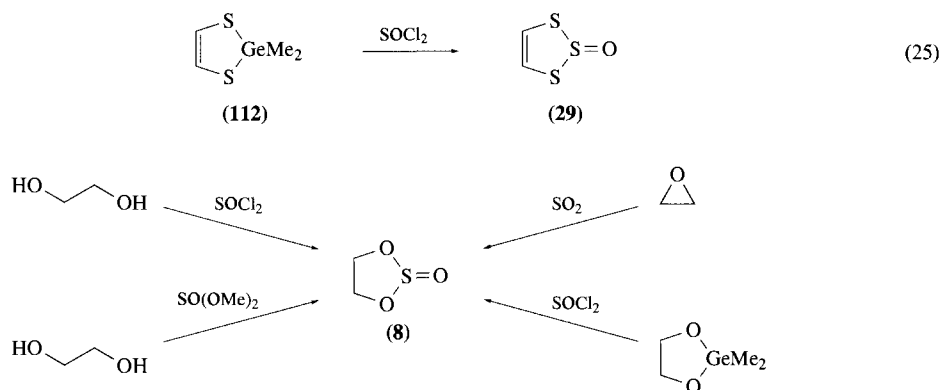
4.15.7.2 Synthesis of Particular Classes of Compounds

4.15.7.2.1 Parent systems (including S-oxides and S,S-dioxides)

The only method available for the generation of 1,2,3-trioxolane is the reaction of ozone with ethene. When this ozonation was conducted under suitable low-temperature conditions (−175 °C), the formation of 1,2,3-trioxolane (**1**) was observed (81JA2578, 88JA7991) (cf. Sections 4.15.3.2 and 4.15.3.5). However, because of its thermal instability, this compound cannot be isolated; at temperatures above −100 °C it rearranged to 1,2,4-trioxolane (42LA(553)187). The mechanism of this ring transformation has been described briefly in Section 4.15.4.1, and is discussed in more detail in Chapter 4.16. The mechanism of the reaction of ozone with ethene has been studied by *ab initio* calculations, which indicate that the reaction is a concerted [3 + 2] cycloaddition with an intermediate O₃–ethene complex lying in a shallow energy minimum prior to the transition state (91JA2412). Experimental evidence for the concerted nature of the cycloaddition was provided by a microwave study of the reactions of the stereochemically pure *cis* and *trans* isomers of 1,2-dideuteroethene with ozone, which afforded only *cis* (*endo* and *exo* forms) and *trans* 4,5-dideutero-1,2,3-trioxolane, respectively (88JA7991). The intermediate van der Waals complex has also been observed by microwave spectroscopy (91JA2412).

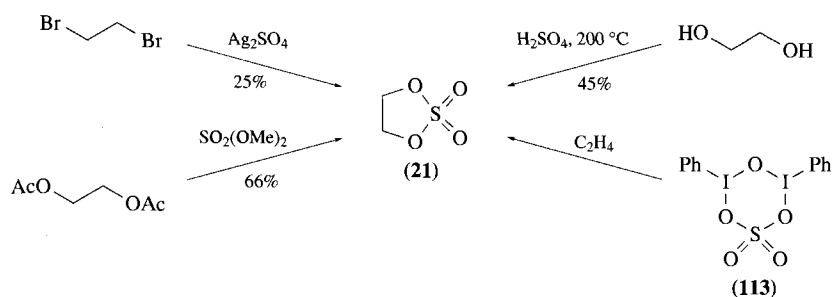
In the 1,2,3-trithiole series, 1,2,3-trithiole 2-oxide (**29**) was obtained in 39% yield from the reaction of 2,2-dimethyl-1,3,2-dithiagermole (**112**) with thionyl chloride (Equation (25)) (88RTC440). 1,3,2-Dioxathiolane 2-oxide (**8**) is conveniently prepared by reaction of 1,2-dihydroxyethane with either thionyl chloride (66HC(21-1)1) or dimethyl sulfite (76CRV747) (Scheme 26). An alternative method,

which involves the reaction of oxirane with sulfur dioxide, may lead directly to (8), or, depending on the reaction conditions, may first form a polymer which depolymerizes on heating to afford (8) <66HC(21-1)1>. 1,3,2-Dioxathiolane 2-oxide has also been obtained from the reaction of 2,2-dimethyl-1,3,2-dioxagermolane with thionyl chloride <89SR149>.



Scheme 26

1,3,2-Dioxathiolane 2,2-dioxide (21) has been obtained from the reaction of 1,2-dibromoethane with silver sulfate <66HC(21-1)1>, from the reaction between 1,2-diacetoxyethane and dimethyl sulfate <66HC(21-1)1>, from 1,2-dihydroxyethane and sulfuric acid at elevated temperatures <88EUP343053>, and from reaction of the cyclic hypervalent iodine species (113) and ethene <86TL3971> (Scheme 27). In contrast to the ready formation of 1,3,2-dioxathiolane 2-oxide from 1,2-dihydroxyethane and thionyl chloride or from oxirane and sulfur dioxide, the corresponding reactions with sulfuryl chloride <68JHC289> or sulfur trioxide <66HC(21-1)1> afforded only small amounts of (21). 1,3,2-Dioxathiolane 2,2-dioxide has also been obtained from the oxidation of 1,3,2-dioxathiolane 2-oxide <63JA602> (cf. Section 4.15.5.2.3). Dechlorination of 4,5-dichloro-1,3,2-dioxathiolane 2,2-dioxide (cf. Section 4.15.5.5) using magnesium afforded 1,3,2-dioxathiole 2,2-dioxide (22) <68JA2970>.



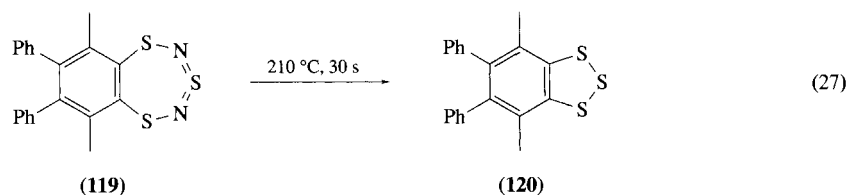
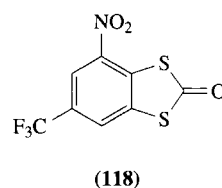
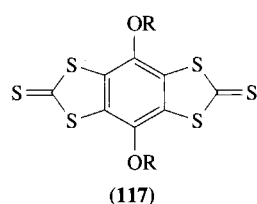
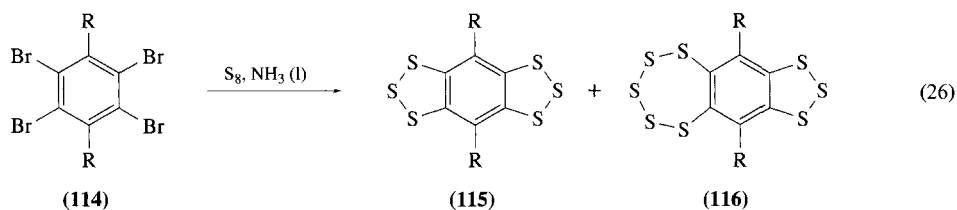
Scheme 27

In a similar manner to the preparation of 1,3,2-dioxathiolane 2-oxide from 1,2-dihydroxyethane and thionyl chloride, 1,2,3-oxadithiolane 2-oxide was prepared from 2-mercaptoethanol and thionyl chloride <75ACS(A)414>. 1,2,5-Oxadithiolane 2,5-dioxide (66), the cyclic anhydride of ethane-1,2-disulfonic acid, was obtained by controlled hydrolysis of ethanebis(disulfinyl) chloride <76CRV747>. The corresponding 2,2,5,5-tetroxide (67) was obtained by treatment of ethane-1,2-disulfonic acid with thionyl chloride <66HC(21-1)1>.

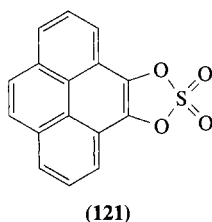
4.15.7.2.2 Benzo derivatives

Although 1,2,3-benzotrithiole itself is not known, the preparation of a number of substituted derivatives has been reported. Thus, treatment of the tetrabromobenzenes (114; R = Me, Et) with elemental sulfur in liquid ammonia afforded a mixture of the benzenebis(trithiole) and trithiolobenzopentathiepin products, (115; R = Me, Et) and (116; R = Me, Et) (Equation (26)) <89TL3453>. Similar treatment of the benzenebis(trithiocarbonates) (117; R = Me, Et, Prⁱ, Bn) afforded trithiolobenzopentathiepins (116; R = OMe, OEt, OPrⁱ, OBn) <88TL6291>. Reaction of the

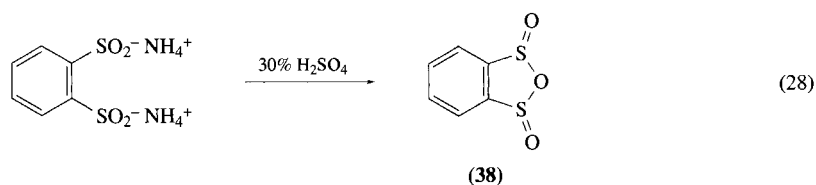
dithiocarbonate (**118**) with sodium hydrosulfide gave the benzotrithiole (**13**) <80JOC4806>. No details of the precise mechanisms of any of these reactions have been reported, though there is evidence that the formation of (**13**) from (**118**) proceeds via a dibenzotetrathicin <80JOC4806>. The thermolysis of the benzotrithiadiazepine (**119**) proceeded with loss of nitrogen forming the 1,2,3-benzotrithiole (**120**) in 44% yield (Equation (27)) <91JCS(P1)317>. The equilibration of benzotrithioles and benzo-pentathiepins has been noted in Section 4.15.5.2.4.



1,2,3-Benzotrithiole 2-oxide (**41**) was obtained in 76% yield from the reaction of benzene-1,2-dithiol with thionyl chloride <93TL673>. Similarly, 1,3,2-benzodioxathiole 2-oxide was prepared from 1,2-dihydroxybenzene and thionyl chloride <66HC(21-1)1>, and 1,2,3-benzoxadithiole 2-oxide was obtained from 2-mercaptophenol and thionyl chloride <81AG(E)570>. Reaction of the monosodium salt of 1,2-dihydroxybenzene with sulfuryl chloride afforded an intermediate chlorosulfate ester, which was dehydrochlorinated to 1,3,2-benzodioxathiole 2,2-dioxide by the action of pyridine <66HC(21-1)1>. The substituted 1,3,2-benzodioxathiole 2,2-dioxide (**121**) was isolated from the photolysis of pyrenedione in the presence of sulfur dioxide <87TL2057>.



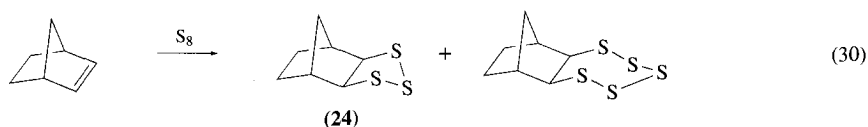
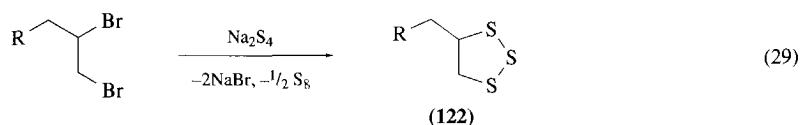
The benzannelated 1,2,5-oxadithiole 2,5-dioxide (**38**) was obtained upon acidification of diammonium benzene-1,2-disulfinate (Equation (28)) <81JOC2691>. The corresponding tetroxide was similarly prepared by treatment of dipotassium benzene-1,2-disulfonate with chlorosulfonic acid <66HC(21-1)1>.



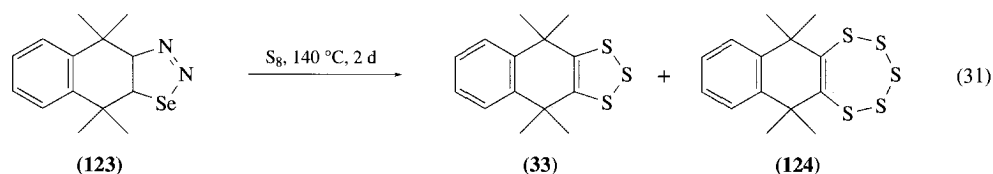
4.15.7.2.3 C-Linked substituents

Like the parent compound (1), alkyl- and/or aryl-substituted 1,2,3-trioxolanes can be generated only at low temperatures by the cycloaddition of ozone to alkenes. The concerted nature of the cycloaddition is reflected in the stereochemistry of the products observed; aliphatic *cis* alkenes afford only *cis* 4,5-dialkyl-1,2,3-trioxolanes, and the analogous *trans* alkenes yield only *trans* 4,5-dialkyl-1,2,3-trioxolanes. 1,2,3-Trioxolanes derived from aliphatic *cis* alkenes tend to be the least stable, rearranging to 1,2,4-trioxolanes at much lower temperatures than those formed from the corresponding *trans* alkenes. The most stable monocyclic 1,2,3-trioxolanes bearing simple alkyl or phenyl substituents are *trans*-4,5-di-*t*-butyl-1,2,3-trioxolane, which rearranges at ca. -60°C <60CB689>, and 4-phenyl-1,2,3-trioxolane, which is stable up to ca. -55°C <79JA2524>. A monocyclic 1,2,3-trioxolane bearing chloromethyl substituents at both the 4- and 5-positions has been reported to be unusually stable up to -10°C <83JCS(P1)1319>; this compound is also unusual in that it appears to be formed by a nonconcerted cycloaddition of ozone to 1,4-dichloro-2-butene. The only 1,2,3-trioxolane stable enough to be isolated at room temperature is the fused example (31) (cf. Section 4.15.4.1).

Only a few simple monocyclic 1,2,3-trithiolanes have been reported. These are typically prepared from a 1,2-dithiol and a divalent sulfur species; treatment of propane-1,2-dithiol with thiobis(imidazole) afforded 4-methyl-1,2,3-trithiolane <88JA7813> and reaction of butane-1,2-dithiol with thiobis(phthalimide) gave 4-ethyl-1,2,3-trithiolane <77UP 415-01>. In a similar manner, reaction of ethane-1,2-dithiol with dichloromethylsulfonium hexafluoroantimonate yielded the hexafluoroantimonate salt of the 2-methyl-1,2,3-trithiolanium cation (12) <90ZAAC(591)150>. Some substituted-alkyl-1,2,3-trithiolanes (122; R = SO_3Na , $\text{O}(\text{CH}_2)_2\text{SO}_3\text{Na}$ and $\text{S}(\text{CH}_2)_2\text{SO}_3\text{Na}$) have been obtained from the reaction of the corresponding 1,2-dibromide with disodium tetrasulfide (Equation (29)) <67UKZ596>. Strained bicyclic alkenes react with elemental sulfur to give trithiolanes and pentathiapanes, for example, norbornene affords a 3.5 : 1 mixture of the *exo* trithiolane (24) and the corresponding pentathiapane (Equation (30)) <87JOC4937> (equilibration of these products has been discussed in Section 4.15.5.2.4); dicyclopentadiene <86AX(C)332>, tricyclopentadiene <79AX(B)2119> and dibenzobarrellene <92SUL247> afford the analogous 1,2,3-trithiolanes upon sulfuration. Strained cyclic alkenes also afford 1,2,3-trithiolanes on treatment with diatomic sulfur <90JA7819, 92CC1460>. The 1,2,3-trithiolane 1,1-dioxide (43) was formed, among other products, from the dimerization of phenylsulfine <68JCS(C)1612>.

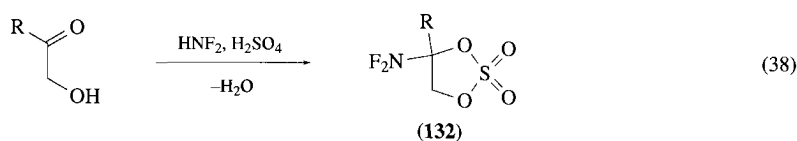
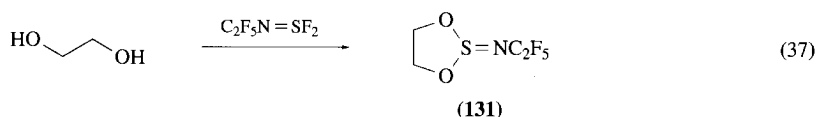
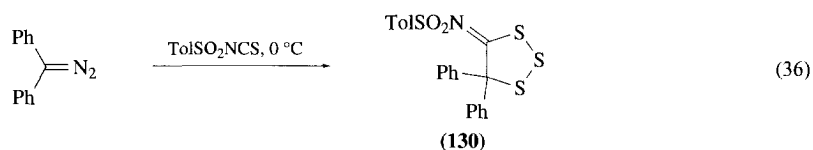


Very few C-linked 1,2,3-trithioles have been reported. The trithiole (33) was obtained, along with the pentathiapin (124), from the thermal reaction of selenodiazole (123) with elemental sulfur (Equation (31)) <88CL657>; trithiole (34) was similarly prepared <90TL5323>. Reaction of 1,2-bis(trifluoromethyl)ethyne with a mixture containing $\text{S}_8(\text{AsF}_6)_2$ and $\text{S}_4(\text{AsF}_6)_2$ species afforded the 7π radical cation (15) as its hexafluoroarsenate salt (Equation (32)) <91CC358>. 4,5-Dicyano-1,2,3-trithiolane 2-oxide (125) was obtained from the reaction of the disodium salt of 2,3-dimercapto-maleonitrile with thionyl chloride (Equation (33)) <66HC(21-1)1>.



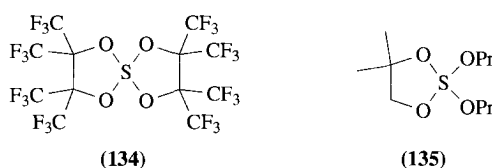
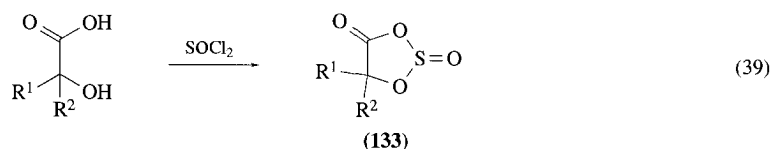
4.15.7.2.4 N-Linked substituents

The 4-*N*-toluenesulfonylimino-1,2,3-trithiolane (**130**) was isolated in ca. 1% yield from the reaction of diphenyldiazomethane with toluenesulfonylisothiocyanate (Equation (36)) <80JOC4366>. Pentafluoroethyliminosulfur difluoride reacted with 1,2-dihydroxyethane in the presence of anhydrous sodium fluoride to give the imine derivative (**131**) of 1,3,2-dioxathiolane 2-oxide (Equation (37)) <79IC213>; the analogous imino derivatives (**35**) and (**36**) of 1,3,2-benzodioxathiole 2-oxide were similarly obtained from 1,2-dihydroxybenzene and 2,3-dihydroxynaphthalene, respectively <81JFC(18)357>. Reaction of α -hydroxyketones with difluoramine in fuming sulfuric acid afforded substituted 4-difluoramino-1,3,2-dioxathiolane 2,2-dioxides (**132**) (Equation (38)) and, under similar conditions, α,β -diketones gave rise to 4,5-bis(difluoramino) derivatives <69JOC917>.



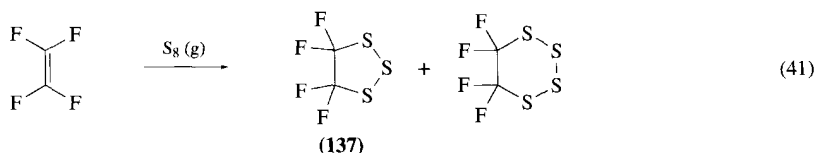
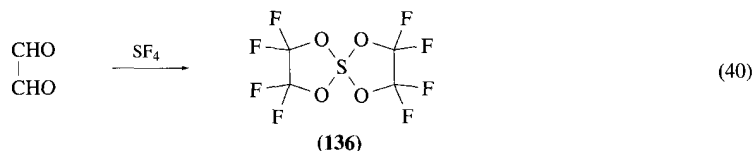
4.15.7.2.5 O-Linked substituents (including keto derivatives)

1,3,2-Dioxathiolan-4-one 2-oxides (**133**) are prepared by reaction of α -hydroxy carboxylic acids with thionyl chloride (Equation (39)) <66HC(21-1)1>. Similar reaction of α -mercaptocarboxylic acids with thionyl chloride affords 1,2,3-oxadithiolan-4-one 2-oxides <77MI 415-02>. The bicyclic orthosulfite (**134**) has been obtained by treatment of perfluoropinacol either with sulfur dichloride and pyridine <76JA2895>, or with sulfur tetrafluoride <79IZV1913>. Monocyclic orthosulfites such as (**135**), prepared by the low-temperature reaction of 3,3-dimethyldioxetane with dipropyl sulfoxylate, could only be detected in solution at low temperatures, since they decomposed at higher temperatures <75JA3850>. Reaction of a mixture of geometrical isomers of 1,1,1,4,4,4-hexafluoro-2,3-dimethoxy-2-butene with sulfur trioxide afforded the 1,3,2-dioxathiolane 2,2-dioxide (**108**) as a mixture of stereoisomers <77JA1214>.



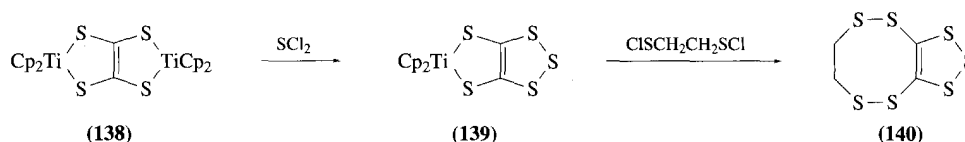
4.15.7.2.6 Halogens attached to ring

The fluorinated orthosulfite (**136**) was obtained from the reaction of glyoxal with sulfur tetrafluoride (Equation (40)) <86ZOR1812>. Tetrafluoro-1,2,3-trithiolane (**137**) is formed along with tetrafluoro-1,2,3,4-tetrathiane from the reaction between tetrafluoroethene and the vapors of boiling sulfur (Equation (38)) <62JOC3995>. The perfluoro-1,3,2-dioxathiolane 2,2-dioxide (**83**) was obtained along with other products from the reaction of perfluoro-2-methyloxirane with sulfur trioxide <73IZV2725>. Reaction of perfluorobutadiene with sulfur trioxide afforded the perfluoroalkenyl-1,3,2-dioxathiolane 2,2-dioxide (**109**) <79IZV118>. Perfluoro 1,3,2-dioxathiolane 2,2-dioxides have also been obtained from the electrolysis of perfluoroalkenes in fluorosulfonic acid <90IZV2048>. The chlorination of 1,3,2-dioxathiolane 2,2-dioxide was described in Section 4.15.5.5.

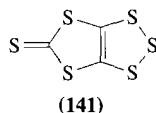


4.15.7.2.7 S- and Si-Linked substituents

Treatment of the bis(titanocene) complex (**138**) with sulfur dichloride afforded the 1,2,3-trithiole derivative (**139**) <90JOM(388)89>; further reaction of (**139**) with ethane-1,2-bis(sulfonyl chloride) afforded the trithiole (**140**) (Scheme 28) <91CB2141>. Electrolysis of a solution of carbon disulfide, followed by oxidation of the resultant mixture, furnished a compound tentatively assigned as the bicyclic 1,2,3-trithiole (**141**) <81JOC775>. 4,5-Bis(trimethylsilyl)-1,2,3-trithiole (**32**) was formed in 5% yield from the thermal reaction of 1,2-bis(trimethylsilyl)ethyne with elemental sulfur <93BCJ623>; the low yield of this product was attributed to extensive C—Si bond cleavage taking place under the reaction conditions.



Scheme 28



Treatment of 1,2-dihydroxyethane or higher 1,2-diols with S_2Cl_2 <65JOC2696>, or with the sulfur transfer agent, thiobis(benzimidazole) <80CC825>, afforded 1,3,2-dioxathiolane 2-thiones.

4.15.8 IMPORTANT COMPOUNDS AND APPLICATIONS

4.15.8.1 Applications in Research and Industry

The formation of 1,2,3-trioxolanes from an alkene and ozone is the first step in the ozonolysis reaction, which is widely used in synthesis to convert alkenes to aldehydes or carboxylic acids. No instances of double bond migration during ozonolysis are known (since the first step is a cyclo-

addition process) and thus ozonolysis may also be utilized in the structure elucidation of certain polymers <58CRV925>. In an industrial context, azelaic and pelargonic acids are produced by the ozonolysis of oleic acid and subsequent oxidative workup <58CRV925>. Perfluorocarboxylic acids $\text{CF}_3(\text{CF}_2)_n\text{CO}_2\text{H}$ are similarly obtained from alkenes of the type $\text{CF}_3(\text{CF}_2)_n\text{CH}=\text{CHR}$ ($n = 5, 7, 9$; $\text{R} = \text{H, Me}$) <77BRP1473807>. Ozonolysis also plays an important role in the treatment of unsaturated waste materials in industrial waters <B-72MI 415-01>.

Some derivatives of 1,2,3-trithiolane have been used as starting materials for sulfur-containing polymers <84MI 415-01>. Industrial applications for 1,2,3-trithiolane derivatives include their use as high-pressure lubricant oil additives <88EGP258606>, plasticizers and antioxidants <89EGP263770>.

The formation of 1,3,2-dioxathiolane 2-oxides from 1,2-diols and thionyl chloride may be used to investigate the stereochemistry of the hydroxy groups in the starting diol <63CRV557>; since the $\text{S}=\text{O}$ group is a chromophore (cf. Section 4.15.3.6) chiroptical methods can be used to study optically active diols <74JOC2073>. Industrial applications for 1,3,2-dioxathiolane 2-oxide (**8**) include its use as a spinning solvent for polyacrylonitrile <55USP2706674>, as a starting material for polyesters and urethanes <57BRP781169>, as a component in hydrogen sulfide scrubbing liquids <62BRP902256>, as a component in washing liquids for the purification of polyalkenes <62BRP903077>, as a component in detergents <62GEP1124962>, as a component in photographic emulsions <63GEP1159760>, and as a nonaqueous electrolyte for use in high-energy batteries <88BRP2202670>. Further uses for substituted 1,3,2-dioxathiolane 2-oxides include their applications as vulcanization accelerators <64FRP1379555>, as components in hair-drying agents <71USP3565571>, as preservatives for photographic developers <73USP3713826>, as polymer stabilizers <87EGP247913>, and as deliming agents for hides <87GEP(O)3527013>. The 1,3,2-dioxathiolane 2-oxide derived from the 5,6-dihydroxy unit of ascorbic acid has been investigated as an antioxidant for use in food <89EUP298399>, and for use in the preservation of wine <91MI 415-01>. 1,3,2-Dioxathiolane 2-thiones have been reported to increase the lubricating properties of mineral oils <67USP3357993>. The use of 1,3,2-dioxathiolane-4-ones as monomers for polymer production has been documented <57USP2811511>.

1,3,2-Dioxathiolane 2,2-dioxides are being used increasingly as epoxide equivalents in organic synthesis <88JA7538>. Industrial applications for 1,3,2-dioxathiolane 2,2-dioxides include their use in introducing acid substituents into various heterocycles, especially into cyanine dyes <58GEP1028718>. Fluorinated 1,3,2-dioxathiolane 2,2-dioxides are useful in imparting wash and wear characteristics to textiles such as cotton <62USP3055913>. 1,3,2-Benzodioxathiole 2,2-dioxide has been patented as a reagent for the *N*-sulfonation of amines <80USP4290975>.

1,2,5-Oxadithiolane 2,2,5,5-tetroxide and the corresponding benzoxadithiole tetroxide may be used to improve the dyeing characteristics of polyesters with basic dyes <71JAP7142631>.

4.15.8.2 Biological Activity

The high toxicity of ozone to man and animals is partly due to the ozonolysis of unsaturated compounds, particularly fatty acids, though this toxicity has been attributed to the final 1,2,4-trioxolane products rather than being associated with the intermediate 1,2,3-trioxolanes <75MI 415-01>. The 1,2,3-trithiolane (**10**) derived from dicyclopentadiene has been reported to show insecticidal properties <89EGP263770>. A series of 1,2,3-benzotrithioles and their corresponding 2-oxides have been claimed to show herbicidal, fungicidal, acaricidal, nematocidal and insecticidal activity <80BRP1571746>. The antibacterial activity of a naturally occurring 1,2,3-benzotrithiole has been demonstrated <91TL911>.

Derivatives of 1,3,2-dioxathiolane 2-oxide have been patented as pharmaceutical <87JMC1054> and agrochemical <92EUP529976> fungicides. In addition, certain derivatives have been reported as inhibitors of calcium dependent, neutral proteases and related enzymes <91MIP9109851>. The toxicology of 1,3,2-dioxathiolane 2-oxides and the corresponding 2,2-dioxides is dominated by their potential bioalkylating properties <75JPR943>; 1,3,2-dioxathiolane 2,2-dioxide (**21**) is more toxic than dimethyl sulfate, inducing local malignant tumors after subcutaneous injection <74MI 415-01>, and showing weak mutagenic properties both *in vitro* and *in vivo* <77MI 415-03>.

4.16

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

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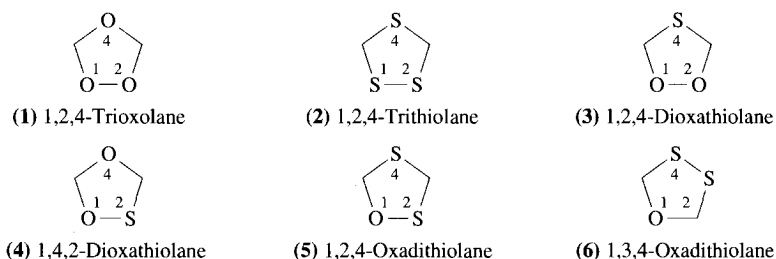
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4.16.1 INTRODUCTION

The first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) covered five-membered rings containing three oxygen or sulfur atoms in either the 1,2,3 or 1,2,4 positions <84CHEC-I(6)851>. The present chapter will cover the 1,2,4 systems and Chapter 4.15 covers rings with oxygen or sulfur in the 1,2,3 positions. Although it will be necessary to include certain points from CHEC-I for clarity, emphasis will be placed on developments since 1982.

The six possible five-membered monocyclic rings containing three oxygen or sulfur atoms in 1, 2, and 4 positions are shown in (1) to (6). Examples of each ring system are known, although 1,2,4-trioxolane (1) and 1,2,4-trithiolane (2) are the only parent rings that have been synthesized and characterized. The other systems are found as derivatives of the parent ring, with 1,4,2-dioxathiolanes and 1,2,4-oxadithiolanes only reported in the form of S-oxides.



All of the six heterocycles have been incorporated into spiro compounds or fused to non-aromatic carbocyclic or heterocyclic rings. 1,2,4-Trithiolanes have been reported in transition-metal complexes (Section 4.16.3.1). 1,2,4-Trioxolanes and 1,2,4-trithiolanes remain by far the most extensively studied ring systems. 1,2,4-Trioxolanes were first proposed as intermediates in the ozonolysis of alkenes by Staudinger in 1925 <25CB1088> and the structure proved by independent synthesis in 1932 <32CB1274>. In 1975, Criegee proposed the three-step mechanism that forms the basis of our understanding of the ozonolysis reaction (Section 4.16.8.2) <75AG(E)745>. Since 1953, 1,2,4-trioxolanes have attracted continued interest as key species in the three-step mechanism and as versatile reactive intermediates in synthetic chemistry. Whilst ozonolysis has been utilized since the mid-nineteenth century, 1,2,4-trithiolane chemistry started a hundred years later. 1,2,4-Trithiolanes are commonly formed as flavor constituents in a very wide range of cooked foods with much research targeted at mimicking their biosynthesis in model systems (Section 4.16.10.2). Many simple 1,2,4-trithiolanes have also been isolated as natural products.

Several reviews of 1,2,4-trioxolane chemistry have appeared since the early 1980s, mainly in the general context of the ozonolysis reaction <B-78MI 416-01, B-82MI 416-01, 83ACR42, B-84MI 416-01, 92CSR79>. Reviews have also covered ozonolysis of more specific types of alkene such as vinyl ethers <91MI 416-01>, cyclic vinylogous esters <93MI 416-01>, and haloalkanes <83IJ446>. 1,2,4-Trioxolanes are also included in treatises on peroxide chemistry <B-92MI 416-01, B-93MI 416-02>.

Fewer reviews have been forthcoming involving 1,2,4-trithiolanes <66HC(21-1)1, 89PS(43)63>. Reference should be made to CHEC-I <84CHEC-I(6)851> for a general review of material up to 1982 for all of the ring systems included in this chapter. In the following sections these ring systems will be discussed in the order (1) to (6).

4.16.2 THEORETICAL METHODS

With advances in technology, theoretical methods have gained importance as a powerful tool. 1,2,4-Trioxolanes have attracted the most interest, undoubtedly because of their pivotal role in the mechanism of the ozonolysis of alkenes. Apart from 1,2,4-trithiolane (**2**) nothing has been reported for the other five-membered rings (**3**)–(**6**) or their derivatives.

Early calculations using the Westheimer–Hendrickson model <69ACS2741>, CNDO/2 <73JA3460> and *ab initio* molecular orbital (MO) theory <79JCP(70)1898> for 1,2,4-trioxolane (**1**) gave insights into conformational preferences showing the O—O half chair to be the lowest in energy (cf. Section 4.16.4). Barriers to interconversion through planar forms and pseudorotational barriers were estimated in each case. In a later study, cyclopentane ring puckering was compared with that of a series of oxolanes using the 6-31G* basis set at the Hartree–Fock level of theory. Substituent effects were estimated on the basis of substituent orientation and π -type HOMO overlap <83IJ72>.

Thermochemical data can also be estimated from *ab initio* calculations <82MI 416-02>. A 1993 molecular mechanics study of alkyl peroxides (including 1,2,4-trioxolane) with MM3 has led to a parameter set that allows the calculation of geometries, energies, vibrational frequencies, and heats of formation for simple peroxides, giving good agreement with experimental and theoretical data <93MI 416-03>. Poorer results were obtained with MM2. In a separate report, available structural parameters were used to calculate chemical thermodynamic functions and the properties of formation of 1,2,4-trioxolane using the rigid-rotor harmonic oscillator approximation in the ideal gas state <92MI 416-02> (Section 4.16.4).

AM1 has been used to study the reaction of ozone with ethylene and 2-butene <91JA735>. Two other methods were discounted: MINDO/3 which is known to give energies that are too negative for molecules containing pairs of adjacent heteroatoms and MNDO which can overestimate atomic distances in the range of those found in cycloaddition transition states. Calculations of the energetics of ozonolysis (including that of fluoroalkenes) from the early 1980s used restricted Hartree–Fock (RHF) and Rayleigh–Schrodinger–Moller–Plesset (RSMP) calculations <84CHEC-I(6)851>.

Insights into the acidolysis of ozonides have been gained using *ab initio* SCF–MO calculations at the split valence 4-31G level (Section 4.16.5.2.1). Comparisons were made between experimental observations of reaction products and calculated stabilities and charge distributions for the species involved <83JOC2366>.

Early molecular mechanics calculations performed on 1,2,4-trithiolane (**2**) <76JA2741> suggested similar conformational results to those obtained for 1,2,4-trioxolane. CNDO calculations were performed to assign photoelectron ionization energies and estimate the dihedral angle $\tau(\text{CS}=\text{SC})$ <76CJC146> (Section 4.16.3.6). Although they were sufficient to give estimates of bond distances and angles, the calculations were not sophisticated enough to give a quantitative answer to more subtle structural features such as the small difference in bond length between C—S_(sulfide) and C—S_(disulfide) or the importance of π orbitals on the sulfur atoms interacting with a CH₂ group to stabilize the twist conformation.

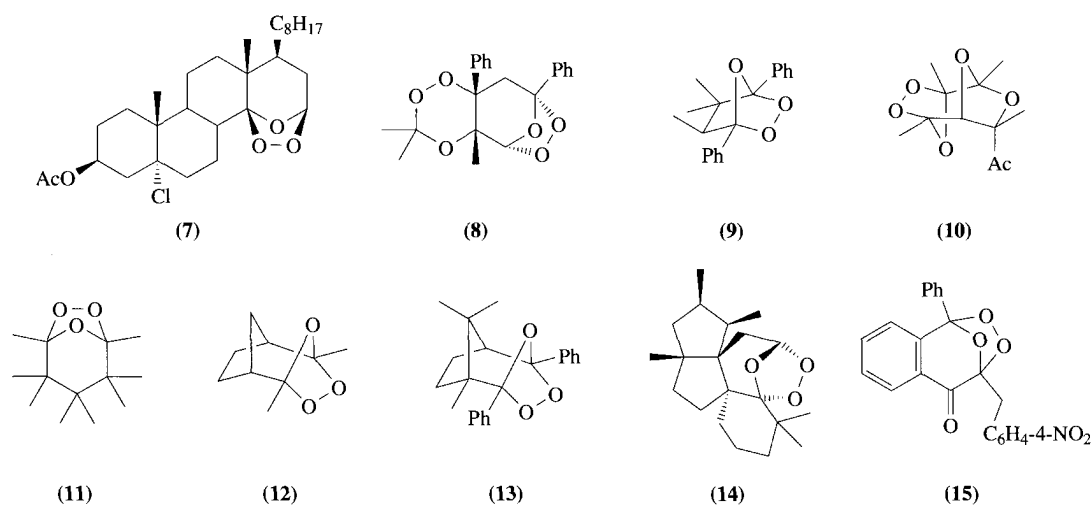
Ab initio calculations have been carried out on several simple 1,2,4-trioxolanes in conjunction with other experimental methods, notably microwave spectroscopy, in order to provide additional insight into the conformations arising from experiments (Section 4.16.3.2).

4.16.3 EXPERIMENTAL STRUCTURAL METHODS

4.16.3.1 Electron and X-ray Diffraction

Many new crystal structure determinations of 1,2,4-trioxolanes have been reported since 1982. The majority of examples are ring-fused or spirocyclic ozonides reflecting the increased stability that this substitution confers. Examples containing fused rings (**7**)–(**15**) are given in Table 1, highlighting that in each case the 1,2,4-trioxolane ring is constrained in an envelope conformation. This ring strain is reflected by the often smaller C—O—C angles and larger O—O bond lengths than those found in 1,2,4-trioxolane itself. Data from microwave spectroscopy supports this suggestion more strongly (Section 4.16.3.2). The C—O—O—C torsion angle in these examples is generally close to 0° compared with 49.1° in 1,2,4-trioxolane. The electron diffraction data for 1,2,4-trioxolane are in agreement with an O—O half chair conformation but do not rule out an O(4) envelope.

Single-crystal x-ray analysis of structures containing isolated 1,2,4-trioxolane rings can give more information regarding preferred conformations (Table 2). In 1970, compound (**16**) gave ambiguous results, however two structures (**17**) and (**18**) have given more concrete answers to the question of

Table 1 Structural parameters of 1,2,4-trioxolane rings where C(3) and C(5) are the ring-junction atoms of a bicyclic or polycyclic system.

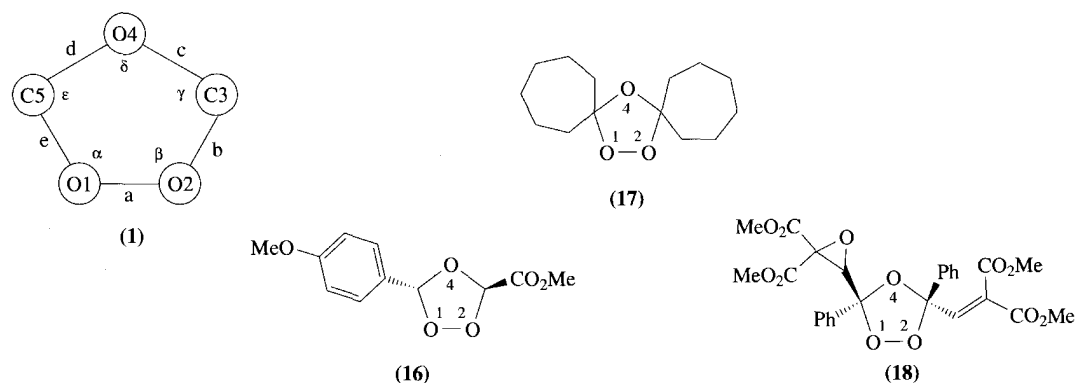
Compound	O—O Bond length (Å)	C—O—C Bond angle (°)	Trioxolane conformation	Ref.
(1) ^a	1.487	105.9	twist chair	69ACS3398
(7)	1.464	—	C(5) envelope	84TL1403
(8)	1.481	101.6	ether O envelope	87AX(C)701
(9)	1.485	95.7	ether O envelope	86AX(C)1239
(10)	1.489	100.9	ether O envelope	85JOC2647
(11)	1.471	104.0	ether O envelope	93AX(C)400
(12)	—	100.6	ether O envelope	91JOC4005
(13)	1.467	101.2	puckered envelope	90AX(C)1942
(14)	1.480	102.4	ether O envelope	90AJC1047
(15)	1.459	104.6	ether O envelope	79JCS(P2)1703

^aElectron diffraction data included for comparison (more recent microwave values are 1.470 Å and 102.83°).

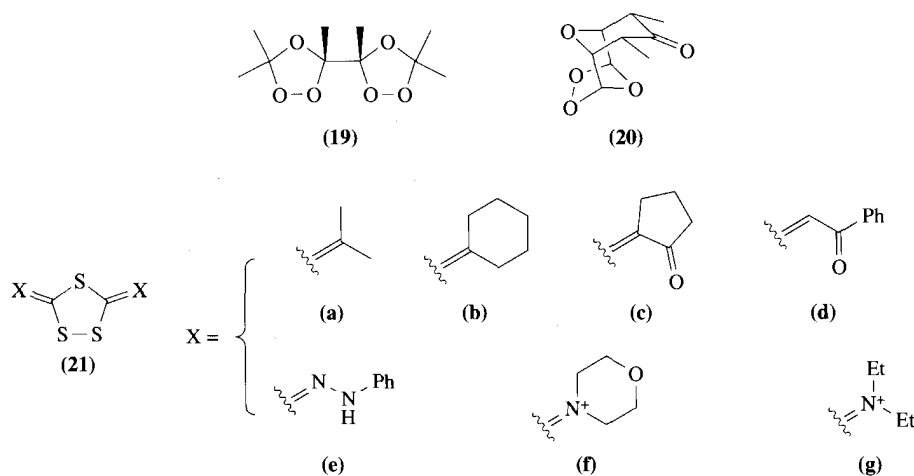
conformation. The nature of the substituents may be an important factor in determining why both have peroxy oxygen envelope conformations. In (17) the dispirocycloheptane rings have their own conformational preferences <91CB391>, and in (18) the large C—O—C and O—C(5)—O bond angles and the short C(5)—O_{ether} bond distance suggest some C(5)—O_{ether} double-bond character, possibly a result of the substituents at C(5) <90G143>. The half-chair and asymmetric peroxy envelope conformations are energetically close so that in crystals, packing forces may also be a dominant factor.

Other interesting compounds which have successfully allowed x-ray analysis are shown in (19) and (20). The dimeric ozonide (19) exhibits an asymmetric peroxy envelope conformation in each ring <89JOC383>. In (20) the ether oxygen is only 2.66 Å away from the carbonyl carbon <83JCS(P1)167>. This seems to be a stabilizing interaction since reduction of the carbonyl produces labile products. Many of the reported 1,2,4-trithiolane ring crystal structures reported are of type (21) with two exocyclic double-bond substituents <90JCS(D)3697>. The diisopropylidene derivative (21a) adopts an exact half chair conformation <82AG(E)291, 82CB3653>. Most of the others are similar, except (21d) where a sulfide envelope is preferred to avoid sulfur-carbonyl interactions.

In an isolated example, 1,1'-dibenzoylferrocene reacted with tetraphosphorus decasulfide to give a crystalline ferrocene derivative with the two cyclopentadiene rings bridged by a 1,2,4-trithiolane ring <90JCS(D)3697>. All of the bond lengths were longer than those found in the previous x-ray structures, with the two carbon atoms essentially tetrahedral and the trithiolane ring adopting an ether envelope conformation. *Trans*-3,5-bis(cymantrenyl)-3,5-dimethyl-1,2,4-trithiolane has also been isolated. The trithiolane ring adopts an S—S half-chair conformation (cymantrenyl = η^5 -C₅H₄Mn(CO)₃) <92MI 416-03>.

Table 2 Structural parameters and conformations of 1,2,4-trioxolane rings obtained from x-ray diffraction compared with data for 1,2,4-trioxolane from electron diffraction.^a

No.	Bond lengths (Å)					Bond angles (°)					Conformation	Ref.
	a	b	c	d	e	α	β	γ	δ	ϵ		
(1)	1.487	1.414	1.414	1.414	1.414	99.2	99.2	105.3	105.9	105.3	O-O half chair	69ACS3398
(16)	1.479	1.401	1.468	1.559	1.338	102.2	98.0	107.9	102.1	103.3	data not conclusive	70ACS2137
(17)	1.465	1.435	1.433	1.430	1.443	102.1	100.7	103.0	107.9	104.3	peroxy oxygen envelope	91CB391
(18)	1.468	1.468	1.440	1.382	1.449	102.1	100.0	102.7	107.3	106.0	peroxy oxygen (O(2)) envelope	90G143

^aNotation for bond lengths and angles is as shown for 1,2,4-trioxolane (1).

4.16.3.2 Microwave Spectroscopy

1,2,4-Trioxolanes remain the most studied ring system by microwave spectroscopy and recently, 1,2,4-trithiolane also became the subject of attention. In all cases, isotopically labelled derivatives were made which have very different rotational constants. These aid assignment of structures and also provide useful tools for looking at the mechanism of the ozonolysis reaction. Rotational constants for the parent compounds and their calculated dipole moments are given in Table 3.

Results from the early 1970s, obtained from 1,2,4-trioxolane (ethylene ozonide) <72JA6337> and 3-methyl-1,2,4-trioxolane (propylene ozonide) <74JA348> indicated an O—O half-chair conformation, supporting the suggestion from electron diffraction results (Section 4.16.3.1). The methyl group in 3-methyl-1,2,4-trioxolane was shown to occupy the equatorial position, playing little part in determining conformation.

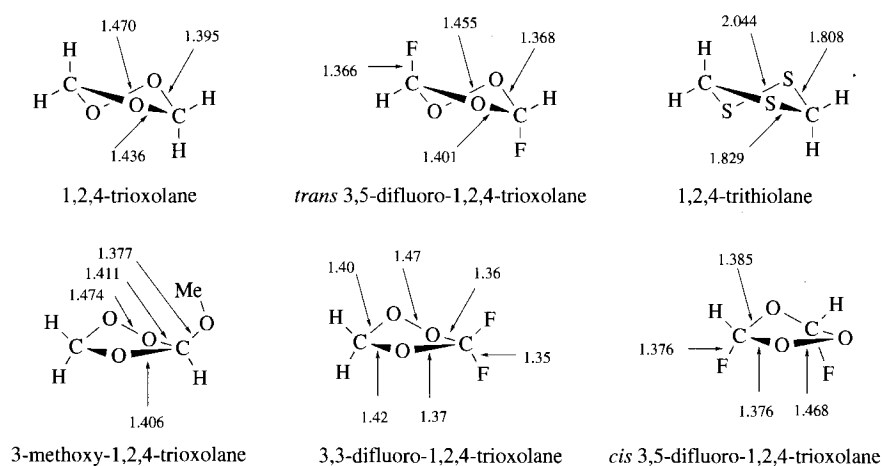
Cyclobutene ozonide <88JST(190)125> revealed a long O—O bond of 1.492 Å relative to cyclopentene ozonide (1.475 Å) <83JPC5381> and also a smaller C—O—C angle of 94.0° compared with

Table 3 Ground state rotational constants and dipole moments for 1,2,4-trioxolanes and 1,2,4-trithiolane.

Compound	Dipole moment (D)	Rotational constants (MHz)			Ref.
		A	B	C	
1,2,4-trioxolane	1.09	8243.84	8093.80	4584.74	72JA6337
3-methyl-1,2,4-trioxolane	1.29	7574.36	3476.33	2644.79	74JA348
<i>trans</i> -3,5-dimethyl-1,2,4-trioxolane	1.34	6022.05	2103.08	1695.66	74JA348
3-fluoro-1,2,4-trioxolane	—	6774.0	3196.3	3122.7	76JA4012
3,3-difluoro-1,2,4-trioxolane	2.74	4966.561	2570.661	2456.797	82JPC1415
<i>trans</i> -3,5-difluoro-1,2,4-trioxolane	—	6093.333	2287.188	2001.709	86JPC3092
<i>cis</i> -3,5-difluoro-1,2,4-trioxolane	0.994	4256.68	2923.67	2347.38	84JPC2025
3-methoxy-1,2,4-trioxolane	1.99	4815.386	2435.852	2336.675	88JA2081
1,2,4-trithiolane	0.465	3819.367	2621.105	1710.601	84JA841
cyclopentene ozonide	2.48	3035.187	2655.594	2149.477	83JPC5381
cyclobutadiene monoozonide	2.62	4470.470	3839.377	3361.047	89JPC2276
cyclobutene ozonide	2.857	4199.674	3587.994	3066.135	88JST(190)125

101.0° respectively. These results are both indicative of increased strain in the cyclobutene ozonide. The effect is even more pronounced in cyclobutadiene monoozonide where the C—O—C angle is 93.8° <89JPC2276>. This evidence of strain is also apparent in certain x-ray structures (Section 4.16.3.1).

3-Methoxy-1,2,4-trioxolane has a peroxy envelope conformation and an axial methoxy group with a short C—OMe bond of 1.377 Å <88JA2081> (see below). The methyl group exhibits an unusual orientation *anti* to the ring hydrogen, placing it over the ozonide ring. The anomeric and *exo*-anomeric effects are dominant in determining this conformation. This situation is mirrored in the conformations of several fluorinated 1,2,4-trioxolanes (Figure 1). *Trans*-3,5-difluoro-1,2,4-trioxolane (*trans*-difluoroethylene ozonide) shows an O—O half-chair conformation with C₂ symmetry and diaxial fluorines with long C—F bonds <86JPC3092>. The shortening of the C—O_{peroxy} bonds (both 1.368 Å) is apparent relative to C—O_{ether} (1.401 Å). *Ab initio* calculations at the HF/6-31G* level were also carried out and the results were rationalized by anomeric interactions of the σ_{CF}^{*} orbitals with peroxy oxygen lone pairs. The structure of *cis*-3,5-difluoro-1,2,4-trioxolane (*cis*-difluoroethylene ozonide) consistent with the data obtained was an ether oxygen envelope with axial fluorines and C_s symmetry <84JPC2025>. As in other fluorinated ozonides, the conformation is a balance of interactions between the substituents and the ring puckering forces, with the anomeric effect playing a dominant role. 3,3-Difluoro-1,2,4-trioxolane (1,1-difluoroethylene ozonide) was shown to sit in a peroxy oxygen envelope <82JPC1415>.

**Figure 1** Selected bond distances (Å) and representations of the conformations of 1,2,4-trioxolanes and 1,2,4-trithiolanes obtained from microwave spectroscopy.

The microwave spectra of 1,2,4-trithiolane and several deuterated analogues suggest an S—S half-chair conformation with C₂ symmetry <84JA841>. This is in agreement with MM calculations showing the C₂ conformation to be the lowest in energy. The S—S bond length of 2.044 Å is identical

to that found in MeSSMe and other structural parameters are similar to those in open chain compounds. It was noted (as it has been for 1,2,4-trioxolanes) that there were no vibrational perturbations from ring fluxionality. The ground and excited vibrational states observed are well below the barriers to ring pseudorotation or inversion. A lower limit of approximately 1.5 kcal mol⁻¹ was estimated for the pseudorotation barrier.

4.16.3.3 Nuclear Magnetic Resonance Spectra (NMR)

4.16.3.3.1 Carbon-13 and proton NMR

The ¹H NMR spectrum of 1,2,4-trioxolane (**1**) exhibits a singlet at δ_{H} 5.20 ppm in acetone-*d*₆ at -80 °C <79JOC3181>. Similarly 1,2,4-trithiolane (**2**) gives a singlet at δ_{H} 4.17 ppm in CS₂ at -117 °C <72T3489>. The protons in each ring are magnetically equivalent, a consequence of the low barriers to pseudorotation. This effect is observed in symmetrical disubstituted derivatives which also give a singlet proton resonance.

The routine use of NMR techniques in the analysis of 1,2,4-trioxolanes and related rings has increased considerably in the last two decades. A general summary of proton chemical shifts reported for various substituted and unsubstituted compounds is given in Table 4. A similar summary of carbon chemical shifts (Table 5) illustrates their use in the analysis of substituted trioxolanes.

Table 4 A general summary of reported ¹H NMR chemical shifts (δ) for ring hydrogens of 1,2,4-trioxolanes, 1,2,4-trithiolanes, and 1,2,4-dioxathiolanes.^a

Substituent Z	δ_{H} (ppm)	Substituent Z	δ_{H} (ppm)
Hydrogen	4.91–5.64	—CO ₂ R	5.35–5.91
Alkyl (R)	4.63–5.60	—OCOR	7.03–7.14
Substituted-phenyl (Ar)	5.82–6.78	F	7.63
Alkoxy (OR)	5.95–6.35	Vinyl	5.30–5.96

5.50–5.94

6.05–6.86

4.50–4.98

5.18–5.29

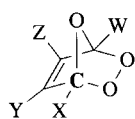
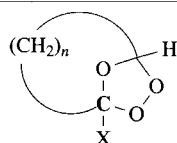
^aThe values given here cover a range of substituents X, Y, Z and R and several solvents.

For simple 3,5-dialkyl-1,2,4-trioxolanes and trithiolanes, it has been a general assumption that at least one of the ring protons is found at lower field in the *cis* isomer <84MI416-02>. Exceptions to this empirical rule do exist, for example with aryl- and vinyl-substituted 1,2,4-trioxolanes <92JOC1649>. In certain cases the stereochemistry has been correlated with high-pressure liquid chromatography (HPLC) retention times (Section 4.16.4). Nuclear Overhauser effects (NOEs) are often small in 1,2,4-trioxolane ring systems, so may not give unambiguous assignments of stereochemistry <89JOC115>. NOE studies on 3-methyl-1,2,4-trioxolane (propylene ozonide) did, however, suggest that the proton *cis* to the methyl group was at δ 5.038 ppm (*H_c*) with the *trans* proton at δ 5.178 ppm (*H_b*) (Figure 2) <86MRC1044>. This assignment was confirmed by correlating NMR peak integral changes with variation in the intensity of peaks in the microwave spectra of deuterated analogues <85JOC3371>.

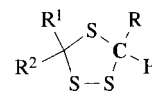
The investigation of propylene ozonide also revealed a long range coupling of 0.50 Hz between *H_b* and the methyl group. This is indicative of the bis-equatorial arrangement of these two substituents, arising from the O—O peroxy twist in the trioxolane ring. *H_a* and *H_c* are diaxial so do not give a similar result. The coupling constant of 0.48 Hz between *H_b* and *H_c* is typical of the very small couplings (often zero) observed for geminal protons in 1,2,4-trioxolane and trithiolane rings. This is considered to be an effect of the electronegative neighboring heteroatoms <91H(32)437>.

Table 5 A general summary of reported ^{13}C NMR chemical shift (δ) for ring carbons of 1,2,4-trioxolanes and 1,2,4-trithiolanes.^a

Substituents		δ_{C} (ppm)	Substituents		δ_{C} (ppm)
Y	Z		Y	Z	
H	H	93.5–96.6	R	OCOR	119.0–120.1
H	R	101.9–104.8	R	CN	97.8–98.3
R	R ¹	108.6–111.6	R	CF ₃	104.6–104.8
H	OR	111.9–114.7	OR	CO ₂ Me	113.5
R	OR	119.0–122.2	H	CO ₂ Me	106.6–107.3
H	Ar	97.8–106.7	Ar	Ar	110.8
H	OCOR	106.1–107.2	OR	CF ₃	114.3–117.4

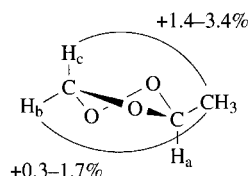


X = H, 98.7–104.3
 X = alkyl, 107.3–115.4
 X = alkoxy, 124.3–125.3
 X = Cl, 119.8–122.8



64.1–66.7

^aThe values given here cover a range of substituents W, X, Y, Z and R and several solvents.

**Figure 2** Average NOE difference spectra measurements for 3-methyl-1,2,4-trioxolane.

4.16.3.2 Oxygen-17 NMR

^{17}O NMR resonances for several 1,2,4-trioxolanes have been reported <91CC816> (Table 6). The ether and peroxide signals are very distinct proving the value of ^{17}O NMR as an analytical tool for characterization of ozonides. It can be used to determine unequivocally whether a compound is an ozonide (peroxide δ 295–327 ppm) or tetroxane ((**26**), for example δ = 256 ppm). This is often a competing product from the ozonolysis reaction of alkenes (Section 4.16.8.2).

It has been suggested that there may be a relationship between conformational changes and ^{17}O

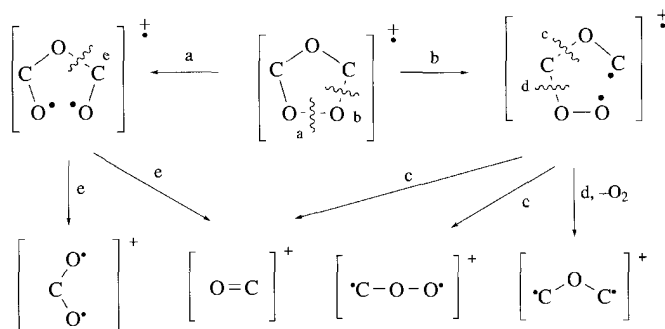
Table 6 ^{17}O NMR Chemical shifts (δ) of selected 1,2,4-trioxolanes (ppm) <91CC816>.

Compound	ether O	O—O
(22a)	106	306
(22b)	106	297
(23)	139	310
(24a)	172	327
(24b)	162	319
(25)	129	295
(26)	—	256

NMR shifts for a series of cyclic peroxides <85JOC4484>. Since the shifts observed for ozonides were large (Table 6), it was inferred that the C—O—O—C angles in these examples may be close to 0°. The 1,2,4-trioxolane ether oxygen resonances (δ 106 to 172 ppm) are also large compared with simple dialkyl ethers (δ - 52 to 76 ppm). This is probably a result of strong β -deshielding, comparable to the shifts of acetal oxygen resonances relative to ethers.

4.16.3.4 Mass Spectrometry

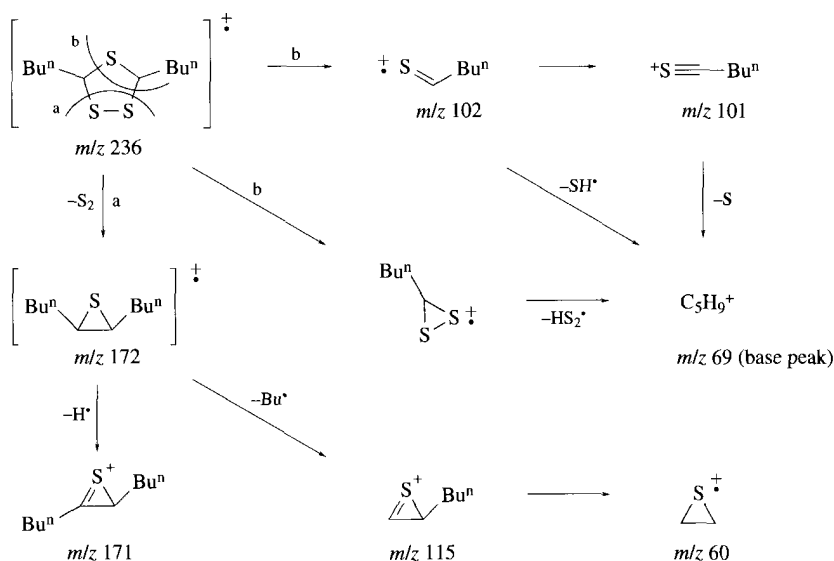
Simple 1,2,4-trioxolanes often give low intensity or undetectable molecular ions in their mass spectra. Two pathways have been suggested as the main fragmentation processes (Scheme 1): path (a), O—O bond cleavage followed by C—O bond cleavage; path (b), C—O bond cleavage followed by elimination of O₂ or repeated C—O fragmentation. Both are supported by ¹⁸O labelling studies <69CJC919>.



Scheme 1 Schematic summary of 1,2,4-trioxolane mass spectral fragmentations.

Mass spectrometry has been used to investigate the mechanism of ozonolysis <79JOC3185, 80JA4763> and to study the gas-phase reaction of furans with singlet oxygen in which endoperoxides are intermediates.

1,2,4-Trithiolanes tend to give much stronger molecular ions than their 1,2,4-trioxolane counterparts <81JPR169>. Mass spectrometry is thus effective in the determination of products obtained from volatile plant extracts which contain simple 1,2,4-trithiolane natural products <81MI 416-01, 90MI 416-02> (Section 4.16.10.2). The similar structures and small quantities of material involved make other analytical techniques more difficult. A typical 1,2,4-trithiolane fragmentation pattern is shown in Scheme 2 <86MI 416-04>.

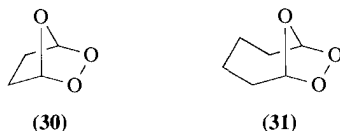


Scheme 2 Fragmentation pattern for 3,5-di-*n*-butyl-1,2,4-trithiolane.

The splitting $\Delta\epsilon$ of the first two ionization potentials of peroxides can be related to the O—O torsion angle ϕ by the equation $\Delta\epsilon = 2.08\cos \phi + 0.15$ (eV). Thus it is possible to infer information

about gas-phase conformations of 1,2,4-trioxolanes by analysis of their photoelectron spectra <79LA1473>. Bicyclic ozonides with restricted conformational freedom are predicted to have smaller O—O torsional angles than 1,2,4-trioxolane (Table 8).

Table 8 Vertical ionization potentials I_v of 1,2,4-trioxolanes and predicted O—O torsion angle φ <79LA1473>.



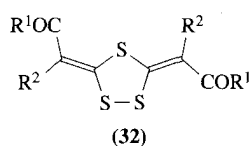
Compound	$I_v(\text{O—O})$ (eV)		$I_v(\text{ether O})$ (eV)	$\Delta\varepsilon(\text{O—O})$ (eV)	φ
(1)	12.40	10.96	10.67	1.44	52
(30)	11.78	9.60	10.21	2.18	13
(31)	11.55	9.60	10.24	1.95	30

The photoelectron spectra of 1,2,4-trioxolane and 1,2,4-trithiolane were in good agreement with theoretical calculations which assumed a half-chair conformation as a starting point. 1,2,4-Trithiolane gave the following characteristic vertical ionization potentials (eV): 8.72 ($n^-(\text{SS})$), 9.10 ($n^+(\text{SS}) - n(\text{S})$), 10.99 ($n^+(\text{SS}) + n(\text{S})$), and 11.06 ($\sigma(\text{CS})$) <76CJC146> (see also Section 4.16.2 for energy calculations).

4.16.3.7 Other Physical Methods

The *cis* and *trans* isomers of 1,2,4-trioxolanes <71CB1807> and 1,2,4-trithiolanes have been assigned by comparison of their dipole moments, the *cis* isomer having the larger value. This has also formed the basis for assignments of stereochemistry based on HPLC analysis, with the *cis* isomer judged to have the longer retention time because of its larger dipole moment <92MI 416-04>. Dipole moments calculated from microwave spectra are summarized in Section 4.16.3.2.

UV absorption of saturated five-membered ring heterocycles generally mirrors the acyclic aliphatic compounds. The $n\text{--}\sigma^*$ transitions involving the heteroatom lone pairs are most important. 1,2,4-Trithiolanes with exocyclic double bonds such as (32) show a $\pi\text{--}\pi^*$ transition for the carbonyl system at 230–250 nm <66T3001, 70BCJ2938, 71CJC1477>. There is also an intense absorption at 320–350 nm indicating a near planar ring with proposed delocalization through the sulfur *d*-orbitals.



4.16.4 THERMODYNAMIC ASPECTS

It is a common assumption that secondary ozonides are thermodynamically and chemically unstable species. It is clear from the number of reported ozonide isolations (many chromatographically stable and with sharp melting points) that this is not always the case. Nevertheless, caution should always be exercised when handling peroxidic materials. When a 1,2,4-trioxolane is highly substituted, the ring system can be very robust, for example (11) (Section 4.16.5.3.4) which is stable to reduction by triphenylphosphine in refluxing tetrahydrofuran (THF) <94JOC5055>. The *gem*-dimethyl effect accelerates the intramolecular cycloaddition of carbonyl oxide and ketone during the ozonolysis of the corresponding cyclopentenone. Semi-empirical PM3 calculations for the product suggest that the increase in conformational strain produced during lengthening of the O—O bond is greater with more substitution.

Structural, conformational, and energetic properties of cyclopentane and 1,2,4-trioxolane were

investigated and compared using theoretical methods. It was found that puckering and inversion barriers for cyclic peroxides increase with the number of O—O bonds but decrease with the number of ether bridges. Although the O—O half chair was found to be the most stable, a multitude of conformers exist at room temperature because of free pseudorotation [83IJ72].

For 1,2,4-trioxolanes, calculations consistently show that the symmetrical O—O half chair (g) is the lowest energy conformation of the seven possible (Figure 3) (see also Section 4.16.2). This prediction is confirmed experimentally by microwave spectroscopy (Section 4.16.3.2) and electron diffraction (Section 4.16.3.1). *Ab initio* results suggest the following order of decreasing stability for 1,2,4-trioxolane (1): (g) > (c) > (e) > (b) > (f) > (d) > (a) [79JCP(70)1898]. Barriers for interconversion through the planar form and pseudorotation were calculated at 13 kJ mol⁻¹ and 25 kJ mol⁻¹ respectively. For 1,2,4-trithiolane (2), results are similar, with calculations showing the symmetrical S—S half chair conformation as the lowest in energy, and the following order of decreasing stability: (g) > (c) > (b) > (d) > (a). The interconversion and pseudorotation barriers were estimated at 13.0 kJ mol⁻¹ and 18.8 kJ mol⁻¹ respectively [76JA2741].

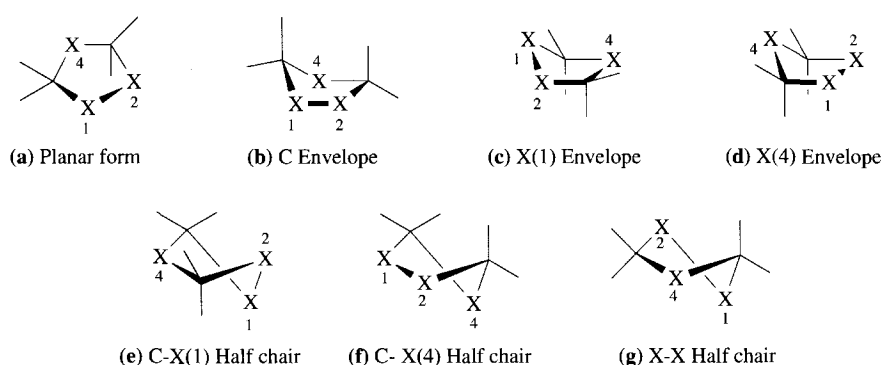


Figure 3 Possible conformations of five-membered heterocycles where X = O, S.

Substituents can play important roles in determining conformation. It is clear from microwave analysis of fluorinated and alkoxy substituted 1,2,4-trioxolanes, where the substituents are mostly axial and C—O bonds in the rings are shorter, that the anomeric effect is dominant (Section 4.16.3.2). The trioxolane ring twists in order to maximize overlap of oxygen lone pairs with the σ^* orbital of the C—(substituent) bond. Peroxy lone pairs prefer to lie in a staggered orientation to minimize electrostatic repulsion [93MI 416-03].

When 1,2,4-trioxolane rings are conformationally constricted in some way, perhaps by fusion to another ring, the increased strain is highlighted by smaller C—O—C bond angles and often longer O—O bonds (Sections 4.16.3.1 and 4.16.3.2). In many cases the constraints imposed by a C(3)—C(5) linking group overcome the usual destabilization arising from an oxygen ether envelope conformation and this is the one observed. In one example, x-ray analysis of 1,2,4-trioxolane (20) showed a very short distance (2.66 Å) between the ether oxygen of the trioxolane ring and the carbon of a nearby ketone carbonyl. This stabilizing interaction for the ether oxygen envelope conformation of the trioxolane was removed on reduction of the ketone.

1,2,4-Trithiolane is a stable compound at room temperature, although it will polymerize eventually and is best kept cool and sealed from the atmosphere. Separation of *cis/trans* mixtures of 3,5-dialkyl-1,2,4-trithiolanes is possible on alumina. Reverse-phase HPLC has been used to separate cyclic methylene sulfides, and tellurides with retention times and capacity factors dependant in a systematic way on ring size, number and type of chalcogens and the number of heteronuclear bonds within the ring.

Microwave analysis of 1,2,4-trithiolane showed that many of the structural parameters were close to those of analogous acyclic compounds (see Section 4.16.3.2) [84JA841]. It was also discovered that the pseudorotational barrier was significantly higher than the ground and excited energy states observed. Presumably this barrier is still low enough to lead to the absence of geminal H—H coupling in the ¹H NMR spectrum (i.e. fluxional behavior) on the NMR time scale (Section 4.16.3.3).

It has been suggested that there may be an important interaction between π orbitals on the three sulfur atoms with the CH₂ moieties which stabilizes the twist conformation in (2). It is possible that this is also an important factor in the stabilization of the twist-chair of ethylene ozonide

<79JCP(70)1898>. Analysis of bonding and antibonding interactions of substituents with these π -type bonds can be used to predict their effect on conformation <83IJ72>.

Although there are no experimental values for thermodynamic functions of any of the 1,2,4-trioxolanes or trithiolanes, it has been possible to estimate values for ethylene ozonide using available structural parameters and fundamental frequencies (Table 9) <92MI 416-02>. The ideal-gas thermodynamic properties are given for the single temperature of 298.15 K, although these were reported over a range of temperatures from 0–1500 K. $\Delta_f G^\theta$ was estimated by comparison of enthalpies of formation for other five-membered rings. In 1993, 1,3,4-oxadithiolanes were isolated for the first time, notably in a highly substituted ring-fused form <93BCJ1714>.

Table 9 Thermodynamic functions for 1,2,4-trioxolane calculated from experimental structural parameters.

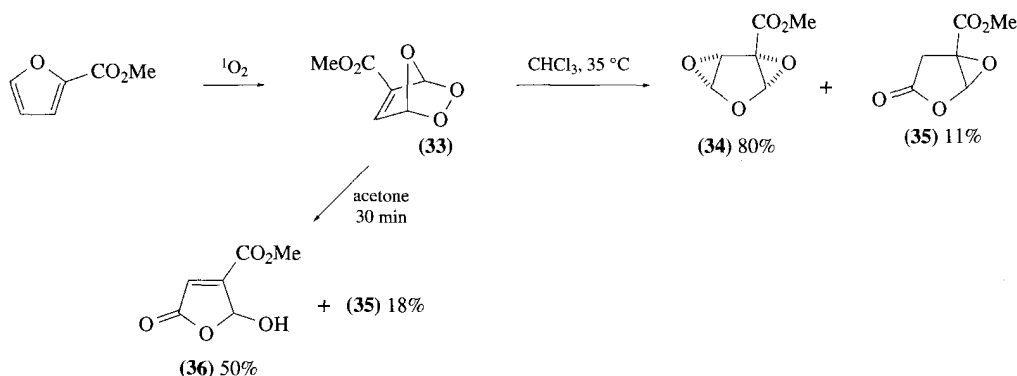
T^θ (K)	C_p^θ (J K ⁻¹ mol ⁻¹)	S^θ (J K ⁻¹ mol ⁻¹)	$-(G^\theta - H_o^\theta)/T$ (J K ⁻¹ mol ⁻¹)	$H^\theta - H_o^\theta$ (kJ mol ⁻¹)	$\Delta_f H^\theta$ (kJ mol ⁻¹)	$\Delta_f G^\theta$ (kJ mol ⁻¹)	$\log K_f^\theta$
298.15	68.846	285.237	238.973	13.794	-2.1×10^5	-121.950	21.365

4.16.5 REACTIVITY OF RING SYSTEMS

4.16.5.1 Thermal and Photochemical Reactions Formally Involving No Other Species

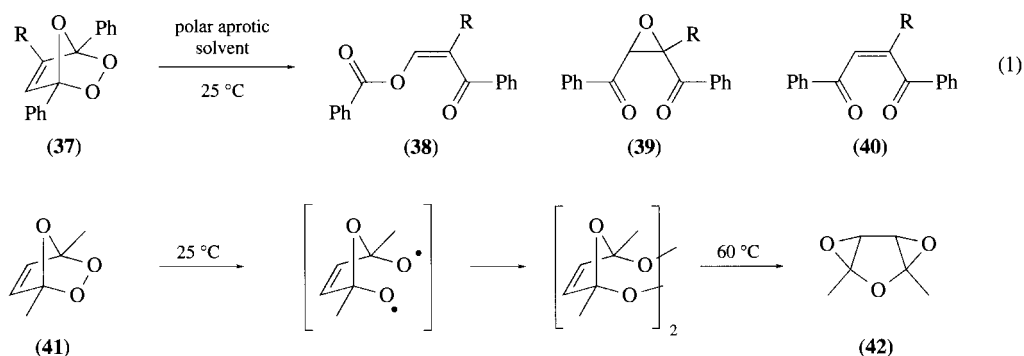
4.16.5.1.1 Rearrangements

Normally 1,2,4-trioxolanes and 1,2,4-trithiolanes undergo fragmentation under thermal conditions (cf. Section 4.16.5.1.2). In bicyclic or other fused ring systems there is more chance of rearrangement occurring. The photooxygenation of substituted furans, oxazoles and thiophenes gives rise to the corresponding endoperoxides in which subsequent transformations are dependent on the substitution patterns, with several rearrangement pathways possible <85T2057>. 3,5-Disubstituted furan endoperoxides such as (33) rearrange in chloroform to the *cis* diepoxide (34) and the epoxyfuranone (35) (Scheme 3) <85CC124, 87JCS(P1)1833>. It was suggested that a concerted process was involved although a radical pathway could not be ruled out. In more basic solvents such as acetone, 5-hydroxyfuran-2(5*H*)-ones (36) are the major products, probably via ion-pair intermediates <85S1151>.



Scheme 3

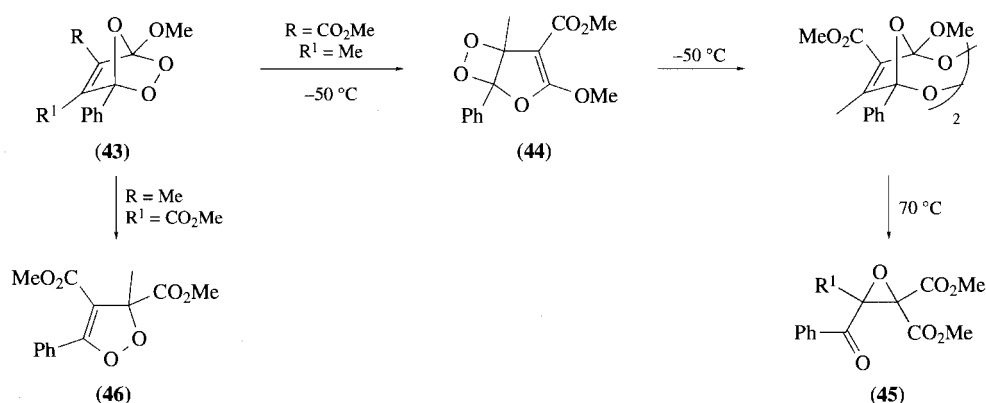
Endoperoxides of furans substituted in the 2- and 5-positions such as (37) undergo different rearrangements giving the enol ester (38) and epoxy diketone (39) as the main products together with a small amount of dione (40) (Equation (1)) <83JCS(P1)2071, 84S66>. The relative thermal instability of furan endoperoxides is related to the electron density in the bicyclic unsaturated ring. Aryl substituted endoperoxides give mainly furans (by elimination of $^1\text{O}_2$), epoxides and enol esters, whereas alkyl substituents generally lead to diepoxides. 2,5-Dimethylfuran endoperoxide (41) slowly dimerizes at room temperature and, on warming to 60°C in dipolar aprotic solvent, gives the diepoxide (42) (Scheme 4) <85T2057>.



Scheme 4

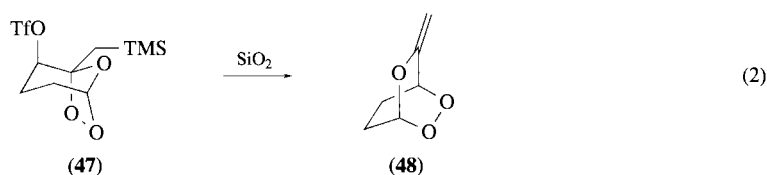
More complex examples exist where the 2-substituent on the furan is a polyhydroxyalkyl or glycosyl moiety <89CAR(191)209>. In these cases, the rearrangement products provide useful intermediates for the preparation of heterocycle-substituted sugar derivatives. Sometimes Baeyer–Villiger-type products are observed, such as 3-keto enoic esters instead of 3-keto enol esters <81TL1443>.

Some novel intermediates have been identified at low temperature in the thermal rearrangement of endoperoxides of 2-alkoxyfurans (43) (Scheme 5). The first example of a furan dioxetane (44) was identified from the rearrangement of (43) at -50°C <91CC1061> and, one example has been isolated <93AG(E)80>. Subsequent dimerization at -50°C followed by heating to 70°C gave the epoxide (45) as the isolated product. If the electron-withdrawing group is positioned at the furan 4-position, an unusual 3*H*,1,2-dioxole (46) is formed and was identified by low-temperature NMR spectroscopy. Further rearrangement occurred on warming <89JCS(P1)241, 91JCS(P1)1479, 92JCS(P1)1855>.



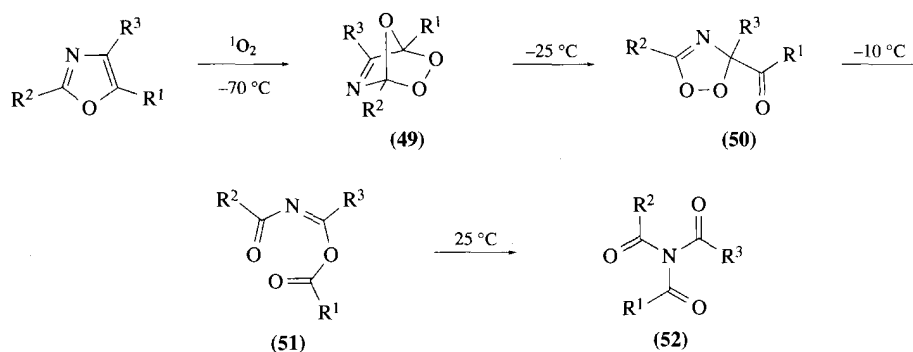
Scheme 5

The first ring expansion of a 1,2,4-trioxolane to a 1,2,4-trioxane was observed with (47) where the orientation of the peroxide group was crucial in assisting the triflate to leave (Equation (2)). A 1,2-peroxide shift then follows with loss of silicon giving the methylene substituted 1,2,4-trioxane (48) as the product <91JA8168>. The equatorial triflate does not undergo rearrangement.



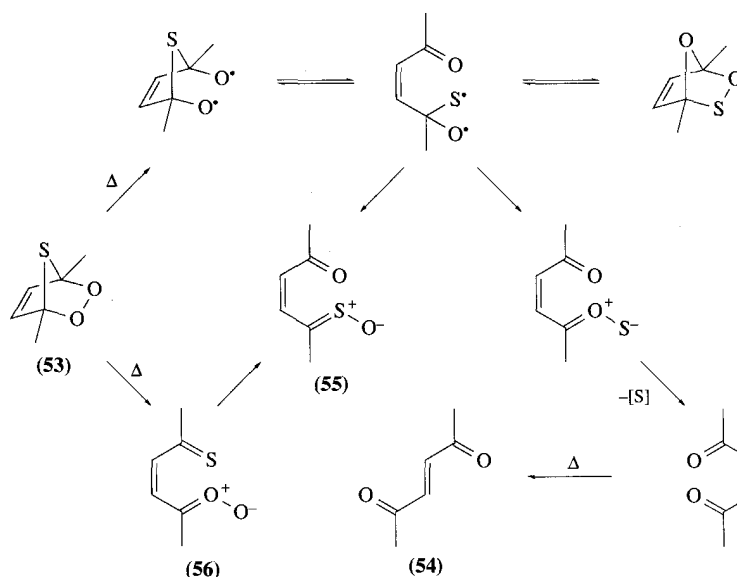
The endoperoxides (49) of oxazoles also undergo clean rearrangements following the path outlined in Scheme 6 <88TL1007>. The initial product is a dioxazole (50) identified at low temperature by NMR spectroscopy <90JCS(P1)1011>. Subsequent products are the imino anhydride (51) followed by

a triacylamine (**52**), which is prone to hydrolysis <91JCS(P2)1085>. Rearrangement temperatures vary slightly depending on the substituents (for a review, see <88MI 416-01>).



Scheme 6

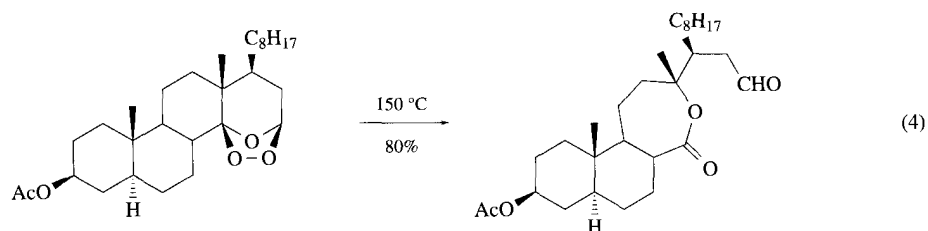
2,5-Dimethylthiophene endoperoxide (**53**) was first isolated in 1970 but reported to decompose violently at room temperature. More recently, in the mid 1980s, a controlled thermal rearrangement has given rise to two products: an alkenedione (**54**) and a thiocarbonyl-S-oxide (**55**) (Scheme 7) <84TL4921>. The key step in the rearrangement of the 1,2,4-dioxathiolane is homolytic cleavage of the peroxide bond to give a diradical species which can follow several pathways. No addition products are observed upon thermolysis in alcohol solvents, casting doubt on the intermediacy of a carbonyl oxide (**56**).



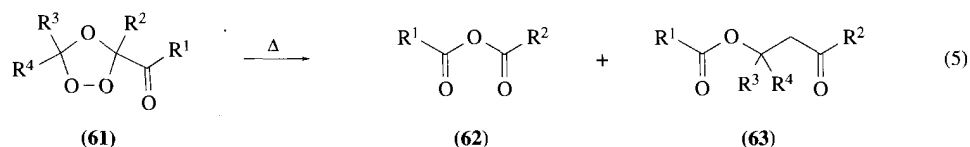
Scheme 7 Possible thermal rearrangement pathways of 2,5-dimethylthiophene endoperoxide.

4.16.5.1.2 Thermolysis

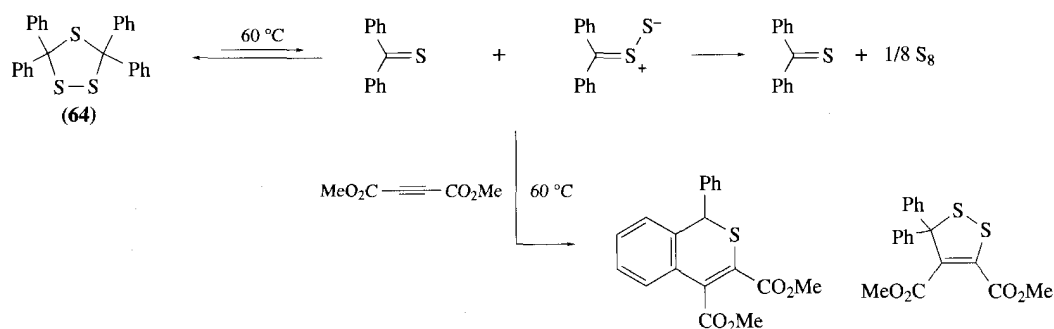
1,2,4-Trioxolanes (**57**) containing at least one ring hydrogen undergo quantitative thermolysis to give a carboxylic acid and carbonyl derivative (Scheme 8) <89JOC383>. Monosubstituted ozonides (**57**; $R^2 = R^3 = H$) tend to give formaldehyde and the substituted acid. For unsymmetrical disubstituted ozonides (**57**; $R^3 = H$, $R^1 \neq R^2$) two aldehydes and two acids are possible. A concerted bond cleavage has been suggested with the involvement of solvent in the hydrogen transfer <72CJC4029, 72JPC2659>. Similar products are observed in the vapor-phase thermolysis of 1,2,4-trioxolanes, along with hydrocarbons, CO and CO₂ <68TL5397>. The intramolecular hydrogen transfer, which occurs con-



3-Acyl-1,2,4-trioxolanes (**61**) are generally thermally labile, although their 2,4-dinitrophenylhydrazone (DNP) derivatives appear to be much more stable $\langle 91CB947 \rangle$. In addition to the anhydrides (**62**), the previously unknown isomeric nonperoxide compounds (**63**) were found as products (Equation (5)).

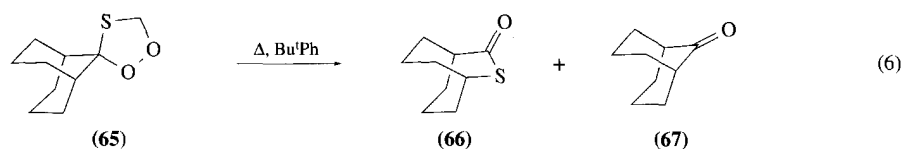


3,3,5,5-Tetraphenyl-1,2,4-trithiolane (**64**) undergoes reversible thermolytic fragmentation upon warming at 60 °C to give thiobenzophenone, with its characteristic deep blue color, and thiobenzophenone *S*-sulfide $\langle 87JA902, 89PS(43)63 \rangle$. At higher temperatures, the latter eventually loses sulfur to give further quantities of thiobenzophenone. It is possible to trap both the *S*-sulfide and thiobenzophenone via cycloaddition reactions with DMAD (Scheme 11). There is the possibility of using other thiocarbonyl derivatives as trapping agents, leading to unsymmetrical 1,2,4-trithiolanes (Section 4.16.9.2). Other 1,2,4-trithiolanes give similar reactions, for example 1,2,4-trithiolane pyrolysis leads to thioformaldehyde and sulfur $\langle 77CC287 \rangle$ although spiro[bis(flourene)]-1,2,4-trithiolane was stable in boiling chloroform $\langle 87JA902 \rangle$.



Scheme 11

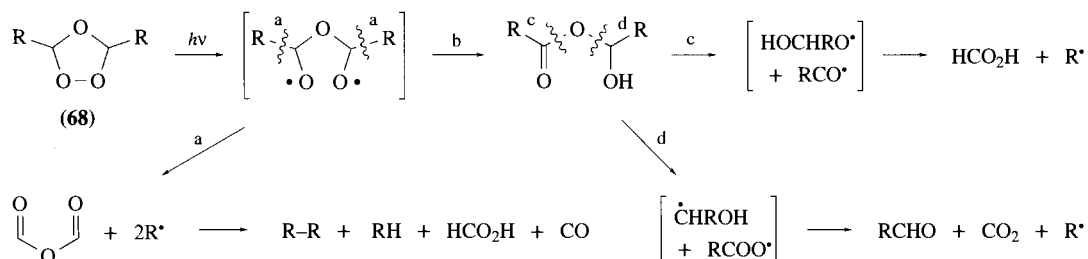
Thermolysis of the 1,2,4-dioxathiolane (**65**) (a thioozonide) in refluxing *t*-butylbenzene gave a mixture of the thiolactone (**66**) (31%) and the ketone (**67**) (65%) (Equation (6)) $\langle 91JCS(P1)3043 \rangle$. The former product is consistent with a thermolytic pathway similar to that observed for ozonides of allylic compounds and of methylene cyclobutanes (see earlier in this section).



4.16.5.1.3 Photolysis

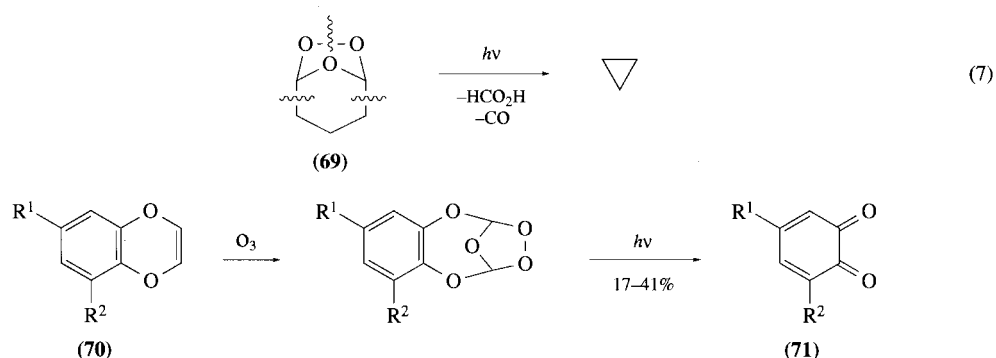
The photolytic reactions of ozonides have been reviewed $\langle 74AG(E)619 \rangle$. Ozonide photolysis in the gas phase has been studied for its implications on the constitution of 'smog'. The first step is

generally accepted as a homolytic cleavage of the O—O bond (Scheme 12). Photolysis of several simple 1,2,4-trioxolanes (**68**) showed that double β -scission (path (a)) accounted for only 4–13% of the subsequent steps $\langle 83BCJ655 \rangle$. The main reaction path was proposed to be intramolecular hydrogen abstraction (path (b)) followed by a unimolecular decomposition. The contribution of double β -scission is greater as the number of methyl substituents increases. Similar results were obtained from photolyses carried out in xenon matrices at low temperature $\langle 82JPC4548 \rangle$.

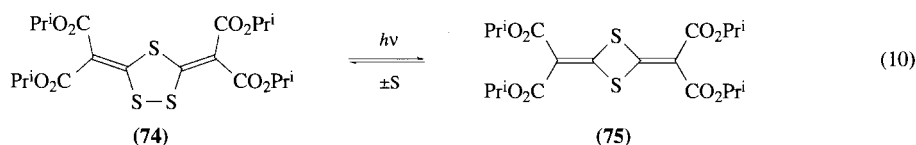
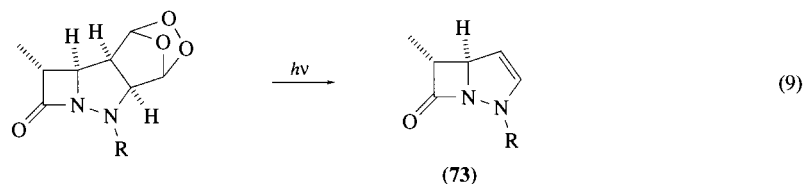
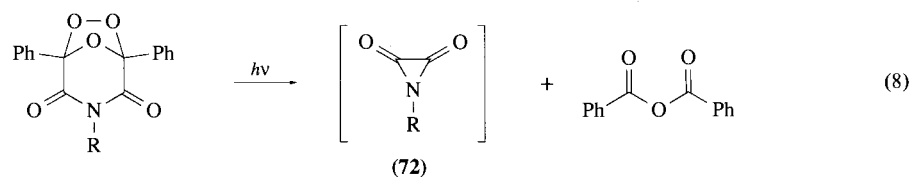


Scheme 12

The double β -scission pathway becomes dominant in bicyclic systems (Equations (7)–(9) and Scheme 13). Thus, cyclopentene ozonide (**69**) gives cyclopropane (Equation (7)) $\langle 68TL3291 \rangle$. Photolysis of the ozonide derived from 1,4-benzodioxins (**70**) provides a method for the preparation of labile *o*-benzoquinones (**71**) (Scheme 13) $\langle 87JOC5616 \rangle$. Photolysis can also provide a route to unstable compounds and transient species such as the aziridine-2,3-dione (**72**) (Equation (8)), identified at 77 K using infrared spectroscopy $\langle 80JA6902 \rangle$. Relatively unstable azacarbapenems (**73**) have been prepared by photolysis of tricyclic compounds containing a cyclobutene ozonide (Equation (9)). On silica, the 1,2,4-trithiolane (**74**) underwent photo-equilibration (Equation (10)) with the 1,3-dithetane (**75**) and sulfur.



Scheme 13



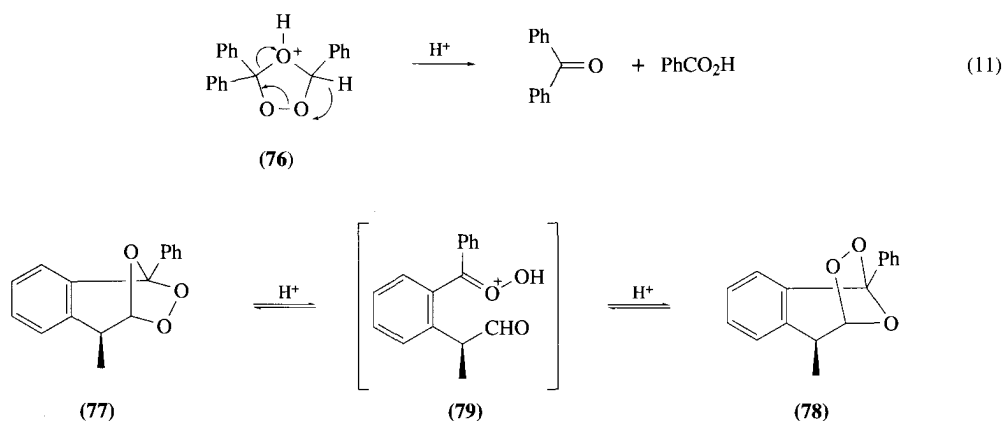
4.16.5.1.4 Polymerization

Acid-catalyzed dimerization and oligomerization of 1,2,4-trioxolanes will be covered in Section 4.16.5.2.1. In general, ozonides are not prone to spontaneous polymerization. Polymeric products can be obtained from the ozonolysis of alkenes but most likely arise from reaction of the primary ozonide. Bicyclic 1,2,4-trioxolanes such as 2,5-dimethylfuran endoperoxide can dimerize on warming in CCl_4 (Section 4.16.5.1.1). 1,2,4-Trithiolane tends to polymerize at room temperature especially if left open to air, whilst more highly substituted ring systems are stable.

4.16.5.2 Reactions with Electrophiles

4.16.5.2.1 Reactions with Lewis acids and protons

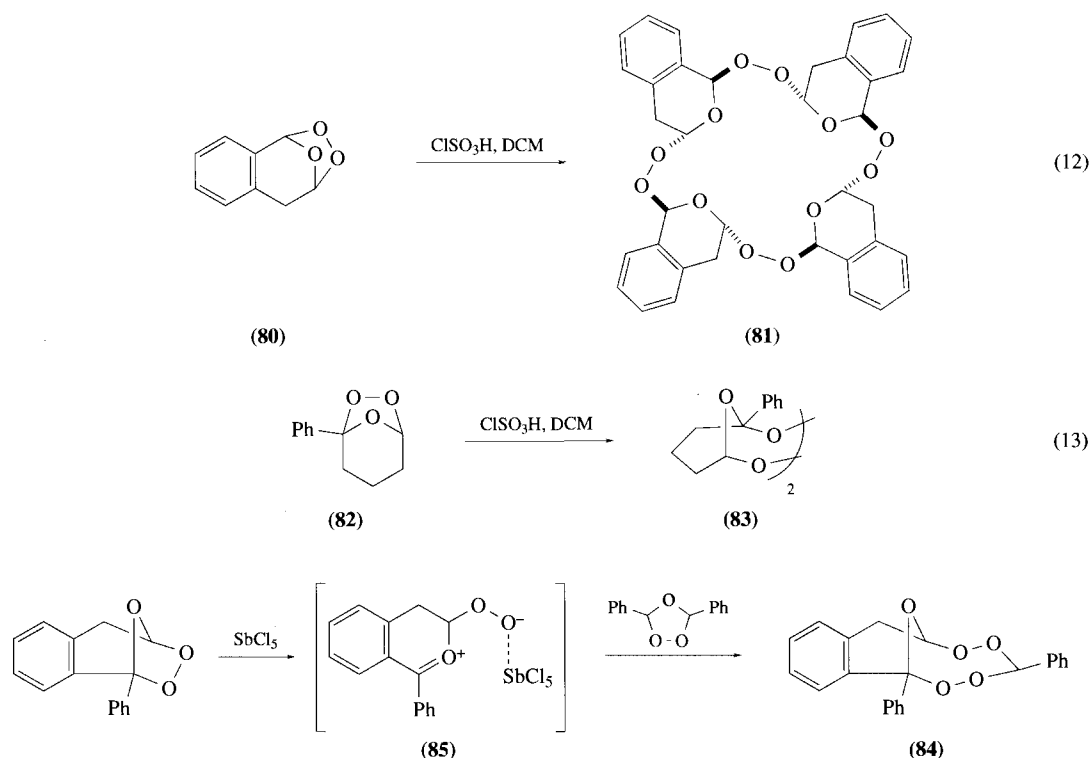
The course of acidolysis of 1,2,4-trioxolanes is dependent on both trioxolane structure and reaction conditions. A typical reaction is the formation of an acid and carbonyl compound by protonation at the ether oxygen followed by heterolytic O—O bond cleavage. An example is the production of benzophenone and benzoic acid from 3,3,5-triphenyl-1,2,4-trioxolane (**76**) (Equation (11)) <80JA288>. The pure *exo* and *endo* phenylindenes (**77**) and (**78**) undergo isomerization to a 7 : 3 mixture of the two on treatment with an acid <83JA2414>. This has been explained by peroxy oxygen protonation followed by reversible ring opening to a protonated carbonyl oxide (**79**) (Scheme 14).



Scheme 14

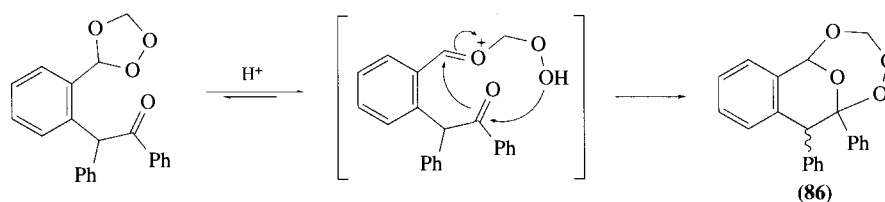
In order to analyze the acidolysis reaction, several possible intermediates from ethylene ozonide were investigated using *ab initio* SCF-MO calculations at the split valence 4-31G level <83JOC2366>. The protonated ether and peroxy oxygen species were investigated along with their corresponding ring-opened forms. The ether oxygen was found to be the more basic site, although the ring-opened carboxonium ion was calculated to be 1 kcal mol⁻¹ less stable than the ether protonated species. This situation changes for peroxy oxygen protonation where the ring opened carboxonium ion is more stable by 18 kcal mol⁻¹, implying a rapid ring opening process if the peroxy moiety is protonated.

Treatment of indene ozonide (**80**) with chlorosulfonic acid at 0°C gave the highly symmetrical macrocyclic peroxide (**81**) in a remarkably stereoselective process (Equation (12)) <93CC931>. Under similar reaction conditions, the analogous 1-phenylcyclopentene ozonide (**82**) undergoes dimerization to the 1,2,4,5-tetraoxane (**83**) (Equation (13)). The intermediate protonated carbonyl oxides apparently have different steric requirements in their reactions. It is possible to form unsymmetrical products by reaction of two different 1,2,4-trioxolanes in the presence of an acid catalyst. The product of a bicyclic ozonide reacting with a monocyclic ozonide is a pentaobicycloundecane such as (**84**) (Scheme 15). In this example, with antimony pentachloride as catalyst, the stable ring-opened intermediate (**85**), analogous to a carbonyl oxide, has been characterized by NMR <81JA1789>. Whether an ozonide opens via peroxy or ether protonation will depend on the structure, substituents and acid used.

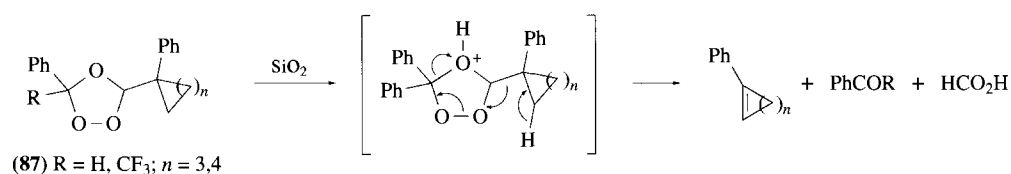


Scheme 15

In certain favorable cases, molecules containing both an ozonide and a ketone group can rearrange in the presence of TFA to 1,2,4,6-tetroxepanes (**86**) (Scheme 16) <94JCS(P1)643>. The reaction fails when the two moieties are separated by a cyclopentane ring and cannot achieve close proximity. In a recent example, fragmentation of cycloalkyl-substituted ozonide (**87**) was accompanied by loss of a proton to form cycloalkene derivatives (Scheme 17) <94JCS(P1)2449>. Smaller rings ($n = 1$ or 2) were stable for several days under these conditions. The fragmentation process seems to be disfavored if the product would be a highly strained cycloalkene.



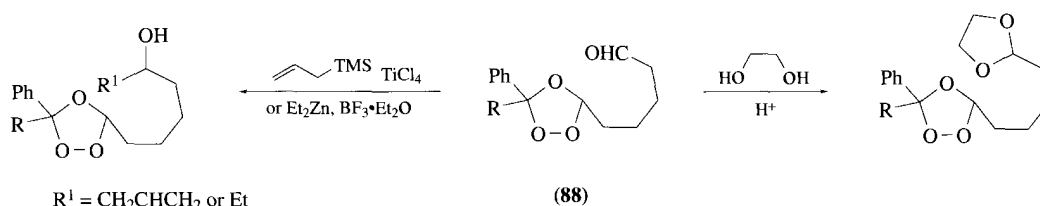
Scheme 16



Scheme 17

Most of the examples given here involve fairly strong acid catalysts to effect fragmentations. Many ozonides are stable to mild acids, so that if a molecule contains other functionality, chemoselective reactions are possible. Reactions of compounds containing both an aldehyde and ozonide group (**88**) have been studied. The aldehyde could be protected as an acetal using ethylene glycol with

PPTS catalysis and more interestingly, in the presence of Lewis acids (TiCl_4 , SnCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$), organometallic reagents preferentially attacked the carbonyl (Scheme 18) <94TL1743>.



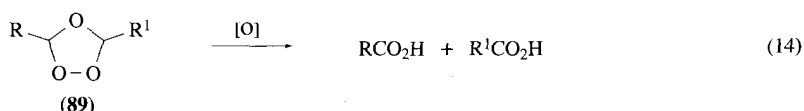
Scheme 18

4.16.5.2.2 Reaction at double bonds

Several 1,2,4-trioxolanes are known which contain a double bond linked in some way to the ring, with interest focusing on furan endoperoxides. The alkene moiety of 2,5-dimethylfuran endoperoxide (41) can be selectively functionalized in the presence of the 1,2,4-trioxolane ring. Reaction with diimide gives the saturated ozonide <81TL3509> and a single addition product was obtained with *p*-nitrophenylazide, although the stereochemistry of the reaction was not determined.

4.16.5.2.3 Oxidation

Reaction of 3,5-disubstituted-1,2,4-trioxolanes (89) with oxidants (usually under basic conditions) leads to carboxylic acids (Equation (14)). This reaction is often carried out as the work up procedure for alkene ozonolysis, avoiding the need to isolate the intermediate ozonide. Typical oxidants are basic hydrogen peroxide or peracids and this type of oxidative decomposition is useful for both synthetic and degradative studies.



1,2,4-Trithiolanes are generally oxidized at the ring sulfur atoms prior to any ring cleavage reactions. Under suitably mild conditions, the 1- or 4-*S*-oxides can be obtained, for example with sodium periodate <76JOC2465> or hydrogen peroxide catalysed by V_2O_5 <77CC287>. More substituted 1,2,4-trithiolanes such as tetraphenyl-1,2,4-trithiolane tend to be more difficult to convert to the *S*-oxides and stronger oxidants lead to ring cleavage.

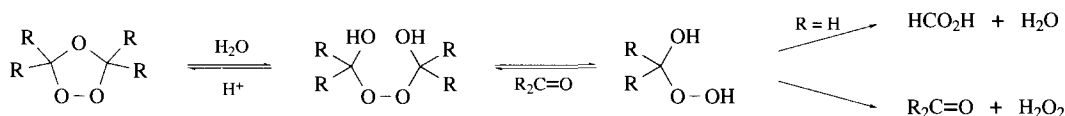
4.16.5.3 Reactions with Nucleophiles

4.16.5.3.1 O- and S-Nucleophiles

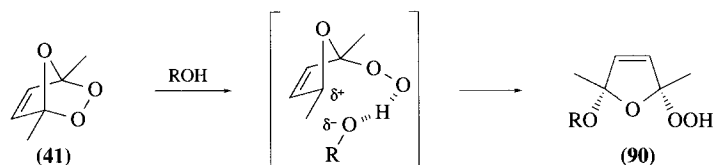
Ozonolysis of alkenes in 'participating' solvents such as alcohols often leads to trapping of intermediates. Most commonly, an alcohol will react with the carbonyl oxide zwitterion, generated from cycloreversion of the primary ozonide (Section 4.16.8.2), to give an alkoxy hydroperoxide. The secondary ozonide (1,2,4-trioxolane) is usually more stable to nucleophilic attack from alcohols.

Aqueous acid hydrolysis of 1,2,4-trioxolanes proceeds via the hydroperoxide (Scheme 19) <58CRV925>. Reactions can occur between certain 1,2,4-trioxolanes and alcohols, for example, 2,5-dimethylfuran endoperoxide reacts readily with methanol, ethanol and isopropanol to give the corresponding *cis* alkoxy hydroperoxides (90) (Scheme 20). The stereochemistry has been ascribed to a solvent-assisted ring opening, the positive charge generated being stabilized in the allylic position <85T2057>. Reaction with *t*-butanol gives an alternative fragmentation path akin to that observed in thermolysis (Section 4.16.5.1.2). Furan endoperoxide (cyclobutadiene monoozonide) in methanol gives the alkoxy butenolide (91; $\text{R} = \text{Me}$), which presumably arises via the same sort of

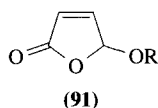
intermediate as (90) but which can eliminate H_2O_2 . Endoperoxides of 2-methoxyfurans react with methanol to give 5-hydroperoxyfuran-2(5*H*)-ones (91; $\text{R} = \text{OH}$) (94S944).



Scheme 19



Scheme 20

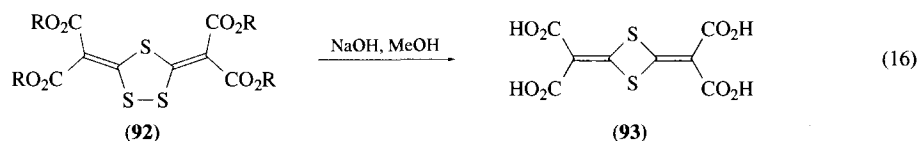


1,2,4-Trioxolanes can undergo fragmentation with hydroxide ion or alkoxide via removal of one of the ring protons, giving a carboxylate and a carbonyl product (Equation (15)). This is similar to thermal fragmentation in certain solvents (cf. Section 4.16.5.1.2) (67AHC(8)165) and reaction with amines (Section 4.16.5.3.2).



Substituents can play a part in the reaction of 1,2,4-trioxolanes with oxygen nucleophiles, for example 3-acyl or 3-aldehydic substituents can lead to fragmentation pathways via attack at the carbonyl (Section 4.16.6.2). Also, it is possible to displace suitable leaving groups in the 3-position with alcohol nucleophiles (Sections 4.16.6.3 and 4.16.9.4).

1,2,4-Trithiolanes are more stable to basic hydrolysis than their 1,2,4-trioxolane relatives. Tetra-alkyl substitution imparts extra stability. Potassium hydroxide in methanol, however, will give cleavage to the corresponding ketone (66HC(21-1)1). When the dialkyl substituents are replaced by methylene moieties as in (92), ring contraction and ester hydrolysis occur to give the dithietane (93) (Equation (16)) (71CJC1477).



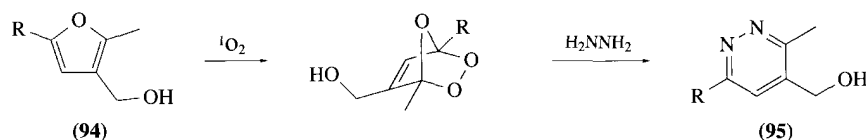
Oxazole endoperoxides react with methanol to give oxazole hydroperoxides which undergo further decomposition (91JCS(P2)1085). Thiophene endoperoxide rearranges to the same thermally derived products observed in nonpolar aprotic solvents (Section 4.16.5.1.2) (84TL4921). Few reports have appeared on the reactions of 1,2,4-trioxolanes or sulfur analogues with sulfur nucleophiles, although sulfides are commonly used to work up ozonolysis reactions of alkenes under reductive conditions. Typically, dimethyl sulfide is the reagent of choice and is believed to attack the secondary ozonide at the peroxy oxygen. As well as obtaining ketone or aldehyde products, the sulfide is oxidized to DMSO.

4.16.5.3.2 N-Nucleophiles

In an analogous fashion to that described for hydroxide ion in Section 4.16.5.1, amines will cause the fragmentation of 1,2,4-trioxolanes which have a ring proton. In fact, triethylamine has been

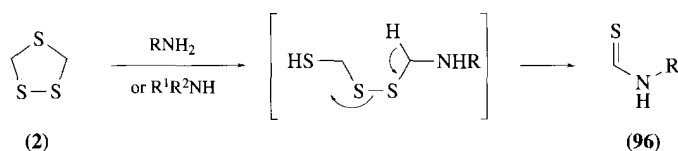
shown to have advantages over dimethyl sulfide in the work up of alkene ozonolysis reactions. Improved yields and shorter reaction times were achieved <93SC1543>.

Photooxygenation of C-glycosyl and polyhydroxyalkyl furans (**94**) leads to the corresponding endoperoxides. These can be reacted directly with hydrazine to give pyridazines (**95**) (Scheme 21) <84CAR(132)233>. 2-Acyl-1,2,4-trioxolanes are relatively unstable. Although they survive 2,4-dinitrophenylhydrazone formation, these derivatives were found to be very stable when the other trioxolane ring positions were substituted <91CB947>. It is also possible to make *O*-methyl oximes of 3-acyl-1,2,4-trioxolanes <94TL1163>. The reactions of hexadecene ozonide with triethylamine or *N,N'*-diphenyl-1,4-phenyldiamine were used to model the ageing of stabilized rubbers.

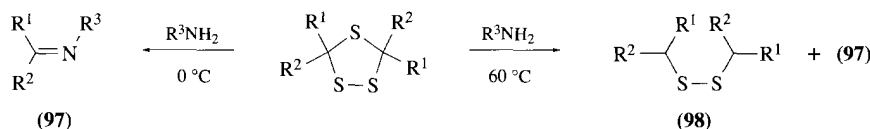


Scheme 21

1,2,4-Trithiolane (**2**) reacts with primary and secondary amines to give thioformamides (**96**) via thermal decomposition of an initial ring-opened intermediate (Scheme 22) <67CPB988>. Substituted 1,2,4-trithiolanes lead to imines (**97**) at low temperature (0°C) and also disulfides (**98**) as the temperature is raised (60°C) (Scheme 23) <59LA(627)195>.

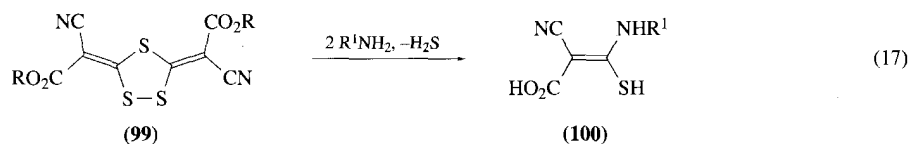


Scheme 22



Scheme 23

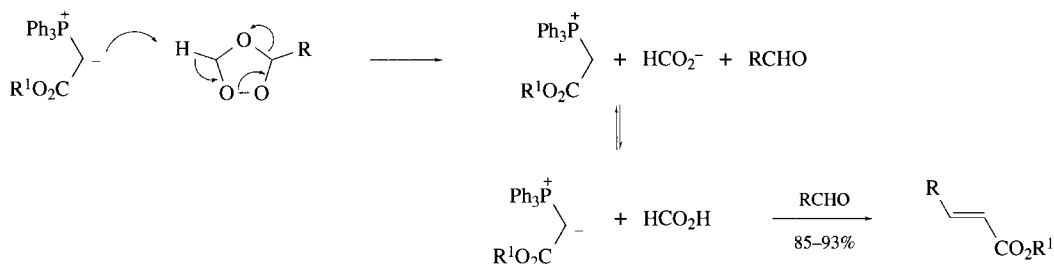
3,5-Bismethylene-1,2,4-trithiolanes (**99**) undergo reaction with various nitrogen nucleophiles to give loss of hydrogen sulfide and the thioamide product (**100**) (or tautomer thereof) (Equation (17)). A range of amines, hydrazines or anilines can be used and if the amine is bifunctional, as in a hydrazine or *o*-substituted aniline, intramolecular reaction with the nitrile group will lead to heterocycle formation <B-82MI 416-01>.



4.16.5.3.3 C-Nucleophiles

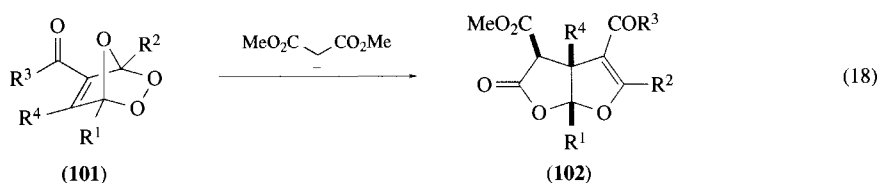
The ozonides derived from mono-substituted alkenes react with ester- or ketone-substituted phosphoranes to give the corresponding *trans*-unsaturated esters or ketones (Scheme 24) <93MI 416-03>. Only 1.3 equivalents of phosphorane are required, the first step being base-catalyzed fragmentation of the 1,2,4-trioxolane ring (Section 4.16.5.3.1). The carboxylate anion deprotonates the phosphonium salt which can then react with the aldehyde. Cycloalkene ozonides react with 2.2 equivalents of phosphoranes to give *E,E*-unsaturated dicarbonyl derivatives <92SC429>. For steric reasons, it is usually a proton from the unsubstituted carbon that is removed. If, however, the R group is phenyl, the acidity of the proton on the substituted carbon is increased and this leads to

competitive deprotonation. If the side chain R contains a ketone moiety, the reaction is selective for the ozonide $\langle 90CC1627 \rangle$.

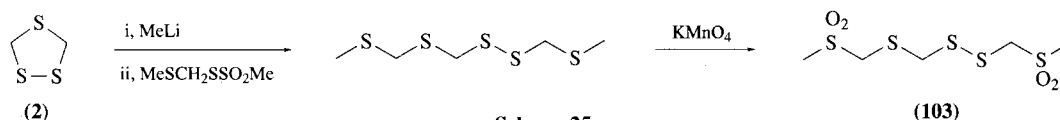


Scheme 24

It has already been shown that certain organometallic reagents under Lewis acid catalysis will react selectively with an aldehyde in the presence of a 1,2,4-trioxolane ring (Section 4.16.5.2.1) $\langle 94TL1743 \rangle$. Grignard reagents will, however, eventually give carbinol products. Addition of the sodium salt of dimethyl malonate to the endoperoxides of furans, substituted at C(3) with a carbonyl group (**101**), led to bicyclic compounds (**102**) (Equation (18)) $\langle 84S64 \rangle$.



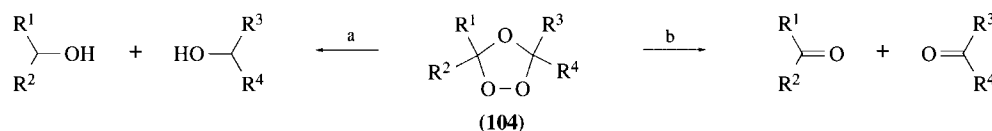
1,2,4-Trithiolane is attacked at one of the disulfide sulfur atoms with methyl lithium at -78°C . The resulting ring-opened intermediate can be quenched with an electrophile as in the synthesis of dyoxysulfone (**103**) (Scheme 25) $\langle 94JOC2273 \rangle$.



Scheme 25

4.16.5.3.4 Reduction and reductive ring cleavage

1,2,4-Trioxolanes (**104**) are readily reduced to carbonyl compounds or alcohols depending on the reagent involved (Scheme 26) $\langle 82CB2000, B-82MI 416-03, 83CC229, 89JOC1430 \rangle$. These reducing agents are often used in the work up of the ozonolysis reaction of alkenes to avoid isolation of ozonides and any other potentially hazardous peroxides.

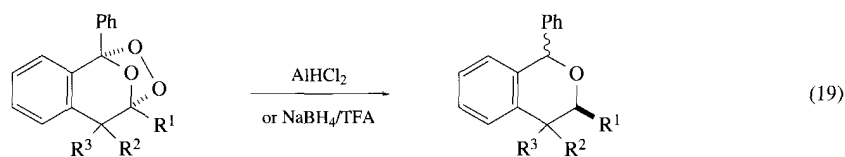


(a) LiAlH_4 , NaBH_4 or $\text{BH}_3 \cdot \text{THF}$

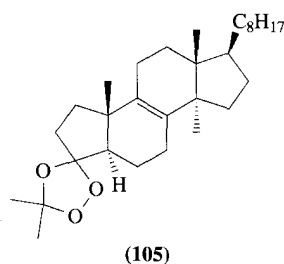
(b) Zn , Raney Ni , Pd/H_2 , Fe^{2+} , Sn^{2+} , I^- , R_2S , SO_2 , HSO_3^- , pyridine, Ph_3P , P_2I_4 , PCl_3

Scheme 26

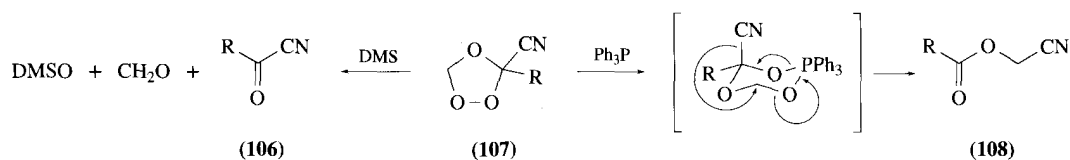
Dichloroaluminium hydride in ether or sodium borohydride in TFA can lead to formation of ethers from ozonides by reductive cleavage of the two C—O bonds of the peroxide bridge (Equation (19)) $\langle 85JOC275 \rangle$.



Highly substituted or bicyclic 1,2,4-trioxolanes are often resistant to reduction, for example **(105)** was stable to dimethyl sulfide, decomposing only with zinc in acetic acid or potassium hydroxide in methanol/benzene <88CJC2130>. The highly substituted cyclopentene ozonide **(11)** was stable to zinc in acetic acid at 20°C, with elevated temperatures needed for reduction <94JOC5055>. Triphenylphosphine in refluxing THF was also ineffective. An example of a 1,2,4-trioxolane, resistant to sodium borohydride reduction, where a ketone side chain was chemoselectively reduced to give the alcohol has been reported <89JA7612>. The use of diimide to selectively reduce the double bond in an ozonide bicyclic ring system has already been described in Section 4.16.5.2.2.

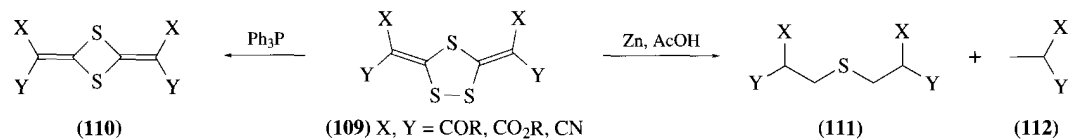


3-Cyano-substituted 1,2,4-trioxolanes **(107)** react with dimethyl sulfide at -78°C to give the expected keto nitriles **(106)** <90TL3299>. Triphenylphosphine gives an unexpected result, with the involvement of a cyclic intermediate and a 1,3-cyano shift used to explain the product **(108)** obtained (Scheme 27).



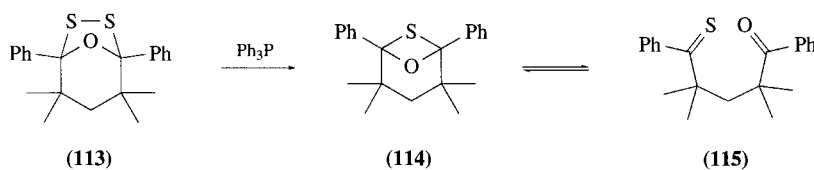
Scheme 27

1,2,4-Trithiolanes can be reduced to the corresponding thiols with lithium aluminum hydride but are generally stable to triphenylphosphine. Exceptions are the 3,5-bismethylene derivatives **(109)** which undergo ring contractions to the 1,3-dithietanes **(110)** (Scheme 28) <71CJC1477>. Compare this with Section 4.16.5.3.1 where NaOH was used to carry out a similar reaction. Zinc in acetic acid will effect a desulfurization to give sulfides **(111)** and eventually alkyl derivatives **(112)** (Scheme 28) <71TL1781>.

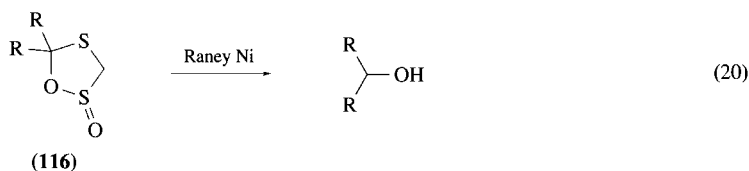


Scheme 28

Reaction of the bicyclic 1,3,4-oxadithiolane **(113)** with triphenylphosphine in refluxing toluene led to an equilibrium mixture of the 1,3-oxathietane **(114)** and the thiocarbonyl derivative **(115)** (Scheme 29) <93BCJ1714>. Raney nickel can be used to desulfurize both 1,2,4-trithiolanes (to methylene compounds) and 5,5-disubstituted 1,2,4-oxadithiolane 2-oxides **(116)** which give rise to secondary alcohols (Equation (20)) <90BSB265>.



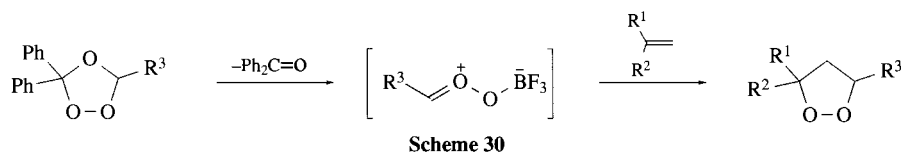
Scheme 29



4.16.5.4 Reactions with Alkenes

Although none of the five-membered ring systems containing 1,2,4-oxygen or sulfur atoms reacts directly with an alkene, reactions are known in which the heterocycle is thermolyzed in the presence of the alkene and the intermediates trapped (see also Section 4.16.5.1.2). Di-*t*-butylisobenzofuran endoperoxide was thermolyzed in the presence of norbornene to give an epoxide, whilst naphthalene gave hydroxy derivatives $\langle 81\text{TL}1697 \rangle$. Furan endoperoxides will oxidize tetramethylethylene to its corresponding epoxide, sulfides to sulfoxides and adamantone to a lactone. A carbonyl oxide intermediate has been suggested as the O-atom donor $\langle 80\text{JA}404 \rangle$.

The reactions of a number of ozonides and alkenes in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in the formation of *E*- and *Z*-1,2-dioxolanes in 12–70% yields (Scheme 30) $\langle 83\text{JA}6279 \rangle$. 2,5-Dimethylthiophene endoperoxide can act as a sulfur- or oxygen-atom transfer agent in analogous reactions to those shown by furan endoperoxides $\langle 86\text{JA}2775 \rangle$.



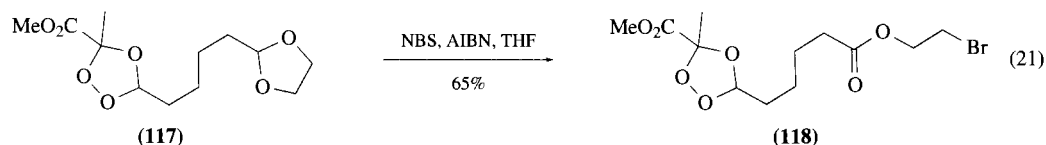
Scheme 30

4.16.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBONS

4.16.6.1 H-Substituents

The acidity of hydrogens attached to 1,2,4-trioxolane ring carbons has been highlighted in previous sections, notably Section 4.16.5.3.1 where it was described how bases will induce fragmentation of the ring via proton removal. This also forms the basis of the first step in the reaction of 1,2,4-trioxolanes with phosphorous ylides (Section 4.16.5.3.3).

An interesting example shows the stability of a 1,2,4-trioxolane ring hydrogen to radical abstraction relative to that on a 1,3-dioxolane. Reaction of (117) with *N*-bromosuccinimide under radical conditions gave selective formation of the bromoethyl ester (118) (Equation (21)) $\langle 94\text{TL}1743 \rangle$.

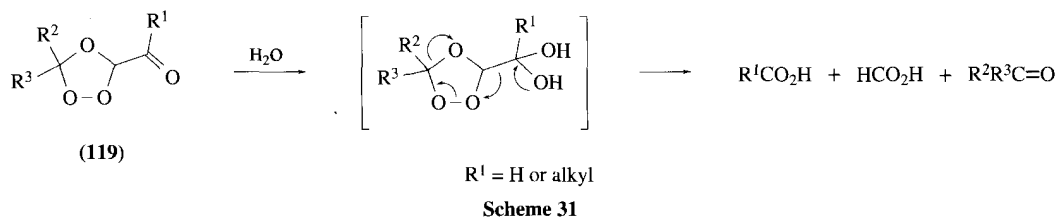


4.16.6.2 C-Substituents

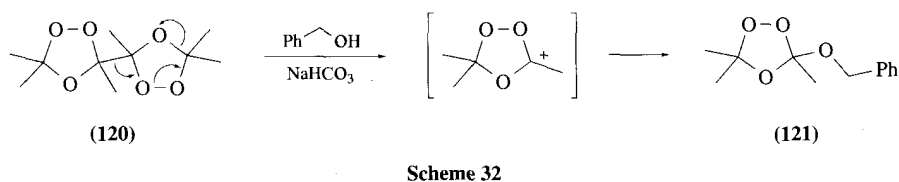
When a 1,2,4-trioxolane has a side chain containing a ketone or aldehyde, it is possible to selectively functionalize the carbonyl group, leaving the trioxolane intact. Examples of such reactions

appear in other sections, for example organometallic additions to aldehydes and protection of an aldehyde as a 1,3-trioxolane (Section 4.16.5.2.1) and reduction of a ketone to an alcohol (Section 4.16.5.3.4).

For 3-acyl-1,2,4-trioxolanes and related aldehydes, the carbonyl is more directly involved with the reactivity of the ring system. It is possible to form stable hydrazones and oximes without ring cleavage but solvolysis in aqueous or alcohol solvent can lead to anomalous products to those observed with alkyl substituted 1,2,4-trioxolanes. The oxygen nucleophile attacks the ketone carbonyl of **(119)** <91CB947> or an aldehyde <85T2057> and a fragmentation follows with loss of the carbonyl carbon as an acid or ester (Scheme 31). Substituents can play a large role in determining products from thermolysis (Section 4.16.5.1.2) and acid-catalyzed rearrangements (Section 4.16.5.2.1).

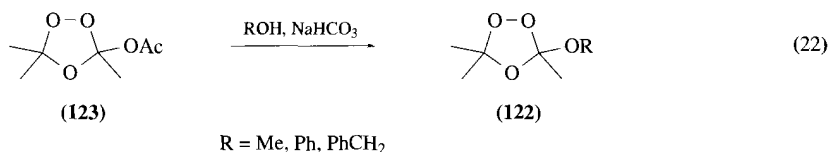


Formation of the diozonide **(120)** as a mixture of *meso*- and ($\pm$)-isomers was achieved by ozonolysis of the corresponding diene on polyethylene (Section 4.16.9.2). This compound underwent an unusual reaction with benzyl alcohol in the presence of NaHCO_3 , leading to the formation of a 3-benzyloxy-1,2,4-trioxolane **(121)** (Scheme 32) <89TL1511>. It was suggested that the C—C bond linking the two ozonide rings is cleaved giving rise to an intermediate carbocation.



4.16.6.3 O-Substituents

A 1989 report describes preparation of 3-alkoxy-1,2,4-trioxolanes **(122)** by reaction of the corresponding 3-acetoxy derivative **(123)** with an alcohol under basic conditions (Equation (22)) <89TL1511>. Apart from the unusual related reaction of diozonide **(120)** in Section 4.16.6.2, this sort of nucleophilic substitution at an ozonide is rare.



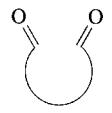
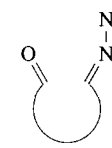
4.16.7 RING SYNTHESSES CLASSIFIED BY THE NUMBER OF RING ATOMS IN EACH COMPONENT

The synthesis of five-membered rings containing three oxygen or sulfur atoms in the 1,2 and 4 positions can be placed into one of two broad groups:

- (i) Transformations of another ring (covered in Section 4.16.8).
- (ii) One-step sequences involving acyclic precursors. This group will be covered in this section and can be further classified according to the number of components involved ($X = \text{O or S}$):
 - (a) One component: formation of a single C—X or X—X bond in a cyclization step.
 - (b) Two components: a $[3 + 2]$ or a $[4 + 1]$ process.
 - (c) Three components: possibilities are $(\text{CX}_2 + \text{C} + \text{X})$; $(2\text{CX} + \text{X})$; or $(\text{CX} + \text{C} + \text{X}_2)$.
 - (d) Multi-component: usually only found for 1,2,4-trithiolanes.

Representations of those possibilities that have been exemplified are given in Table 10. The more synthetically useful processes are discussed in greater detail in Section 4.16.9 and reference is given to the relevant subsection in the table. (Note: Cycloreversion of a 1,2,3-trioxolane to give a carbonyl oxide, which can undergo [3 + 2] reactions with carbonyl derivatives, is included in Section 4.16.8.)

Table 10 Ring synthesis of five-membered heterocycles containing three oxygen or sulfur atoms in the 1,2,4-positions from nonheterocyclic compounds.

Arrangement of heteroatoms in starting material	Starting components utilized	Ring skeleton obtained ^a	Reference or section in which process is mentioned
(i) One-component			
	$S=C-S-C=S$	$\xrightarrow[-2I^-]{I_2}$	1,2,4-[C ₂ S ₃] 4.16.93
	$HO-C-O-O-C-OH$	$\xrightarrow{-H_2O}$	1,2,4-[C ₂ O ₃] 32CB1274
	$HS-C-S-S-C-SH$	$\xrightarrow{-H_2S}$	1,2,4-[C ₂ S ₃] 74AC(R)305
	$S=C-S-S-C=S$	$\xrightarrow[-2I^--[S]]{I_2}$	1,2,4-[C ₂ S ₃] 4.16.9.3
	$HO-C-O-C-O-OH$	$\xrightarrow{TFA}$	1,2,4-[C ₂ O ₃] 4.16.9.2
(ii) Two-component			
	$Cl-C-S-S-C-Cl + Na_2S$	$\xrightarrow{-2 NaCl}$	1,2,4-[C ₂ S ₃] 4.16.9.2
	 ,  or 	$\xrightarrow[-[S]]{[O]}$	1,2,4-[C ₂ S ₃] 4.16.9.2
(iii) Three-component			
	 +  + I_2O_2	$\xrightarrow{-N_2}$	1,2,4-[C ₂ O ₃] 4.16.9.2
	 + B_2S_3	$\longrightarrow$	1,2,4-[C ₂ S ₃] (bicyclic) 4.16.9.2
	 + S_2Cl_2	$\xrightarrow[-N_2-2HCl]{amine}$	1,3,4-[C ₂ OS ₂] (bicyclic) 4.16.9.2
	$2 Cl-C-S-Cl + 2 Na_2S$	$\xrightarrow{-4NaCl-[S]}$	1,2,4-[C ₂ S ₃] 72T3489
	$3 (CH_3)_2C=S$	$\xrightarrow[-acetone]{[O]}$	1,2,4-[C ₂ S ₃] 4.16.9.2
(iv) Multi-component			
	$2 (CH_3)_2C=O + 2 H_2S + S$	$\xrightarrow[-2H_2O]{amine}$	1,2,4-[C ₂ S ₃] 4.16.9.2
	$2 R_2CCl_2 + Na_2S_{2.5}$	$\xrightarrow[-[S]]{-4NaF}$	1,2,4-[C ₂ S ₃] 4.16.9.1

^a1,2,4-[C₂O₃] = 1,2,4-trioxolane; 1,2,4-[C₂S₃] = 1,2,4-trithiolane; 1,3,4-[C₂OS₂] = 1,3,4-oxadithiolane.

4.16.8 SYNTHESSES BY RING TRANSFORMATIONS

4.16.8.1 Introduction

The most commonly employed transformations for the construction of five-membered rings containing three sulfur or oxygen atoms in the 1,2,4-positions are shown in Table 11. These have attracted more interest than the syntheses from acyclic components. The rearrangement of a 1,2,3-trioxolane (primary ozonide) to a 1,2,4-trioxolane (secondary ozonide) is the most generally applicable method for preparation of this ring system and will be discussed further in Sections 4.16.8.2 and 4.16.9.2. The other methods are discussed further under the relevant subsection headings or are referenced in Table 11. Chapter 4.15 covers the chemistry of 1,2,3-trioxolanes in more detail. Other methods are: the photooxygenation of epoxides; photooxygenation of furans, thiophenes and oxazoles to give bicyclic systems; the reaction of thio-epoxides with thiocarbonyl derivatives; and the rearrangement of 1,2,4-trithiolanes in the presence of thiocarbonyl compounds to give unsymmetrical ring systems. The latter method is advantageous over many of the procedures summarized in Section 4.16.7 which are mainly limited to symmetrical 1,2,4-trithiolane syntheses.

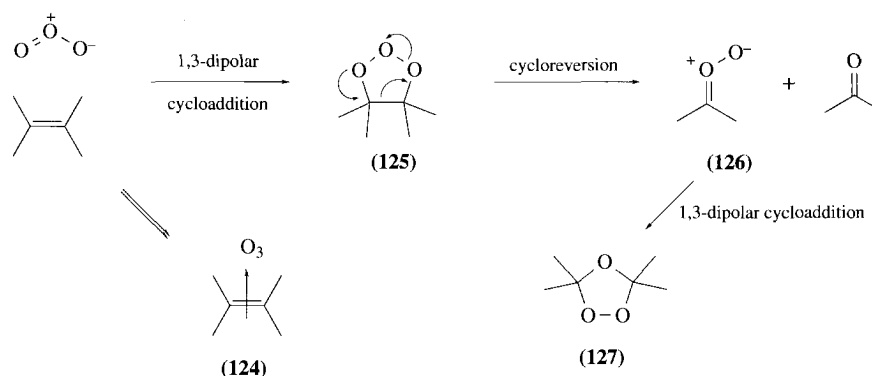
Table 11 Formation of five-membered heterocycles containing three oxygen or sulfur atoms in the 1,2,4-positions by ring interconversions.

Type of transformation	Starting ring system		Ring skeleton produced	Section(s) in which process is mentioned
Rearrangement				4.15, 4.16.8.2, 4.16.9.2, 4.16.9.4, 4.16.9.5
Insertion of O ₂		$\xrightarrow[\text{sensitiser}]{h\nu, \text{O}_2}$		4.16.9.2
Addition of ¹ O ₂		$\xrightarrow{{}^1\text{O}_2}$		4.16.9.2
		$\xrightarrow{{}^1\text{O}_2}$		4.16.9.2
Insertion of sulfur		$\xrightarrow[\text{or } \begin{array}{c} \text{H} \\ \text{N} \diagup \text{N} \diagdown \\ \text{N} \text{---} \text{S} \text{---} \text{C} \text{---} \text{S} \end{array}]{h\nu, [\text{S}]}$		4.16.9.2
Desulfurization		$\xrightarrow{-[\text{S}]}$		4.16.9.2
Extrusion and [3+2] cycloaddition		$\xrightarrow[\text{SO}_2]{-\text{N}_2}$		4.16.9.2
Desulfurization of thiirane		$\xrightarrow[\text{-CH}_2\text{CH}_2]{2 \text{ R}_2\text{C}=\text{S}}$		4.16.9.2
retro [3+2] then [3+2]		$\xrightarrow[\text{-(R}^1)_2\text{C}=\text{S}]{(\text{R}^2)_2\text{C}=\text{S}}$		4.16.9.2

4.16.8.2 The Ozonolysis Reaction

The ozonolysis of alkenes has been comprehensively covered in several excellent reviews (see Section 4.16.1) and will therefore not be discussed in detail here. It is pertinent, given the importance of 1,2,4-trioxolane synthesis, to highlight the key points of the ozonolysis reaction mechanism and several other developments.

The generally accepted mechanism is outlined in Scheme 33. An initial π -complex (**124**) between ozone and the alkene has been proposed, and evidence exists for its occurrence in the gas phase. The next step is a concerted 1,3-dipolar cycloaddition of ozone and the alkene to give a 1,2,3-trioxolane (**125**) (primary ozonide or 'molozonide'). These structures are discussed in Chapter 4.15. The key step, first proposed by Criegee, is cycloreversion of the primary ozonide to give a carbonyl oxide (**126**) and a carbonyl fragment. These two intermediates can then undergo [3 + 2] cycloaddition to give a 1,2,4-trioxolane (**127**) (the secondary ozonide, often referred to as the "final ozonide"). If the carbonyl fragment is unreactive enough, the carbonyl oxide will escape from the solvent cage and undergo competing reactions such as dimerization to 1,2,4,5-tetraoxanes or polymerization. It is possible to trap carbonyl oxides with methanol to give a methoxyhydroperoxy product and more usefully, trapping with another carbonyl species provides access to ring systems that may otherwise be difficult to prepare (see Section 4.16.9.2). Carbonyl oxides can have *syn* or *anti* stereochemistry and this will have implications for the stereochemistry of the final ozonide. For unsymmetrical alkenes, four carbonyl oxides are possible. The cleavage of the primary ozonide tends to occur along the path which results in an electron-donating group on the carbonyl oxide, although alkoxy groups disfavor incorporation in this species (91MI 416-01, 93JOC4212). *Ab initio* calculations have been performed on the ozonolysis reaction of ethylene (cf. Section 4.16.2) and over the years, a substantial amount of research has been carried out into stereochemical and electronic effects in the mechanism of ozonolysis. This is covered fully in the reviews mentioned, although aspects specific to certain syntheses will be discussed in Section 4.16.9.



Scheme 33 The Criegee mechanism of ozonolysis

4.16.9 SYNTHESSES OF PARTICULAR CLASSES OF COMPOUNDS

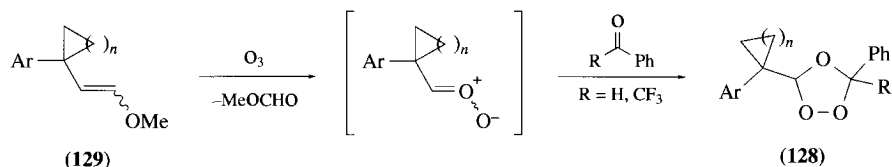
In this section, structures will be discussed in the order in which they appear in Section 4.16.1.

4.16.9.1 Parent Systems Including S-Oxides and S,S-Dioxides

1,2,4-Trioxolane (**1**) has only been prepared by the ozonolysis of ethylene. The rearrangement of the primary ozonide occurs above -100°C to give 1,2,4-trioxolane as a colorless, explosive liquid (42LA(553)187). 1,2,4-Trithiolane (**2**) is still best prepared by a classical reaction of $\text{Na}_2\text{S}_{2.5}$ with excess dichloromethane. Some 1,2,4,5-tetrathiolane is also produced, but (**2**) can be isolated as a pale-yellow distillable liquid. It is best kept stored under inert atmosphere below 0°C to avoid polymerization (67CPB988). Parent compounds (**3**)–(**6**) are not known and the 1- and 4-S-oxides for 1,2,4-trithiolane have been mentioned previously (see Section 4.16.5.2.3).

4.16.9.2 C-Linked Substituents

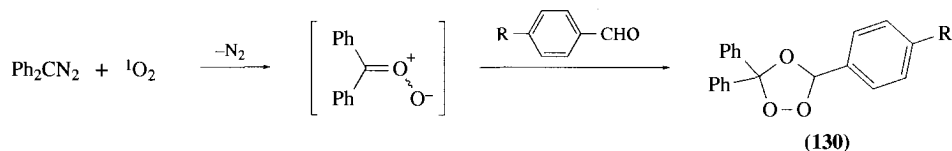
Ozonolysis remains the most exemplified method for the preparation of 1,2,4-trioxolanes <B-92MI 416-01, B-93MI 416-02>. The reaction mechanism is described in Section 4.16.8.2, where it was pointed out that the intermediate carbonyl oxide can be trapped with 'foreign' carbonyl species to give other 1,2,4-trioxolanes. Alkenes with alkoxy substituents tend to undergo ozonolysis such that the alkoxy group ends up in the carbonyl fragment rather than the carbonyl oxide <93JOC4212>. Thus, enol ethers ozonize predictively to give a carbonyl oxide and an ester fragment. The latter is often less reactive than added carbonyl species such as aldehydes or trifluoromethyl ketones, so that in the example given, cycloalkyl substituted ozonides (**128**) could be prepared by ozonolysis of the enol ether (**129**) (Scheme 34) <94JCS(P1)2449>.



Scheme 34

The ozonolyses of enol ethers has been reviewed <91MI 416-01>. The relative dipolarophilicity of certain species to attack by carbonyl oxides has been investigated and, in general, the order of reactivity is aldehydes > enol ethers > esters $\approx$ ketones. It is apparent that enol ethers are very reactive towards carbonyl oxides, so much so that 1,2-dioxolane formation can be a major reaction pathway (especially for formaldehyde-*O*-oxide) <85JOC3365>.

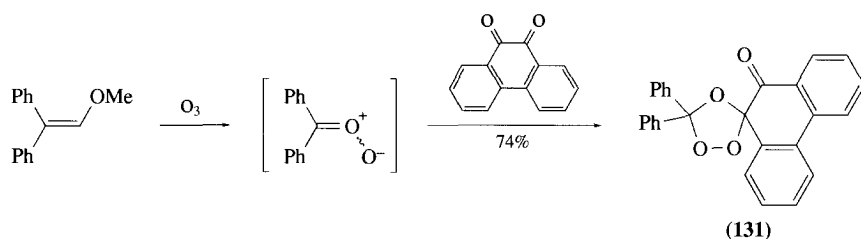
Carbonyl oxides can be obtained from species other than those generated in the ozonolysis reaction, for example benzophenone-*O*-oxide is formed from the photooxygenation of diphenyl-diazomethane (Scheme 35). Reaction *in situ* with a series of *para*-substituted benzaldehydes gave 1,2,4-trioxolanes (**130**) at rates which were treated with the Hammett relationship and were consistent with the Criegee mechanism <91JOC684>. The reactions of propionaldehyde-*O*-oxide (generated via ozonolysis of *cis*-hexene) have been investigated in a similar manner <91JOC6123>. The relative reactivity of formaldehyde-*O*-oxide, acetaldehyde-*O*-oxide and propionaldehyde-*O*-oxide were studied with a range of dipolarophiles from activated alkenes to ketones. Formaldehyde-*O*-oxide, unlike the others, reacted with unactivated alkenes and showed a greater preference for vinyl ethers <92CB2493>.



Scheme 35

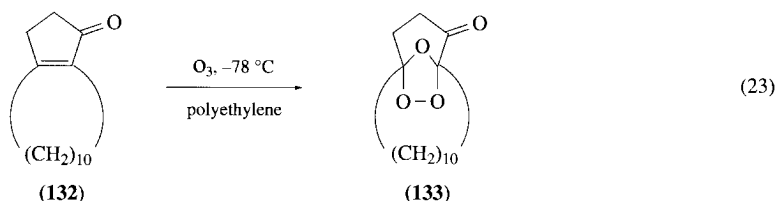
The preparation of (**128**) (Scheme 34) highlights the use of the trifluoromethyl group to increase the dipolarophilicity of a ketone. This activating effect of electron withdrawing groups is also taken advantage of in the preparation of 3-carbonyl substituted 1,2,4-trioxolanes (**131**) via the ozonolysis of a vinyl ethers in the presence of a 1,2-dicarbonyl compound (Scheme 36) <91JOC6591>.

Although alkenes with at least one vinylic hydrogen usually lead to ozonide formation, tetra-



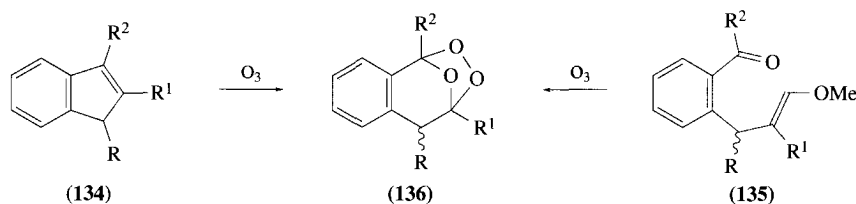
Scheme 36

substituted alkenes do not normally give 1,2,4-trioxolanes when ozonolyzed in solution. Instead 1,2,4,5-tetraoxanes or polymeric peroxides are formed <93JOC315>. This has been attributed to the poor reactivity of the ketone fragment which arises from cycloreversion of the primary ozonide (Scheme 33). Exceptions do occur: (i) when the substituents contain electron-withdrawing groups which activate the ketone to attack by the carbonyl oxide; (ii) if the alkene is part of a cyclic system (especially five-membered rings—Equation (23)) the carbonyl oxide/ketone reaction is then intramolecular and more likely to occur; (iii) when ozonolysis is carried out with the alkene immobilized on a solid support. Silica has been used <82TL3623, 85JOC2647> but polyethylene (PE) has found more widespread applications as an inert support <85JA5309>. The procedure involves adsorption of the compound onto the PE and treatment of this with a flow of ozone (without solvent). In the case of tetrasubstituted alkenes, it has been suggested that the carbonyl oxide and ketone are held in close proximity, favoring recombination.



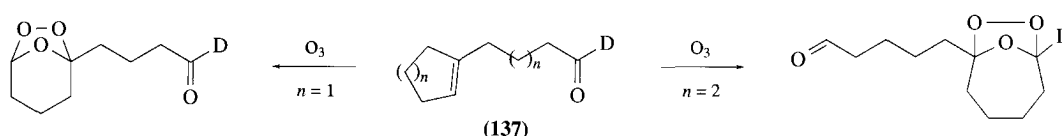
An example which takes advantage of these favorable effects is shown in Equation (23) where the bicyclic unsaturated ketone (132) undergoes ozonolysis on polyethylene to give the 1,2,4-trioxolane (133). Ozonolysis of the compound without the carbonyl group or reactions in solution were unsuccessful <94TL1163>.

Other bicyclic ozonide examples are given in Scheme 37. The number of examples available reflects the inherent stability of this type of trioxolane ring system. The x-ray structures of several of these 1,2,4-trioxolanes have been discussed in Section 4.16.3.1. Substituted indene derivatives (134) or the vinyl ethers (135) both give the stable 1,2,4-trioxolanes (136) via ozonolysis <91JA1786>. The *exo/endo* ratios of products have been related to the nature of the substituents *R*–*R*² <85JOC1504, 89JA1799, 93JOC135>. A related study of the effects of substituents on the ozonolysis of cyclopentenones was carried out by analysis of the product stereochemistry <92JOC729>. These systems lend themselves to mechanistic studies because of the stable products and efficient conversions. The chemical stability of bicyclic ozonide (11) is described in Section 4.16.5.3.4 <94JOC5055> and its x-ray structure is also mentioned (Section 4.16.3.1). Steroidal ozonides have also attracted interest due to their relative stability and ease of characterization <84TL1403, 90JCS(P1)1220>.



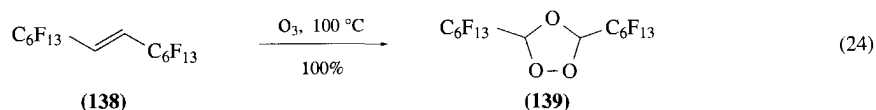
Scheme 37

It is a general observation that cyclopentenones will form 1,2,4-trioxolanes much more readily than cyclohexenones. This has been attributed to the fact that cyclohexene primary ozonides rearrange to give predominantly the *anti* carbonyl oxide whilst cyclopentene primary ozonides give the *syn*. Intramolecular 1,2,4-trioxolane formation can only occur if the carbonyl oxide is *syn* with respect to the tethered carbonyl fragment. This fact was highlighted in a practical determination of carbonyl oxide geometry based on ozonolysis of the cycloalkenes (137) which contain a tethered labelled aldehyde (Scheme 38) <92JA7577>.



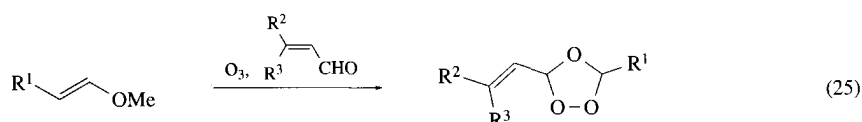
Scheme 38

Ozonolysis is generally carried out in solution as part of a synthetic route. Many 1,2,4-trioxolanes are isolated because of their 'unusual' stability. In deliberate preparations of 1,2,4-trioxolanes, reactions in solution may not always be the most efficient process. Several ozonides can be prepared by 'dry' ozonolysis where the alkene is reacted without solvent, for example the highly stable perfluoroalkyl 1,2,4-trioxolane (**139**) was obtained by heating the alkene (**138**) to 100 °C in the presence of ozone (Equation (24)) <85TL2889>.

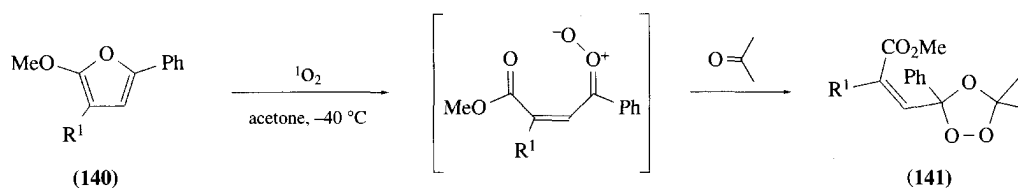


Ozonolysis of alkenes on solid supports, notably polyethylene <85JA5309>, has greatly increased the scope of the reaction in the preparation of 1,2,4-trioxolanes. Competing reactions of intermediates are avoided and the mild conditions often allow isolation of relatively unstable or previously unobtainable 1,2,4-trioxolanes.

Labile 3-cyano- <90TL3299> and 3-keto- <91CB947> substituted 1,2,4-trioxolanes are accessible, and 3,3,5,5-tetramethyl-1,2,4-trioxolane was prepared for the first time in 1985 and shown to be a very stable compound <85JA5309>. Another labile tetrasubstituted trioxolane is obtained from 2,3-dimethylnorbornene <91JOC4005>. Fused ring systems derived from relatively large rings are also accessible <89JOC383> as are dispiro-1,2,4-trioxolanes <91CB391>. The preparation of vinyl ozonides from dienes <88CB1795> complements the reaction of a carbonyl oxide with unsaturated aldehydes (Equation (25)). The latter reaction usually fails with unsaturated ketones although α -benzylidene cyclohexanones are exceptions <92JOC1649>.



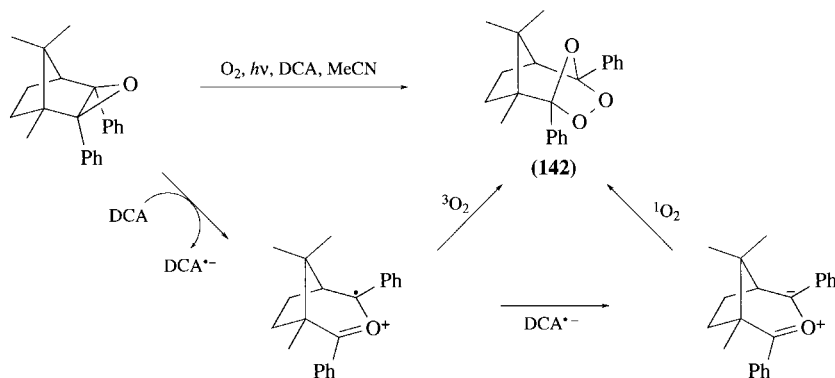
Carbonyl oxides are also obtained from certain 2-methoxy furans (**140**) and can be trapped by carrying out the photooxygenation in acetone to give the vinyl ozonide (**141**) (Scheme 39) <88JCS(P1)1699>. Singlet oxygen, generated from oxygen and a sensitizer under irradiation, will add to certain five-membered ring heterocycles to give the corresponding endoperoxides. This reaction has been described in Section 4.16.5.1.1 where the thermal rearrangement of the products is discussed. At present, examples exist for furans, thiophenes, and oxazoles, although oxadiazoles and isoxazoles were inert under the conditions tried. Singlet oxygen has also been produced under oxygen-free conditions by reaction of titanium dioxide with hypochlorite in methanol and this procedure used to oxidize 2-furoic acid <90MI 416-01>.



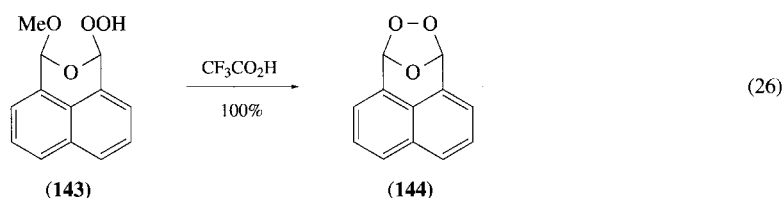
Scheme 39

1,2,4-Trioxolanes can be prepared by electron-transfer photooxygenation of epoxides although the method is generally limited to those that are strained or electron rich (usually phenyl or naphthyl substituted) <84JCS(P1)15>. 2,3-Disubstituted epoxides give stereoselectively the *cis*-1,2,4-trioxolane <85T2229>. The oxidation potential of the epoxide is important, although addition of a co-sensitizer (such as 9,10-dicyanoanthracene) will overcome problems if it is too low <89TL6801>. The possible mechanisms are highlighted in Scheme 40 where formation of the trioxolane ring (**142**) may be via triplet oxygen reacting with a radical cation or singlet oxygen with a zwitterion. Strained cycloalkenes such as 1,2-diphenyl-3,3,4,4-tetramethylcyclobutene also give 1,2,4-trioxolanes, presumably via the corresponding epoxide <85T2069>.

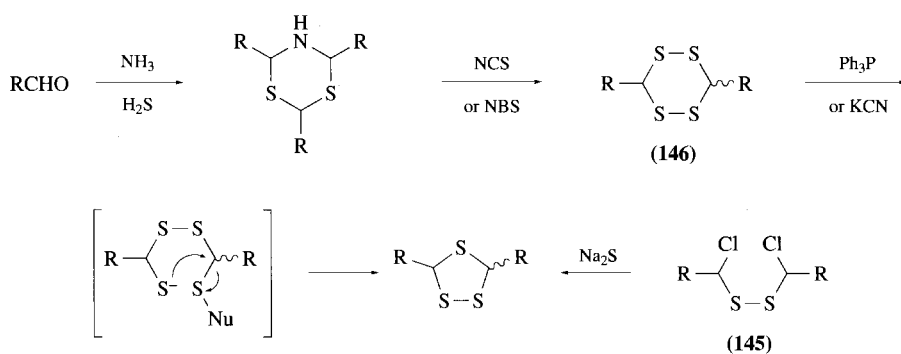
Cyclization of peroxy ethers such as (**143**) can be achieved under acidic conditions to give the corresponding 1,2,4-trioxolane (**144**) (Equation (26)), although the reaction remains of minor preparative importance <90JOC3816>.



Scheme 40



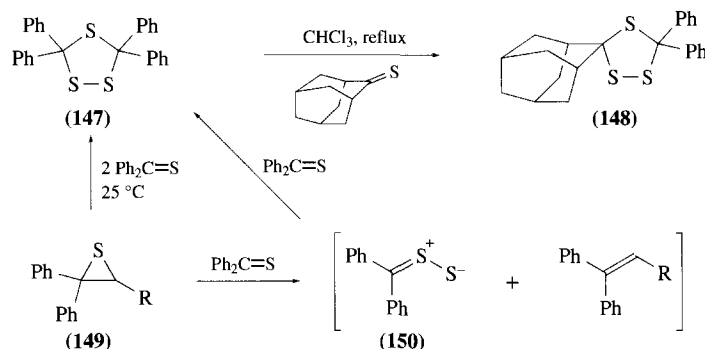
Symmetrical dialkyl 1,2,4-trithiolanes can be prepared by reaction of di- α -chloroalkyl sulfides (**145**) with Na_2S or ring contraction of the tetrathiepane (**146**) using nucleophilic reagents such as triphenylphosphine or cyanide (Scheme 41). Both methods give *cis/trans* mixtures and most examples of the latter involve $R = \text{aryl}$ [88CL1517].



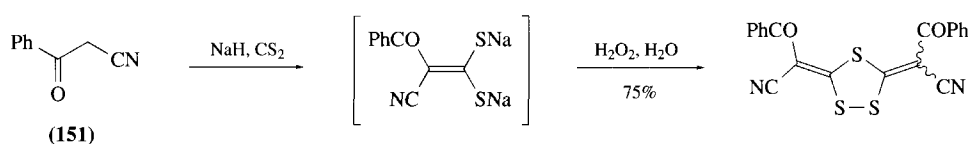
Scheme 41

Several methods exist for the preparation of symmetrical 3,3,5,5-tetrasubstituted 1,2,4-trithiolanes including: (i) the reaction of hydrogen sulfide with ketones in the presence of sulfur and a primary amine [59LA(627)195]; (ii) oxidation of thioketones [71CC179] or geminal dithiols [62JOC4488]. Unsymmetrical tetrasubstituted 1,2,4-trithiolanes have been made by taking advantage of the reversible thermal decomposition of 1,2,4-trithiolanes such as (**147**) to give a thioketone and a thiocarbonyl *S*-sulfide (see Section 4.16.5.1.2). The latter can be trapped with thioketones to give the unsymmetrical trithiolane (**148**) (Scheme 42) [87JA902]. The tetraphenyl 1,2,4-trithiolane (**147**) was synthesized by a novel reaction involving the thioepoxide (**149**) which is desulfurized by thiobenzophenone to give the *S*-sulfide (**150**). Further reaction with thiobenzophenone gives (**147**). Examples of the latter reaction were restricted to highly substituted, symmetrical products.

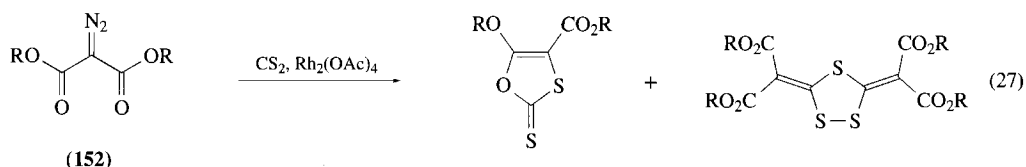
3,5-Bismethylene-1,2,4-trithiolanes are usually prepared from dithio acids and their anions or dianions using one of a large range of oxidants, often bromine [70BCJ2938] or iodine [77JCS(P1)1273]. Examples include the dithio components generated from a diverse set of precursors, such as: 1,1-dichloroalkenes [80S907]; α -cyanoketones (**151**) (Scheme 43) [84T381]; diazo compounds (**152**) (Equation (27)) [90BCJ3096]; or phosphoranes [82AG(E)291, 82CB3653].



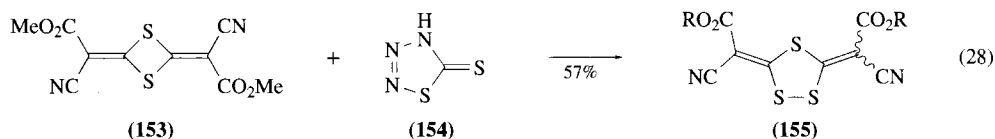
Scheme 42



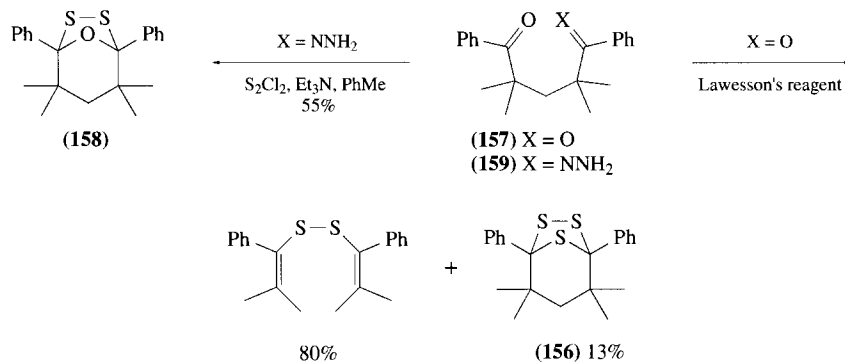
Scheme 43



Ring transformations (shown in Table 11) often lead to 3,5-bismethylene products, for example the 1,3-dithietane (153) reacts with the 1,2,3,4-thiatriazole derivative (154) to give a 1,2,4-trithiolane (155) (Equation (28)) <84BSB405>.



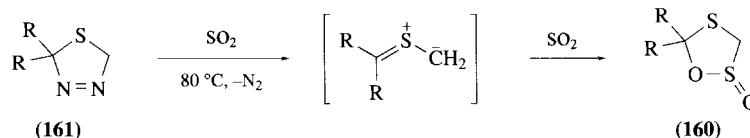
Modest yields of bicyclic 1,2,4-trithiolanes (156) have been obtained from the sulfurization of nonenolizable diketones of type (157) using Lawesson's reagent (Scheme 44) <90JOC2421>. Although the reaction is limited, a similar procedure has provided one of the few routes to 1,3,4-oxadithiolanes (158) from the corresponding keto hydrazone (159) (Scheme 44) <92CC7, 93BCJ1714>.



Scheme 44

5,5-Dialkyl-1,2,4-oxadithiolane-2-*S*-oxides (160) have been synthesized from the dihydro thiazadiazole (161) via nitrogen extrusion and 1,3-dipolar cycloaddition of the intermediate ylide with sulfur dioxide (Scheme 45) <90BSB265>. The formation and trapping of carbonyl oxides is described

earlier in this section. Cyclic thioketones are also suitable dipolarophiles, leading to spiro-fused 1,2,4-dioxathiolanes <91JCS(P1)3043>. Phenyl-substituted thioketones tend to give sulfur oxidation rather than cycloaddition.

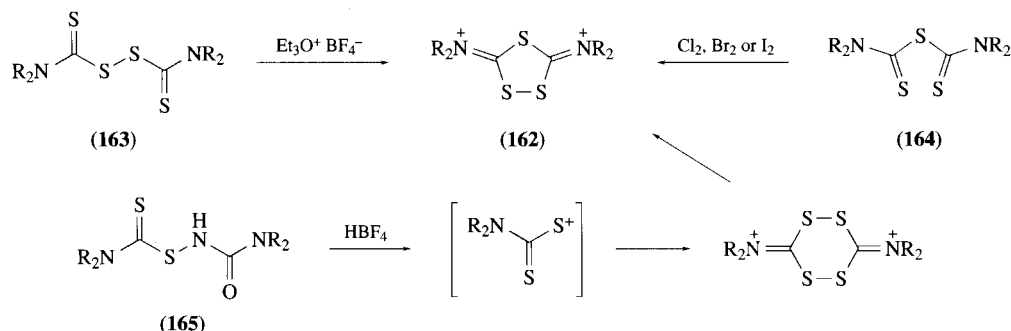


Scheme 45

4.16.9.3 N-Linked Substituents

The only examples of 1,2,4-trioxolanes containing *N*-linked substituents arise from photo-oxygenation of oxazoles. The endoperoxides thus produced are bicyclic, with a 1,2,4-trioxolane ring bridged by an imine moiety and are unstable at ambient temperature. They have been characterized at low temperature and thermal rearrangement is described in Section 4.16.5.1.1.

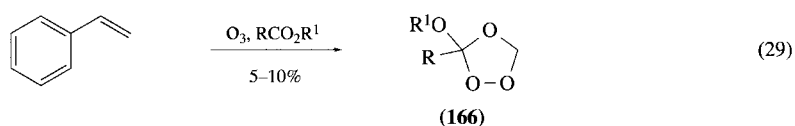
N-linked substituents are much more common in the 1,2,4-trithiolane series, usually in the form of 3,5-bis(*N,N*-dialkyliminium) salts (162) or 3,5-bis(arylhydrazones) <71JCS(B)415>. Iminium salts (162) are available from a range of precursors including cyclization of *N,N,N',N'*-tetraalkylthiuram disulfides (163) with triethyloxonium tetrafluoroborate <93S463>; cyclization of *N,N,N',N'*-tetraalkylthiuram monosulfides (164) with halogens; and reaction of urea derivatives (165) with tetrafluoroboric acid (Scheme 46) <92BCJ920>. The latter reaction involves loss of the urea, dimerization of the intermediate to a 1,2,4,5-tetrathiane and loss of sulfur to give the 1,2,4-trioxolane (162).



Scheme 46

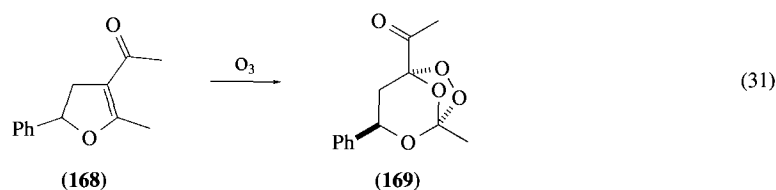
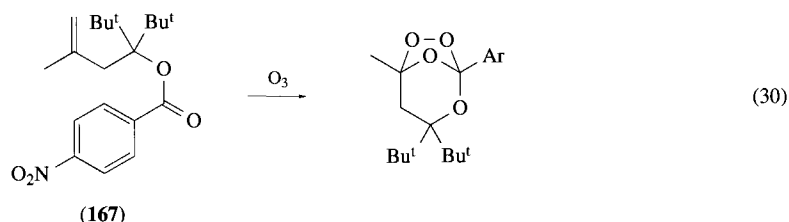
4.16.9.4 O-Linked Substituents

Until the early 1980s, there were virtually no examples of oxygen-linked substituents for any of the five-membered ring heterocycles under discussion. This situation has changed markedly for 1,2,4-trioxolanes. Ozonolysis of styrene in ester solvents gives rise to 3-alkoxy-1,2,4-trioxolanes (166) (Equation (29)). The formaldehyde *O*-oxide is trapped by the excess ester dipolarophile, although yields are low and substituents are limited to small alkyl groups <84JA3383>. α -Trifluoromethyl-substituted esters are much more reactive and can be used to trap carbonyl oxides to give good yields of 3-alkoxy-3-trifluoromethyl-1,2,4-trioxolanes <92JOC3487>.

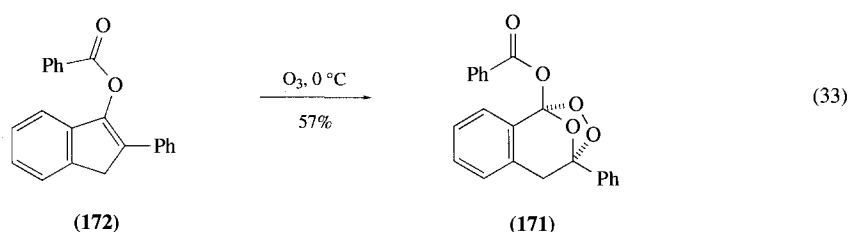
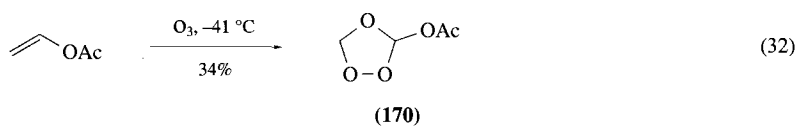


Bicyclic 1,2,4-trioxolanes can also be formed by intramolecular trapping of a carbonyl oxide with an ester as in the ozonolysis of (167) (Equation (30)). With (167), the steric effect of the *gem*-di-*t*-

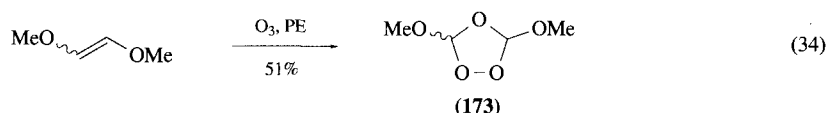
butyl group forces the molecule into a conformation which favors cyclization onto the activated ester $\langle 87JA612 \rangle$. Ozonolysis of cyclic vinyl ethers such as **(168)** also gives rise to bicyclic 1,2,4-trioxolanes **(169)** (Equation (31)) $\langle 89JA7612, 93MI416-01 \rangle$. Singlet-oxygen addition to 2-methoxyfurans results in methoxy-substituted endoperoxides, the thermal rearrangements of which are described in Section 4.16.5.1.1.



Vinyl acetate reacts with ozone in $CDCl_3$ to give 3-acetoxy-1,2,4-trioxolane **(170)** (Equation (32)). Benzoyloxy-substituted ozonides **(171)** can be prepared from cyclic systems such as **(172)** (Equation (33)) $\langle 91JOC1672 \rangle$.



Ozonolysis on PE (Section 4.16.9.2) is by far the most general method for the preparation of 3-acyloxy $\langle 89CB941 \rangle$ and 3-alkoxy-substituted 1,2,4-trioxolanes, e.g. **(173)** (Equation (34)) $\langle 90JOC6153, 92JOC5574 \rangle$. Most of these cannot be prepared efficiently in solution. 2-Substituted and 2,2-disubstituted vinyl ethers generally give the best yields. Trisubstituted vinyl ethers do not lead to 1,2,4-trioxolanes, even on PE. Competing reactions include the addition of carbonyl oxide intermediates to the original vinyl ether to give 1,2-dioxolanes. The alternative route to more highly substituted alkoxy trioxolanes is via displacement of acetate from 3-acetoxy-1,2,4-trioxolanes with alcohols under basic conditions $\langle 89TL1511 \rangle$ (for further details of this reaction, see Section 4.16.6.3).



4.16.9.5 Halogens Attached to the Ring

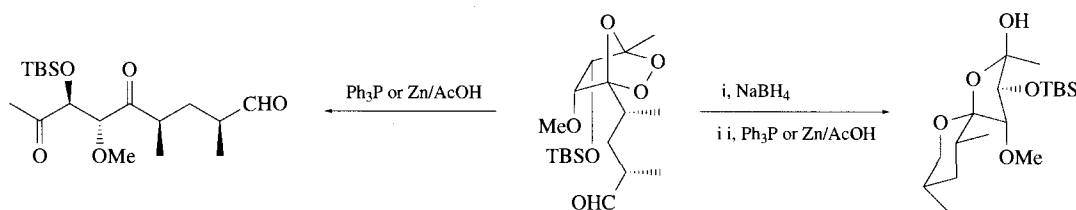
All of the possible ring-fluorinated isomers of 1,2,4-trioxolane are known and these can be prepared by ozonolysis of the corresponding vinyl fluorides: 3-fluoro-1,2,4-trioxolane $\langle 79JOC3181 \rangle$; *cis*- and *trans*-3,5-difluoro derivatives $\langle 77JA7239 \rangle$ and 1,1-difluoro-1,2,4-trioxolane $\langle 83JA5047 \rangle$.

Yields tend to drop as the number of fluorine atoms increases, with ozonolysis of perfluoroethylene only giving a small amount of tetrafluoro-1,2,4-trioxolane $\langle 68\text{Cl(M)}197 \rangle$. Other products observed include epoxides, carbonyl fluoride and cyclopropanes (arising from non-Criegee pathways). Ozonolysis of acyclic vinyl chlorides in solution does not lead to chloro-substituted 1,2,4-trioxolanes $\langle 83\text{IJ446} \rangle$. Reaction of ozone with 2-chlorobutadiene gave selective ozonide formation at the non-chlorinated double bond $\langle 86\text{CJC1553}, 87\text{CB1573} \rangle$. Certain chlorinated 1,2,4-trioxolane rings are now known, however, and can be prepared by ozonolysis of 1-chlorocycloalkenes on PE (Section 4.16.9.2), giving bicyclic products $\langle 90\text{CB391}, 91\text{CC816} \rangle$. Apart from (**24**), there are no reported examples of other halogen substituents on 1,2,4-trioxolane rings or of any other halogenated five-membered ring systems with oxygen or sulfur in the 1,2,4-positions.

4.16.10 IMPORTANT COMPOUNDS AND APPLICATIONS

4.16.10.1 Applications in Research and Industry

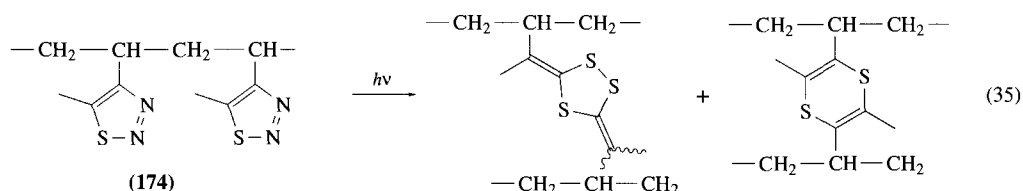
1,2,4-Trioxolanes are key intermediates in the ozonolysis of alkenes (Section 4.16.8.2). This reaction is of considerable importance in synthetic chemistry where ozonide intermediates are often reduced (to aldehydes or alcohols) or oxidized (to carboxylic acids) *in situ*. Advantage has been taken of the stability of certain derivatives to investigate selective chemical reactions. An example of selective reduction is shown in Scheme 47 $\langle 91\text{TL6454} \rangle$ with other uses of the 1,2,4-trioxolane ring as a masked aldehyde or ester referred to in Section 4.16.5.2.1.



Scheme 47

Ozonolysis is important as an analytical tool in that ozonolytic degradation can be used to pinpoint unsaturated bonds in a molecule. This classical approach has been complemented by x-ray structure determinations of stable ozonides and the use of other physical methods (Section 4.16.3.1). The structure of natural rubber was first proved via ozonolysis which produced laevulinic aldehyde. Much research has been focused on trying to prevent this process, as atmospheric ozone can attack rubbers, causing cracking and subsequent degradation. Several reviews have appeared on this subject with attention directed towards the use of antiozonants $\langle 83\text{MI 416-01}, 89\text{MI 416-01}, 90\text{RC426} \rangle$.

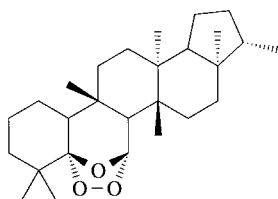
1,2,4-Trithiolanes are commonly found in the volatile flavor components of several cooked foods and have thus attracted considerable interest as potential flavor enhancers (see Section 4.16.10.2). In a very different area of chemistry, irradiation of poly(5-methyl-4-vinyl-1,2,3-thiadiazole) (**174**) gave polymers cross-linked by *p*-dithiin and 1,2,4-trithiolane rings (Equation (35)) $\langle 82\text{CC481} \rangle$. 1,2,4-Trithiolanes have been observed as degradation products in certain pesticides, for example photolysis of the fungicide isoprothiolane $\langle 80\text{ABC2169} \rangle$ and thermolysis of azinphos-methyl $\langle 86\text{AC(R)}19 \rangle$.



4.16.10.2 Natural Occurrence

Several stable triterpenoid natural products containing 1,2,4-trioxolanes have been characterized, for example adian-5-ene ozonide (**175**) isolated from the fern *Adiantum monochlamys* $\langle 90\text{CPB79},$

91YZ120). Hop-17(21)-ene ozonide was obtained from another fern of the genus *Plagiogyria* (87YZ586).



(175)

Biological consequences of ozone as a constituent of atmospheric pollution are discussed in Section 4.16.10.3. Atmospheric ozone can also react with alkene pollutants present in the atmosphere, giving rise to 1,2,4-trioxolane components.

Several cyclic sulfur-containing compounds, including simple 3,5-dialkyl-1,2,4-trithiolanes, have been isolated from sulfur-metabolizing hyperthermophilic archaea (93LA871). Sulfur reduction represents a form of anaerobic respiration and plays a significant role in energy conservation of *Thermococcus* archaea. The highly lipophilic compounds may function as a sulfur reservoir.

Alkyl-substituted 1,2,4-trithiolanes are found naturally in various *Allium* species such as onions (92MI 416-05, 92MI 416-06), leeks (91MI 416-03, 92MI 416-07), chives (83MI 416-02), and garlic (89MI 416-02, 92MI 416-08), and also in mushrooms (86MI 416-01, 92MI 416-09) and yeast extracts (91MI 416-04). An ever-increasing list of cooked foods also contain these compounds as volatile flavor components. Examples are cooked beef (80MI 416-01, 87MI 416-01), egg (81MI 416-01), fried chicken (83MI 416-03, 84MI 416-02), shrimp (86ABC2867), krill (80ABC2677, 82MI 416-01), bacon (85MI 416-01), crab (88MI 416-02), and soybean products (85ABC311).

Structural and electronic factors of 1,2,4-trithiolanes and other organic compounds have been related to known odorant properties (88MI 416-03) and the occurrence of the latter series of compounds in natural flavors has been reviewed (89MI 416-03). 3,5-Diisopropyl-1,2,4-trithiolane enhances the taste of hazelnut-flavored foodstuffs, pork gravy, beef broth, and ground sausage (78USP4259507). The importance of other 1,2,4-trithiolanes in food flavors has attracted attention to the use of model systems which mimic their formation. A number of such systems have been reported, involving a sulfur-containing component such as cysteamine (84MI 416-03), thiamin (92MI 416-10, 92MI 416-11), 2-methyl-3-mercapto-1-propanol (85MI 416-02), hydrogen sulfide, ammonium sulfide, or (most commonly) cysteine. Cysteine has been thermolyzed on its own (86MI 416-02) and in the presence of aldehydes (2,4-decadienal (89MI 416-04), propanal (91ABC1537) or furfural (89MI 416-05)), or sugars (D-glucose (84MI 416-03), 2,5-dimethyl-4-hydroxy-3(2H)-furanone (88MI 416-04), ribose (89MI 416-06), or rhamnose (92MI 416-12)).

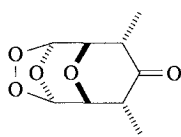
4.16.10.3 Biological Activity

The toxicity of ozone and other components of urban and industrial smog (which may include 1,2,4-trioxolanes) has attracted interest since the early 1980s as concern for the effects of environmental pollution grows (81JA3807). Various model systems of pulmonary surfactants, lung-lining fluids, and pulmonary membranes found in the lungs have been used. Methyl oleate is most often employed as it forms a characteristic 9,10-monoozonide (82MI 416-04). Methyl lineolate ozonide (MLO) has been ozonized in hexane in a thin film, in sodium dodecyl sulphate micelles and in distearoylphosphatidylcholine liposomes (92MI 416-13). Vitamin C seems to reverse the toxic effects of MLO in alveolar macrophages, indicating a different toxicity mechanism to that of cumene hydroperoxide which retains its effects (92MI 416-14). MLO is a substrate for glutathione S-transferases (87MI 416-01) which may act to detoxify ozonide products (89MI 416-07). Methyl lineolate was also autooxidized by allyl benzene ozonide which was used as a model for other polyunsaturated fatty acid ozonides (89MI 416-08). Ozonides of β -oleoyl- γ -palmitoyl-L- α -phosphatidylcholine, an unsaturated lung surfactant component, have been characterized by NMR, FTIR, UV and FAB (fast atom bombardment) MS (92MI 416-15). These have been used to infer that ozonides are formed in small but significant amounts in the lungs of animals breathing polluted air.

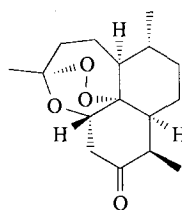
Ozonolysis of pyrethroids generates ozonide products and epoxides which show mild levels of bacterial mutagenicity <86MI 416-03>. This has possible implications for atmospheric oxidation of pesticides or ozonolytic treatment of waste water.

The ozonide (**176**) was prepared as part of a synthetic study towards the antimalarial natural product artemisinin (**177**) <92JCS(P1)3251>. It proved stable enough to allow x-ray crystal structure determination (see Section 4.16.3.1). Other, more complex, polycyclic ozonides were prepared in order to investigate possible antimalarial properties. Compounds were evaluated *in vitro* for antimalarial activity using a multiresistant strain of *Plasmodium falciparum*. Most were found to be weakly active although a thousand times less active than artemisinin.

Very little information on the biological activity of the other 1,2,4 oxygen or sulfur containing five-membered rings has been reported.



(176)



(177)

4.17

Tetrazoles

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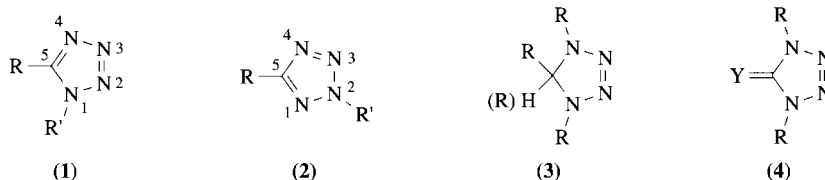
4.17.1 INTRODUCTION

Since the early 1980s, the growth of tetrazole chemistry has continued unabated as judged by the number of publications and patents relating to various types of tetrazoles. Unlike the 1960s and 1970s, most good heterocyclic chemistry books now contain considerable discussion of the tetrazole ring and its place among the azoles (e.g., <B-92MI 417-01>) but major textbooks of organic chemistry usually fail to mention tetrazoles at all or to point out that the tetrazolic acids, $\text{R-CN}_4\text{H}$, are the

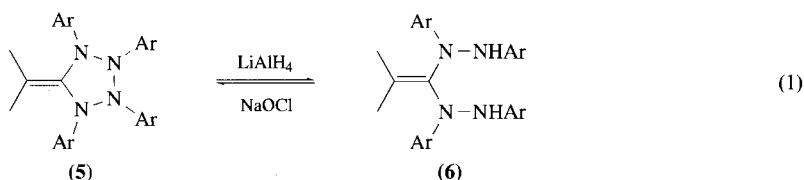
nitrogen analogs of the carboxylic acids, RCO_2H . Further to the major reviews by Benson and Butler already mentioned $\langle 84\text{CHEC-I}(5)791 \rangle$, a number of other relevant reviews have appeared $\langle \text{B-84MI 417-01, 84JHC627, B-92MI 417-02, 92ZOB3, 93AHC}(56)49 \rangle$. A limiting feature of tetrazole chemistry was the fact that there were few, if any, natural tetrazoles known. This appears to be changing and a rich natural chemistry of tetrazoles may emerge in the coming decades from an unexpected region. The atmosphere of Titan, the largest moon of Saturn, appears to be compatible with tetrazole chemistry $\langle 91\text{MI 417-01} \rangle$ and indeed the first claims for tetrazole compounds on Titan have appeared $\langle 92\text{ACR286} \rangle$.

4.17.1.1 Structural Types

Fully conjugated aromatic tetrazole rings have structures (1) or (2) and are numbered as shown. These are discussed in Section 4.17.5. Dihydropyrazoles are dealt with as nonconjugated systems in Section 4.17.6. The most common forms of these are the structures (3) and (4). The Δ^2 -tetrazolines (3) may give diaziridines when heated or if aromatic substituents are present at C-5 cycloreversion to azides and imines may occur $\langle 87\text{BSF525, 88CB1213} \rangle$. The 1,4-dihydropyrazole structure (4) is common for $\text{Y} = \text{S, O, NR and CR}_2$.



Photochemical and thermal fragmentations of these systems are of interest as routes to three-membered rings and since the early 1980s much interest has focused on the behaviour of the alkene bond in structure (4; $\text{Y} = \text{CR}_2$) $\langle 87\text{AG(E)1160, 90CB2195} \rangle$. Tetrahydropyrazoles are rare, the first-claimed examples being the tetraaryl derivatives (5) obtained from the reaction of isopropylidene carbene with substituted azobenzenes. Reduction of (5) gave the acyclic dihydrazines (6) which were readily oxidized back to the tetrahydropyrazoles in quantitative yield (Equation (1)) $\langle 84\text{JA6015} \rangle$.



Tetrazolium salts and tetrazolium-5-ylide structures $\langle 84\text{CHEC-I}(5)791 \rangle$ as well as new tetrazolium-N-ylide structures are also possible. These are covered in Sections 4.17.5, 4.17.7 and 4.17.8.

This chapter is complementary to the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) and the work of the 1970s and earlier decades is not revisited herein except for completion purposes and the mention of special original early work.

4.17.1.2 Metal Complexes

The tetrazole ring contains three doubly-bound (pyridine-type) nitrogens each of which has a lone-pair available for external complexation and hence tetrazole-metal complexes are ubiquitous in the inorganic literature. Metal complexation may also prove useful as a method for separation of isomeric tetrazoles. Complexation of 1,5- and 2,5-disubstituted tetrazoles with CuCl_2 has been used for purification and separation of the isomers $\langle 84\text{DOK}(28)543, 88\text{ZOB825} \rangle$. In metal-tetrazole compounds, the bonding to the metal may involve a normal σ -bond as for example in the compounds (7) $\langle 74\text{JA6298} \rangle$, (8) $\langle 86\text{JCS(P1)1101} \rangle$, and (9) $\langle 89\text{JOM}(361)\text{C5} \rangle$ or it may involve coordination donor bonds with the external lone pairs. Coordination complexes with the external lone pairs may involve a single coordination site on the tetrazole ring as in the new siderophores (iron carriers) (10) which contain three coordinated 1-substituted-5-oxyvinyl-tetrazole units (Equation (2)) $\langle 91\text{AG(E)1494} \rangle$. The tetrazole ring may also adopt a bridging role between two metal atoms using both σ -bonds and

dative bonds as in structure (11) <83CB3867>. Many tetrazole-metal complexes are synthesized from cycloaddition reactions of metal azide complexes with nitriles <83CB2691>. A wide range of metals has been complexed with substituted tetrazole derivatives. Examples which provide an entry to the inorganic literature are listed in Table 1. The influence of metal complexation on tetrazole infrared bands is discussed in Section 4.17.3.3.

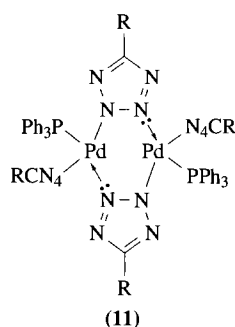
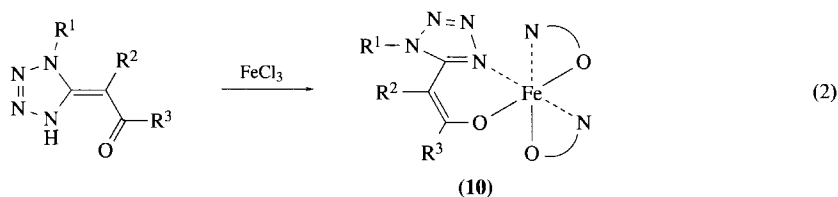
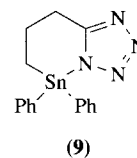
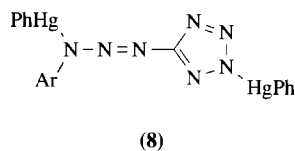
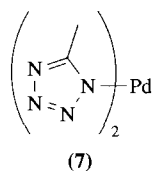


Table 1 Metals complexed with substituted tetrazoles.

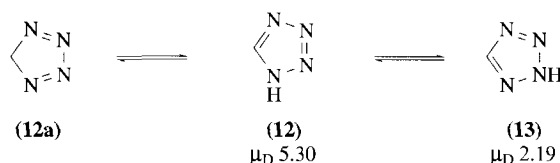
<i>Metal</i>	<i>Tetrazole type or substituent</i>	<i>Ref.</i>
Pd(II)	5-Me; 5-CF ₃	74JA6298, 73JCS(D)371
Pt(II), Pd(II)	5-Br; 5-Ph	70IC2678
Co (oximes)	5-alkyl; -aryl; Me ₂ N—	80JA2968; 81IC1258
Fe(II), Fe(III), Al(III)	1,5-disubstituted	91AG(E)1494
Cd, Cu(II), Zn, Ni(II)	5-(N=CRR)	90MI 417-01
Fe(II), Cu(II)	1,5-disubstituted	92CB2331
In(III)	5-Me; 5-Ph	87JA7228
Co	5-CF ₃ ; 5-R	82IC1226, 86MRC984
Hg	5-(NH—N=N—)	86JCS(P1)1101
Cu(II)	1-substituted; 1,5-disubstituted	88ZOB825, 84DOK(28)543
Ir(I), Pd(II), Pt(II)	5-alkyl; 5-aryl	83CB2691
Rh(I), Ir(I), Pd(II)	5-aryl; 5-pyrid-2'-yl	83CB3867
Sn	5-cycloalkyl	89JOM(361)C5
Li ⁺	1-H; 5-H (6-31G)	89JPC3929
Li ⁺	1-H; 5-H polymeric	93JOM(455)29
Ag(I)	1,5-pentamethylene	72IC1410
Au(III)	1-R; Au-C-5	72JA3370
Zn(II)	1-Me; 5-H	71IC661
General	1,5-disubstituted	69CCR463 ^a , 77AHC(21)340 ^a , 88MI 417-01 ^a

^aReviews.

4.17.2 THEORETICAL METHODS

4.17.2.1 Tetrazole Tautomers and Dipole Moments

The large amount of experimental data which is available on the two tautomers of tetrazole, (12) and (13) (Scheme 1), coupled with the complexity of the ring which contains three pyridine-type nitrogens make the system ideal both for the application of theoretical methods and for the assessment of the different *ab initio* basis sets and semiempirical approaches. *Ab initio* calculations using RHF/6-31G gave the best results from a range of theoretical levels and suggested the 2H form (13) to be 1.7 kcal mol⁻¹ more stable than the 1H form (12) in the gas phase <85JPC460>. Calculated dipole moments were 5.63D for (12) and 2.24D for (13) as against the experimental values of 5.30 and 2.19 from microwave spectra <74JSP(49)423>. *Ab initio* calculations with a 4.31G basis set gave equal energies for both tautomers and suggested that for 2H-tetrazole the mesomeric moment outweighed the primary moment corresponding to the classical valence structure in determining the direction of the molecular dipole moment. Total moments of 5.42D and 1.85D were arrived at for (12) and (13), respectively <82JST(82)283>. Semiempirical CNDO/2 and CNDO/S methods gave (13) as 1.69 kcal mol⁻¹ more stable in the gas phase than (12) and suggested that the excited states of (13) lie significantly lower than those of (12) so that promotion of (13) from its ground state to higher excited states should not lead to a tautomeric change <85JCS(F2)1555>. The dominant form of tetrazole in the gas phase is the 2H form (13) while in solution the 1H form (12) is favoured because of solvation effects <85JCS(F2)1555, 93JA2465>. The results for a range of calculations of dipole moments and energy differences between the tetrazole tautomers are summarized in Table 2. High level *ab initio* calculations have also been applied to the 5H tautomer (12a) which was determined to lie 19.6 kcal mol⁻¹ above (12) and to be a good candidate for experimental observation <93JA2465>. The lowest ionisation energy of tetrazole from its photoelectron spectrum is ca. 11.4 eV <81ZN(A)1246>. Calculated ionization energies for the 2H tautomer from CNDO/2 were 13.23 eV using the HOMO energy from Koopman's theorem and 12.21 eV using the difference between the total energies of the ionized and unionized molecules <83JCS(P2)379>. *Ab initio* calculated ionization potentials of 11.00 eV for 1H-tetrazole and 10.806 eV for 2H-tetrazole have also been determined and compared with Koopman values and results from perturbation theory <91JPC7694>.



Scheme 1

4.17.2.2 Substituted Derivatives

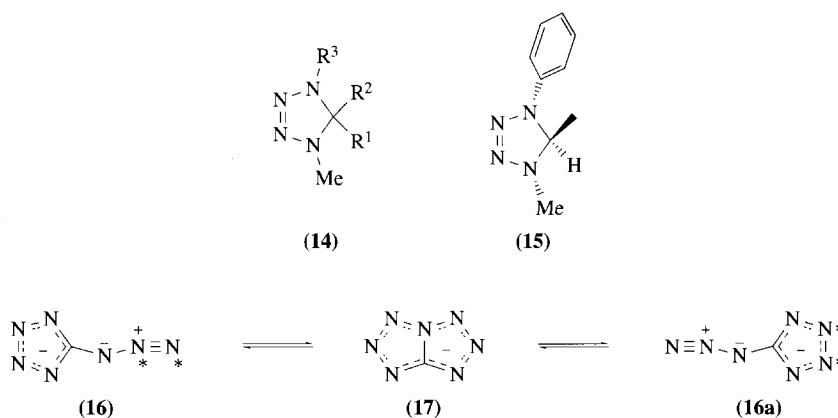
4.17.2.2.1 Molecular and electronic structures

The literature listed in Table 2 gives numerous examples of calculated bond lengths and angles with optimized geometry for the tetrazole tautomers. The electronic structures of the substituted 4,5-dihydro-tetrazoles (14) have been investigated by MNDO and AM1 calculations to explain their photoelectron spectra <88CB1213>. Their electronic structure resembles that of the *cis*-2-tetrazene group and is characterized by three occupied π molecular orbitals (π_1 – π_3) and two n molecular orbitals, n_+ and n_- . For aliphatic substituents, π_3 is the HOMO and the energies for (14; $R^1 = R^2 = R^3 = \text{Me}$) were π_3 , 7.94 eV, π_2 , 9.58, n_- , 10.38, n_+ 11.52, respectively with π_1 lost in the σ -bond region. The tetrazole ring is planar and for $R^3 = \text{Ph}$ MNDO suggested the phenyl ring should be coplanar but AM1 favored a twisted phenyl group. According to AM1 results the most stable configuration has pyramidalized nitrogen atoms as in (15) with the phenyl ring twisted at 23° to the tetrazole plane. The barrier to rotation of the phenyl ring plane is very low and the coplanar conformation is only 0.5 kcal mol⁻¹ less stable than the ring twisted form (15) <88CB1213>. *Ab initio* calculations at 4-31G on the gas-phase Dimroth rearrangement of 1-substituted-5-aminotetrazoles to RNH-CN₄H suggested that ring opening is not the rate-determining step but rather the (Z)/(E) isomerization in the imido-yl azide intermediate or the 1,3-sigmatropic shift of the proton <82JHC943>.

Table 2 Theoretical dipole moments and relative energies of tetrazole tautomers, R—CN₄H.

R	Method	μ_D		Relative energy (kcal mol ⁻¹) (2H-1H)	Ref.
		1-H-Tetrazole	2-H-Tetrazole		
H	RHF/6-31G**//6-31G	5.63	2.24	-1.7	85JPC460
H	RHF/3-21G	5.84	2.32	1.0	85JPC460
H	CNDO/2	5.17	2.34	-6.5	83JCS(P2)379
Me	STO-3G	5.57	2.08	-1.5	84CS84
Me	CNDO/2	5.46	2.11	-6.8	83JCS(P2)379
CF ₃	STO-3G	3.97	3.46	-8.8	84CS84
H	4-31G	5.42	1.85	0	82JST(82)283
H	MNDO (corrected)			-4	85JOC4894
H	CNDO/2			-1.69	85JCS(F2)1555
H	HMO	4.80	2.15		61T237
H	G-FEMO	5.08	2.16		71MI 417-01
H	SCF-LCAO	5.18	2.04		69BSF1097
H	STO-3G	5.22	2.23	-2.5	84CS84
H	CNDO/2	5.23	2.35		67JA6835
H	CNDO/2	5.26	2.04		75BSF(2)1675
H	LGGO	5.17	2.54		74JCS(P2)420
H	QC1SD(T)/6-311 + G(2d, 2p) corrected	5.58	2.43	-1.9	93JA2465
H	6-31G*//6-31G	5.63	2.23	-1.7	86JPC5597

4-31G *Ab initio* and corrected MNDO calculations on the heptaazapentalene anion (**17**) showed it to be a true minimum on the potential hypersurface of CN₇⁻ and suggested that it is only 6.6 kcal mol⁻¹ higher in energy than 5-azidotetrazolate anion (**16**) (Scheme 2). The existence of the species (**17**) was experimentally supported by the observation of ¹⁵N scrambling between the 5-azido group and the 2- and 3-positions of the tetrazole ring in the anions (**16**) and (**16a**) <86CC959>.

**Scheme 2**

4.17.2.2.2 Energy and stability: protonation quaternization

Calculated protonation energies of azoles may be used as measures of basicity where the protonation energy is calculated as the difference between the energy of the azole molecule and the most stable protonated species. Tetrazoles are the weakest bases among the azoles. *Ab initio* calculations at 6-31G**//6-31G gave the following protonation energies for the azole series <86JPC5604>: imidazole, 240.1(318) kcal mol⁻¹; pyrazole 227.0(312); 4*H*-1,2,4-triazole, 231.8(307); 1*H*-1,2,4-triazole 225.1(300), 2*H*-tetrazole 209.6(294); 1*H*-tetrazole 213.4(293). The values in parentheses are from INDO calculations <91JPC7694> and are about 80 kcal mol⁻¹ higher. Both sets of data followed the reverse order of the σ ionization potentials and suggested that the protonation energy of an azole is related to the energy of ionizing an electron from the σ -framework of the molecule. Protonation of both 1*H*- and 2*H*-tetrazole is predicted to occur at N-4 from protonation energies calculated by a range of methods <86JPC5597>. The protonation sites in *N*-aminotetrazoles

are calculated by the INDO method to be at the nitrogen atom most remote from the substituent. Both 1- and 2-substituted tetrazoles are predicted to protonate at N-4. Interestingly for N-amino-substituted tetrazoles ring protonation favors an amino group conformation with the lone-pair orthogonal to the plane of the ring. The energies for protonation of 1-amino- and 2-aminotetrazole at N-4 were determined from INDO//INDO calculations as 356.5 and 355.2 kcal mol⁻¹, respectively <90JCS(P2)237, 93JCS(P2)1687>. The most basic sites of 2-methyl- and 1-methyltetrazole were calculated at the 6-31G level to be N-4 in both cases with protonation energies of 220.5 kcal mol⁻¹ and 224.1 kcal mol⁻¹ respectively. The experimental basic p*K*_a values are 2-methyltetrazole, -3.25 and 1-methyltetrazole, -3.00 <88KGS579, 93MRC791>. MNDO calculations were applied to *N*-methyl quaternary derivatives of 1-methyl- and 2-methyl-5-vinyltetrazoles to obtain heats of formation and dipole moments of the different isomeric tetrazolium salts. The values of Δ*H*_f^o for 1-methyl-5-vinyltetrazole, 62.4 kcal mol⁻¹, 1,4-dimethyl-5-vinyltetrazolium chloride, 83.7 and 1,3-dimethyl-5-vinyltetrazolium chloride, 99.5 suggested that methyl quaternization should occur preferentially at N-4 <93SA(A)135>. MNDO calculations have been applied to a wide range of substituted tetrazole derivatives to determine heats of formation, charge distributions, protonation energies, dipole moments <92IJQ813> and regiospecificity in metallation and alkylation reactions <94JOC773>. Calculated π-electron densities of some tetrazoles and tetrazolium cations are shown in Table 3 <92MRC558>. As for the parent tetrazole, 6-31G level calculations determined the 2*N*-methyl isomer to be 2.9 kcal mol⁻¹ more stable than the 1*N*-methyl isomer <93MRC791>.

Table 3 MNDO calculated π-electron densities^a.

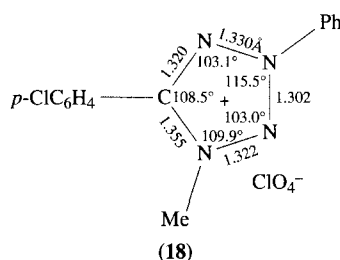
Tetrazole	N-1	N-2	N-3	N-4
1-H-tetrazole	1.5834	1.1588	1.0997	1.2047
1-H-tetrazole ^b	1.592	1.130	1.154	1.262
1,H,4H-cation	1.5178	1.085	1.085	1.5178
5-Me; 1-H	1.5800	1.1607	1.1003	1.2034
5-Me, 1H, 4H, cation	1.5302	1.0868	1.0878	1.5298
1-Me, 5-H	1.5773	1.1562	1.1007	1.2049
2-Me, 5-H	1.2032	1.5406	1.1035	1.1638
1-Me, 5-Me	1.5751	1.1582	1.1010	1.2043
2-Me, 5-Me	1.2020	1.5401	1.1053	1.1612

^a<77IJC(B)168, 86MRC984, 92MRC558>. ^bC-5, 0.862.

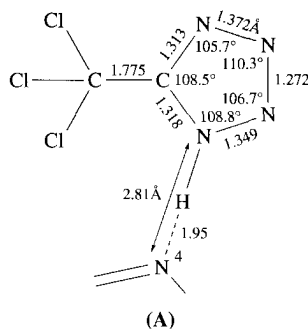
4.17.3 EXPERIMENTAL STRUCTURAL METHODS

4.17.3.1 Molecular Dimensions

X-ray crystal structures of tetrazolate indium(III) complexes <87JA7228> and the organotin tetrazole (**9**) <89JOM(361)C5> have been reported. Compound (**9**) has a polymeric structure with trigonal bipyramidal geometry about tin in which the tetrazole N-4 and the next tetrazole N-1 are at the apical sites. Parent tetrazole is a planar ring with internal bond angles at C-5, 112.5°, N-1, 104.3° and N-2, 109.5° and bond lengths C(5)—N(1), 1.329 Å, N(1)—N(2), 1.348 Å and N(2)—N(3), 1.310 Å as determined from the x-ray crystal structure of sodium tetrazolate monohydrate <84CHEC-I(5)791>. *N*-Methyl quaternization of 2,5-diaryltetrazoles occurs at N-4 and the ring dimensions of 2-phenyl-4-methyl-5-(*p*-chlorophenyl)tetrazolium perchlorate (**18**) have been calculated from an x-ray crystal structure determination <94JCR(S)216>. The tetrazole ring is planar and the 5-(*p*-chlorophenyl) ring is twisted at 40.24° to the tetrazole plane while the 2-phenyl group is twisted at a lesser angle of 27.08° to the tetrazole plane.



An x-ray crystal structure of a 5-trichloromethyltetrazole (A) has also been reported. The molecule is a planar pentagon with bond lengths between single and double and the carbon atom bonded to C-5 also lies in the tetrazole plane. The ring hydrogen is at N-1 and is hydrogen bonded to N-4 of another molecule and this hydrogen bonding gives rise to chains of tetrazoles in the crystal $\langle 87ZN(B)55 \rangle$.



4.17.3.2 NMR Spectroscopy

The main structural method used with tetrazoles since the early 1980s is overwhelmingly NMR spectroscopy.

4.17.3.2.1 Nitrogen-15 NMR spectra

Nitrogen-15 NMR spectra have been reported on a wide range of individual tetrazole compounds. Examples are listed in Table 4. This technique has been applied to the tetrazole annular tautomerism $\langle 82JOC5132 \rangle$ and to substituent tautomerism in tetrazol-5-ones and tetrazol-5-thiones $\langle 85MRC166, 86BCJ3263 \rangle$ which is discussed in Section 4.17.4.3.2. Nitrogen-15 NMR has shown that methyl quaternization of 2-substituted 5-vinyltetrazoles occurs at N-4 while that of 1-substituted 5-vinyltetrazoles occurs at both N-4 and N-3. Quaternization causes an upfield shift of 90–97 ppm for the nitrogen atom being quaternized and 15–25 ppm for adjacent bonded nitrogen atoms $\langle 93SA(A)135 \rangle$. Similar upfield shifts are observed for protonation of tetrazoles. The ^{15}N NMR spectra indicated the protonation site as N-4 since ^{15}N (and ^{14}N) chemical shifts correlate well with π -electron densities $\langle 72T637, 86MRC984, 92MRC558 \rangle$. The highest π density in substituted tetrazoles is on the pyrrole-type singly-bound nitrogen and this has the greatest upfield shift with the shielding of the other nitrogens following their charge densities (compare Tables 3 and 4).

The ^{15}N NMR shifts for the tetrazolium ylides, 2,3-diphenyl-tetrazolium-5-olate and -thiolate are also shown in Table 4. In $\text{CF}_3\text{CO}_2\text{H}$ the 5-thiolate compound showed shifts very close to those of the *S*-methyltetrazolium iodide salt suggesting protonation at the exocyclic sulfur atom $\langle 92MI 417-03 \rangle$. A multinuclear NMR study of mesoionic 1,3-dimethyltetrazoles including ^{14}N and ^{15}N spectra has been reported $\langle 94JCS(P2)1327 \rangle$.

4.17.3.2.2 Carbon-13 and proton NMR spectra

The ^{13}C NMR shift of the tetrazole C-5 is sensitive to the bonding pattern in the ring and allows a distinction of isomers. The signal is generally about 10 ppm deshielded in 2,5-disubstituted derivatives relative to the corresponding 1,5-disubstituted isomers (Table 5). It has been suggested that the carbon shifts may be controlled by electron density at C-5 $\langle 86MRC984 \rangle$ and that a calculated π -charge density of 0.9711 for C-5 in 1,5-dimethyltetrazole as against 0.9616 for 2,5-dimethyltetrazole may account for the shifts of 154.7 ppm and 164.7 ppm respectively. Linear correlations of ^1H and ^{13}C NMR shifts for azoles with HMO calculated π -electron densities have been reported $\langle 77JUC(B)168 \rangle$. *N*-Methyl quaternization at N-4 causes the C-5 shift to move upfield, to higher shielding, by 5–8 ppm with a similar change occurring at the 5-aryl-C-1' $\langle 94JCR(S)216 \rangle$. Shielding effects of similar magnitude have also been found for quaternization of nitrogen substituted 5-vinyl

Table 4 ^{15}N NMR shifts of some tetrazole derivatives from external MeNO_2^{a} .

Substituted tetrazole (solvent)	N-1	N-2	N-3	N-4	Ref.
1-Me, 5-H (DMSO)	−151.4	−10.8	12.3	−50.2	82JOC5132
1-Me, 5-H (C_6D_6)	−151.0	−10.0	12.1	−50.3	92MRC558
2-Me, 5-H (neat)	−75.1	−103.8	−2.3	−49.0 ^d	92MRC558
1,5-diMe (acetone- d_6)	−154.4	−9.4	+8.1	−54.4	86MRC984
2,5-diMe (acetone- d_6)	−77.7	−104.1	0.4	−49.9 ^d	92MRC558, 86MRC984
2-Me, 5-Ph (DMSO- d_6)	−82.2	−103.2	0.4	−54.3 ^d	92MRC558
1-Me, 5-vinyl (DMSO- d_6)	−157.6	−10.3	8.4	−56.6	92MRC558, 93SA(A)135
1-Me, 5-SMe (DMSO)	−158.1	−7.1	11.1	−55.6	86BCJ3263
2-Me, 5-SMe (DMSO)	−81.6	−101.4	2.3	−53.4	86BCJ3263
1,2-diMe, 5-S (DMSO)	−97.3	−70.9	4.5	−47.7	86BCJ3263
2-Bu ⁱ , 5- CF_3 (neat)	−69.2	−76.1	2.8	−48.4	92MRC558
1-Bu ⁿ , 5-H (CDCl_3)	−142.4	−11.9	13.6	−50.0	92MRC558
2-Me, 5-CN	−60.7	−95.9	6.6	−36.5 ^d	86MRC984
<i>Tetrazolium cations (acid)^b</i>					
2-Me, 5-H, 4-H (80% H_2SO_4)	−65.8	−96.8	−20.3	−144.0	92MRC558
1-Me, 4-Me, 5-vinyl ^c	−148.1	−17.5	−17.5	−148.1	93SA(A)135
1-Bu, 5-H, 4-H (95% H_2SO_4)	−130.5	−11.5	−17.0	−147.5	92MRC558
2-Ph, 3-Ph, 5-SMe·I [−] (DMSO)	−67.8	−100.1			92MI 417-03
2-Ph, 3-Ph, 5-OEt·BF ₄ [−] (DMSO)	−94.0	−108.0			92MI 417-03
<i>Tetrazolium ylides</i>					
2-Ph, 3-Ph, 5-S [−]	−64.5	−108.5			92MI 417-03
2-Ph, 3-Ph, 5-O [−]	−97.9	−119.5			92MI 417-03

^a Upfield shifts, negative, downfield shifts positive. ^b 5-Substituted tetrazolate anion shifts in D_2O relative to external NH_4NO_3 have also been listed (86MRC984). ^c Methyl sulfate salt in CD_3OD . ^d Some confusion on N-3 and N-4 shifts in early spectra has been corrected (92MRC558).

tetrazoles (93SA(A)135) for both the tetrazole and the α -C bonded to C-5. Shifts for some tetrazolium 5-ylide structures show a large difference between the C-5 shift of tetrazolium 5-olate and 5-thiolate units (Table 5, entries 17 and 18). When measured in $\text{CF}_3\text{CO}_2\text{H}$, the C-5 shift of 2,3-diphenyltetrazolium-5-thiolate was 167.6 ppm, similar to that of the S-methyl salt (entry 19, Table 5) confirming protonation on the exocyclic sulfur atom (92MI 417-03). Another useful structural correlation in both ^1H and ^{13}C NMR spectra are the changes associated with ring closure of an imido-yl-azide moiety in an aromatic nitrogen heterocycle. The shifts of the tetrazole C-5 and the carbon α to N-1 are shifted upfield (towards TMS) by about 12 ppm and 24 ppm, respectively and the α -H is deshielded by 0.6–1.0 ppm relative to the corresponding imido-yl azide signals. The ^{13}C – ^1H coupling constant at the α -carbon is also increased by about 14 Hz. (88MRC42). Carbon-13 NMR studies of conjugation effects in 1-aryltetrazoles suggest a torsional angle for the 1-phenyl ring of 15–30° (80AJC1763, 81JCR(M)364, 81AJC957, 83M65). Transmission of electronic substituent effects from the 1N-aryl group is particularly weak (compare the $\delta\text{C-5}$, and δH for entries 12 and 13, Table 5) and the $^1J(\text{C-5},\text{H})$ value of 221 Hz is almost independent of the 1N substituents (89MRC611). Proton and carbon-13 NMR spectra of a range of 1N-aryltetrazoles gave a σ_1 value of 0.56 and a σ_{R} value of −0.045 for the tetrazol-1-yl group which is thus comparable to a CN group in its inductive effect and a weak electron donor comparable to aryl groups in its mesomeric effect (89MRC611). Isomeric N-alkyl tetrazoles can be distinguished by both the proton and carbon shifts of the alkyl group directly bonded to the ring nitrogen atom. Alkyl groups bonded at N-2 are deshielded (away from TMS) by the two adjacent doubly bound nitrogens, $=\text{N}-$, relative to those at N-1, which have only one such adjacent nitrogen (Table 5). Irradiation of alkyl groups at N-1 also gives a nuclear Overhauser enhancement in signals for protons at C-5 or nearby protons of substituents at C-5. This effect is very weak or absent for alkyl groups at N-2 and hence can be used to distinguish isomers (92MI027). The 5-CH proton shifts of 1-aryltetrazoles are generally more deshielded than those of 2-aryltetrazoles, about 10.0–10.4 δ versus 9.1–9.5 δ respectively in $(\text{CD}_3)_2\text{SO}$ and the 5-CH shifts of 1-aryltetrazoles are considerably more sensitive to solvent variation, an effect which can be of analytical value (77JPR408).

Proton and carbon NMR studies of interannular conjugation effects in aryl-substituted tetrazoles have been discussed (84CHEC-I(5)791). The use of NMR spectroscopy to study tautomerism in tetrazole systems is covered in Section 4.17.4.

Table 5 ^{13}C and ^1H NMR shifts of some substituted tetrazoles.

No.	Substituted Tetrazole	$\delta 5\text{-C}$ (δH) (ppm)	Other signals					Ref.
			$N\text{-Me}$ δC (δH)	C-1'	C-2'	C-3'	C-4'	
1	1,5-DiMe	152.7 ^c	33.15 (4.0)					77MI 417-01
2	2,5-DiMe	162.35 ^c	39–41 ^f (4.3)					77MI 417-01
3	1-Me, 5-Ph	154.2 ^c	35.0 (4.16)	123.25	128.6	129.3	131.4	78JCS(P2)1087
4	2-Me, 5-Ph	164.25 ^c	39–41 ^f (4.25)	126.7	126.4	129.3	130.7	78JCS(P2)1087
5	1-Me, 5-NH ₂	155.8 ^c	31.5 (3.82)					77MI 417-01
6	2-Me, 5-NH ₂	166.9 ^c	39–41 ^f (4.16)					77MI 417-01
7	1-Ph, 5-NH ₂	154.04 ^d		133.27	123.73	130.29	129.93	83M65
8	1-Me, 5-Cl	146.5 ^c	33.7 (4.24)					77MI 417-01
9	2-Me, 5-Cl	154.5 ^c	38.8 (4.52)					77MI 417-01
10	1-Me, 5-C ₆ H ₄ N ^a	153.85 ^c	36.7 (4.20)	122.0	138.4	126.05	150.3	82JCR(S)122
11	2-Me, 5-C ₆ H ₄ N ^b	163.6 ^c	41.45 (4.48)	124.9	136.05	126.3	148.45	82JCR(S)122
12	1-Ph, 5-H	142.4 ^c (10.08)		134.14	122.65	122.65	134.14	89MRC611
13	1-(<i>p</i> -NO ₂ C ₆ H ₄), 5-H	142.6 ^c (10.29)		138.14	121.76	125.57	147.54	89MRC611
14	1-Me, 5-H	143.4 ^c (9.30)	33.7 (4.09)					92MI027, 77MI 417-01
15	2-Me, 5-H	151.9 ^c (8.91)	38.8 (4.37)					
16	1-Ac, 5-H	(9.24) ^d						
17	2-Ph, 3-Ph, 5-S ⁻	181.4 ^c		133.4	126.3	129.6	132.5	92MI 417-03
18	2-Ph, 3-Ph, 5-O ⁻	169.7 ^c		134.3	126.2	129.5	131.9	92MI 417-03
19	2-Ph, 3-Ph, 5-SMe·I ⁻	167.6 ^c		132.5	126.3	129.9	133.9	92MI 417-03
20	1,4-Di Me, 5-(MeN=)	142.8						90CB2195

^aPyrid-3'-yl; C-5', 153.45. ^bPyrid-3'-yl, C-5', 152.8. ^cSolvent (CD₃)₂SO-D₂O (4:1 v/v). ^dSolvent CDCl₃. ^eSolvent (CD₃)₂SO.^fSolvent overlap.

4.17.3.3 Infrared, Ultraviolet, and Photoelectron Spectra

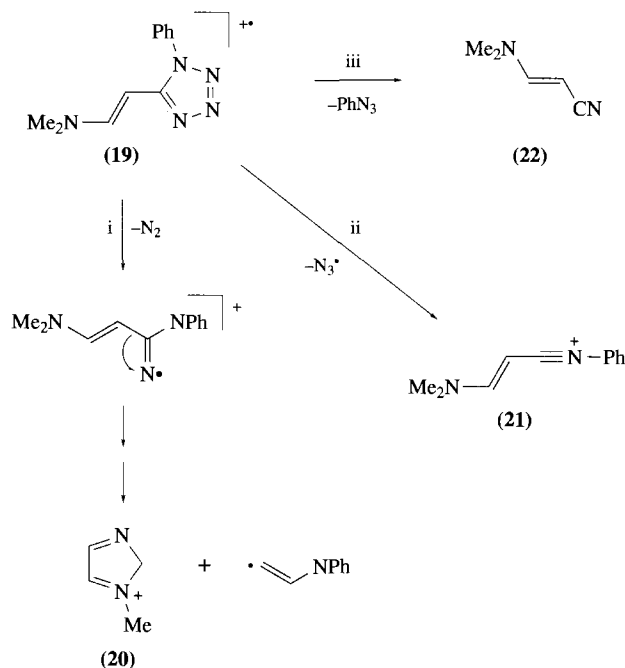
The infrared spectra of substituted tetrazoles are of particular interest because of the information which they can provide on metal complexes and complexation sites. The stretching–deformation vibrations of the tetrazole ring occur in the region 900–1100 cm⁻¹. An *ab initio* analysis of the parent structure suggested that vibrational frequencies in this region correspond to the cyclic C=N=N and N=N=N groups <93JA2465>. Major changes with new bands and new maxima are observed in this region on complexation of tetrazoles with CuCl₂ and Cu(NCS)₂ <87SA(A)349>. Weak to medium intensity bands at 1200–1300 cm⁻¹ in many tetrazoles are due to N–N bond vibrations <75ZOR1744>. These bands become more intense on metal complexation. A strong N–N stretching band which appears at 1270–1300 cm⁻¹ in 1- and 2-alkyltetrazoles is shifted 30 cm⁻¹ to higher frequency on complex formation. The C=N band of 1-alkyltetrazoles occurs at 1450–1500 cm⁻¹ and this is shifted 20 cm⁻¹ to higher frequency on complexation indicating that N-4 is the coordination site for 1-substituted tetrazoles <87SA(A)349>. For complexation of 2-alkyltetrazoles with Cu(II) salts the absorption bands of (C=N) and (N=N) shift to both low and high frequencies suggesting coordination at both N-1 and N-4. The 5-C–H stretching frequency of tetrazole is 3146 cm⁻¹ and a range of *N*-alkyl substituted tetrazoles showed this band shifted to the low frequency side below 3138 cm⁻¹. For example the 5-CH frequencies for 1-methyl- and 2-methyltetrazoles were 3135 cm⁻¹ and 3138 cm⁻¹ respectively and in general 1-substituted isomers have lower 5-CH stretching frequencies than the 2-substituted isomers <87SA(A)349>. Metal complexation may split these C–H bands into two, indicating multiple coordination sites. Linear free-energy relationships for infrared frequencies with σ_m and σ_p values for meta- and para-substituted 5-phenyltetrazoles have been reported <80MI 417-01>.

The tetrazole ring exhibits only weak end absorptions at 200–220 nm in the ultraviolet and only tetrazoles with conjugated auxochromic groups give normal ultraviolet spectra. Absorption maxima are controlled by the conjugation which is usually more extensive in 2,5-disubstituted derivatives relative to the 1,5-disubstituted isomers. Thus 2,5-disubstituted tetrazoles have higher λ_{max} as seen from the following examples: 1-Me,5-Ph, λ_{max} 232 nm, 2-Me,5-Ph, λ_{max} 240 nm; 1-Ph,5-H, λ_{max} 236 nm, 2-Ph,5-H, λ_{max} 250 nm; 1-R, 5-NHR¹, λ_{max} 218–232 nm, 2-R, 5-NHR¹, λ_{max} 254 nm. <84CHEC-I(5)791>. Ultraviolet and infrared absorptions have been reported for an extensive series of 1-aryl-5-(2'-dialkylaminovinyl)-1*H*-tetrazoles. The 5-vinyl C=C stretch appears at 1624–1641 cm⁻¹ and the ultraviolet λ_{max} (MeCN) was at ca. 300 ± 50 nm depending on substituents <88JPR963>. In some 1,5-disubstituted derivatives the conjugated substituent may be twisted significantly out of the tetrazole

plane reducing conjugation and lowering the $\lambda_{\max}$ value. The photoelectron spectra of a range of tetrazolines (**14**) have been described and the ionization potentials have been assigned to molecular orbitals <88CB1213> (Section 4.17.2.2.1). The photoelectron spectra of tetrazole and the 1*N*- and 2*N*-methylisomers have been reported. The lowest ionization energies from the published spectra are: tetrazole, about 11.4 eV; 1-methyltetrazole, about 11.1 eV; and 2-methyltetrazole, about 15.0 eV <81ZN(A)1246>. For comparison of theoretical (BLYP/6-31G*) IR spectra of tetrazole tautomers with experimental spectra in argon matrix at 12 K see <96LA1041>.

4.17.3.4 Mass Spectrometry

The mass spectral fragmentation of the molecular ion of 5-methyltetrazole occurred through a number of pathways the principal one being loss of N₂ mainly from the 1,2- or 3,4-positions. The second mode of decay was loss of HN₂· giving a fragment MeCN₂⁺ and the third pathway was loss of HN₃ giving CH₃CN⁺ <83JCS(P2)379>. These pathways are consistent with earlier mass spectral studies <84CHEC-I(5)791> but an interesting new discovery with 5-CD₃-CN₄H showed that full randomization of the ring NH and 5-CD₃ deuterium atoms occurred after the ionization. Fragmentation of the molecular ion to a nitrile species is a characteristic feature of 5-substituted tetrazoles <83JCS(P2)379>. It can be seen also in the fragmentations followed by the molecular ion of 1-phenyl-5-(2'-dimethylaminovinyl)tetrazole (**19**) (Scheme 3). The main pathway is loss of N₂ (path i) which ultimately leads to a strong peak at *m/z* 83 for the imidazolium species (**20**). The other fragmentations involve loss of N₃· (path ii) and PhN₃ (path iii) to give the nitrilium fragment (**21**) and the nitrile (**22**), respectively <89OMS(24)823, 96JHC815>.

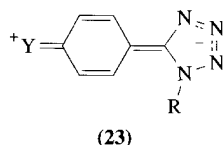


Scheme 3

4.17.3.5 Dipole Moments and Electron-spin Resonance (ESR) Spectra

A number of calculated dipole moments for tetrazoles are given in Table 2 and most of the literature quoted in Section 4.17.2 contains calculations of dipole moments. Measured dipole moments for a series of 5-phenyl-1-methyl and 5-methyl-1-phenyl tetrazoles including some nitrogen unsubstituted derivatives were in the ranges 5.04–5.90 D while the corresponding 2,5-disubstituted derivatives had values of 2.52–2.60 D. Deuteriation of the *N*-methyl group increased μ_D for 1-methyl-5-phenyltetrazole and decreased the moment for the 2-methyl-5-phenyl isomer <84ZOR2464>. The large difference in the dipole moments of disubstituted tetrazoles is mainly due to the vectorial

sum of the exocyclic σ -bond moments at C-5 and N—R which are additive in the 1,5-disubstituted structures and opposing in 2,5-disubstituted tetrazoles. Further examples of measured U_D values are available $\langle 84JCS(P2)721 \rangle$ in the context of their use as models for annular tautomerism. Although interannular conjugation in 1-substituted-5-phenyltetrazoles is weak, dipole moments suggest that canonical forms (**23**) may be significant for these substrates. Thus an increase in dipole moment is observed on passing from 1,5-dimethyltetrazole (μ , 5.30D) to 1-methyl-5-phenyltetrazole (μ , 5.70D) but not on changing from 2,5-dimethyltetrazole (μ , 2.42D) to 2-methyl-5-(*p*-tolyl)tetrazole (μ , 2.41D) $\langle 82JST(82)283 \rangle$. Conjugation of type (**23**) is likely to be stronger when R = H since better complanarity can be achieved and it may explain a correlation of Hammett σ values with the annular tautomerism, $\log K_T$ (where $K_T = N(1)H/N(2)H$), of substituted 5-phenyltetrazoles which was established from both dipole moments and carbon-13 NMR spectra $\langle 84JCS(P2)721 \rangle$. Applications of ESR spectroscopy in tetrazole chemistry have been concerned with tetrazolynyl radicals which are obtained by oxidation of formazans or by reduction of tetrazolium salts $\langle 69AG(E)520, 84CHEC-I(5)791, 90JCS(P2)1619 \rangle$.



4.17.4 THERMODYNAMIC ASPECTS

4.17.4.1 Intermolecular Forces

4.17.4.1.1 Melting and boiling points

There is little in the literature on intermolecular forces between tetrazole molecules. The main intermolecular force involved for tetrazoles containing ring N—H bonds is hydrogen bonding to the pyridine-type nitrogens. Asymmetric disordered hydrogen bonding has been observed in the crystalline complex between 1-methyltetrazol-5-thione and phthalazine $\langle 92JST(274)145 \rangle$. The tetrazole ring NH has a dominating influence on the melting points of tetrazole derivatives (Table 6, entries 1, 2, 7, 8, 10, 14, 16, 20, 21, 22). Its replacement by a methyl group causes a large decrease in melting point. The ring NH allows for the development of hydrogen-bonded chains in the solid state by bridging N-1 and N-4 of adjacent molecules (Structure (A)) $\langle 87ZN(B)55 \rangle$. It probably also generates special stacking arrangements since an active OH or NH located close to the ring but not in the plane has no such dramatic effect. A comparison of the pairs 17, 18, 21, 22, and compound 20 in Table 6 shows that for the presence of CO₂H at C-5 or NH and NHSO₂ groups at ring nitrogens the active H in these groups has little or no influence on the melting points. A comparison of the effects of a series of *ortho*-substituents in 5-phenyltetrazole (Table 6, entries 9–16) shows a large decrease in melting point on introduction of an *ortho*-fluorine into 5-phenyltetrazole. This may suggest some intramolecular hydrogen-bonding of C—F with the tetrazole 1-NH, thereby changing the solid-state structure. It is unlikely to be primarily a steric effect since the melting point rises again for *ortho*-chlorine and *ortho*-bromine substituents. CP-MAS carbon-13 experiments with solid tetrazole suggested that the 1-NH tautomer is preferred in the solid state $\langle 83H(20)1713 \rangle$. In Table 6, entry 12 shows that replacement of the ring NH does not always reduce the melting point but it is likely that the 2*N*-SnMe₃ moiety may have a polymeric structure. When H-bonding is absent, the 1,5-disubstituted tetrazoles usually have higher melting points than the 2,5-disubstituted isomers since they have higher dipole moments. Tetrazole ylide structures, for example (**24**) $\langle 93S873 \rangle$ and (**25**) $\langle 82JCR(S)122 \rangle$ generally have very high melting points.

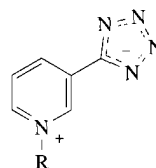
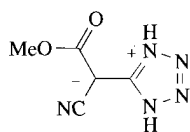


Table 6 Melting and boiling points of series of tetrazoles.

No.	<i>R-CN₄H</i>		<i>R-CN₄ (-1-R')</i>		<i>R-CN₄ (-2-R')</i>		Ref.
	<i>R</i>	<i>M.p.</i> (°C)	<i>R'</i>	<i>M.p./b.p.</i> (°C)	<i>R'</i>	<i>M.p./b.p.</i> (°C)	
1	H	156	Me	39	Me	147 (atm.)	65JOC3472
2	Me	148	Me	73–74	Me	57 (13 mmHg)	65JOC3472
3	Pr	63–64					93S767
4	Bu	46–47					93JOC4139
5	<i>n</i> -C ₅ H ₁₁	41–42					93JOC4139
6	CCl ₃	127					87ZN(B)55
7	pyrid-3-yl	239	Me	78–80	Me	128–130	82JCR(S)122
8	Ph	213	Me	103	Me	51	51JA4470
9	2'-FC ₆ H ₄	162.5–163.5					93JOC5023
10	2'-ClC ₆ H ₄	179–180	Me	68–69	Me	Oil	81JCS(P1)390
11	2'-BrC ₆ H ₄	181–183					93JOC4139
12	2'-(<i>p</i> -tolyl)C ₆ H ₄	144			SnMe ₃	> 250	91JOC2395
13	3'-BrC ₆ H ₄	181–183					93JOC4139
14	4'-MeC ₆ H ₄	252	Me	117–118	Me	108–109	81JCS(P1)390
15	2',6'-Me ₂ C ₆ H ₃	168–169.5					91JOC2395
16	2',6'-Cl ₂ C ₆ H ₃	215–217	Me	74–75	Me	79	81JCS(P1)390
17	CO ₂ H				Me	146–148 (atm.)	84CZ188
18	CO ₂ Et				Me	30–31	84CZ188
19	NH ₂	203	NH ₂	142(0.7 mmHg)	NH ₂	89–91(0.3 mmHg)	69CJC3677
20	CO ₂ Me	—	PhNH	60			92SC309
21	Ph	213	PhSO ₂ NH	179–180			84BCJ539
22	Ph	213	PhSO ₂ NMe	186–187			84BCJ539

4.17.4.1.2 Solubility and chromatography

The behavior of tetrazoles in extraction mixtures of organic solvents with water is strongly influenced by the effect of carbon or nitrogen substituents on the charge distribution in the ring and on the acid–base properties of the particular derivative <89ZPK604>. In general, 2,5-disubstituted tetrazoles, with low dipole moments, tend to be soluble in organic solvents such as Et₂O and may often be separated from their 1,5-isomers by simply being dissolved away in ether. The different dipole moments usually ensure excellent separation of isomers on alumina or silica gel columns with normal eluants. Conductivity data suggest that alkali metal and ammonium salts of 5-phenyl-tetrazole are normally associated in organic solvents. At low concentrations (<10⁻³ M) the salts are completely dissociated in solvents such as MeCN, MeNO₂ and Me₂SO <83KGS1556>. Lower tetrazoles, RCN₄H, like lower carboxylic acids, RCO₂H, are highly soluble in water and cannot be easily crystallized from it. Lower tetrazoles are best crystallized from solvents such as ethyl acetate or toluene–pentane mixtures. Tetrazoles with 5-aryl substituents or with ring nitrogen substituents are generally easily recrystallized from aqueous alcohol.

4.17.4.2 Thermal Stability and Combustion

Combustion and thermal decomposition of tetrazoles is a complicated process which has been extensively studied both in the melt and in the gas phase. The thermolysis proceeds mainly through N₂ elimination which occurs from an acyclic azide in the melt and from the 2-NH tautomer in the gaseous state. In the melt about 5% of the tetrazole decomposes with HN₃ evolution. Intermediate nitrenes and nitrilimines decompose to HCN, N₂, H₂ or cyanamide polymers <89MI 417-01, 90MI 417-02, 90MI 417-03>. The well-known elimination of N₂ from 2,5-diaryl-2*H*-tetrazoles giving nitrilimines has been shown to also occur in the combustion melt and despite the drastic conditions the nitrilimines still give rise to 1,2,4,5-tetrazines and 1,2,4-triazoles <87MI 417-01, 88MI 417-02>. The burning rates of 5-substituted tetrazoles depend on the Hammett sigma values for substituents rather than on the adiabatic combustion temperature and nitrile fragments were major products <91MI 417-02> (see also Section 4.17.12.4.3). The experimental heat of formation of tetrazole is 28.11 eV (2710 kcal mol⁻¹). When compared to values for pyrazole (39.391 eV), imidazole (39.790 eV) and 1,2,4-triazole (34.377 eV) it suggests that tetrazole is less stable than the lower azoles <66JCP759>. Dewar has calculated resonance energies of 26.0 kcal mol⁻¹ for 1*H*-tetrazole and 29.25 kcal mol⁻¹ for 2*H*-tetrazole which compare with values for pyrazole (35.5), imidazole (22.9) and 1*H*-1,2,3-

triazole ($27.9 \text{ kcal mol}^{-1}$) $\langle 66\text{JCP}759 \rangle$. Standard enthalpies of formation of some tetrazole derivatives have been tabulated $\langle \text{B-84MI 417-01} \rangle$. Values for isomeric 1,5- and 2,5-disubstituted tetrazoles are similar and show no structural regularity. For example, the values quoted for 1-methyl- and 2-methyl-5-aminotetrazole were $+46.2 \text{ kcal mol}^{-1}$ and $+50.4 \text{ kcal mol}^{-1}$, respectively, while the respective values for the 1-phenyl- and 2-phenyl-5-amino derivatives were $+69.9 \text{ kcal mol}^{-1}$ and $+65.7 \text{ kcal mol}^{-1}$. The tetrazole ring has an electron-withdrawing inductive effect, $\sigma_1 = 0.56$, and a small resonance effect, $\sigma_R = -0.045$ $\langle 89\text{MRC611} \rangle$. Calculated energies, ionization potentials and structures of fully conjugated derivatives are discussed in Sections 4.17.2, 4.17.3.1, and 4.17.3.3.

4.17.4.3 Tautomerism

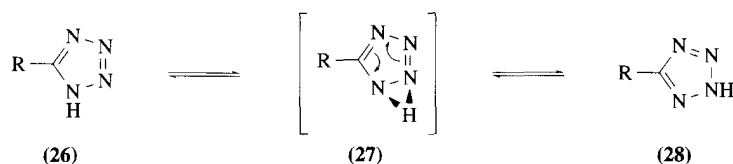
4.17.4.3.1 Annular

Extensive studies of the annular tautomerism of tetrazoles have been reported. These can be broadly divided between the gaseous, liquid solution and solid states.

(i) Gas phase

The observed annular tautomerism in tetrazoles involves the 1H form (**26**) and the 2H form (**28**).

Theoretical discussion of the possibility of an as yet undetected 5H form (**12A**) has been described in Section 4.17.2. A majority of high-level *ab initio* calculations suggest that the 2H form is more stable than the 1H form by $7\text{--}8 \text{ kJ mol}^{-1}$ ($1.7\text{--}1.9 \text{ kcal mol}^{-1}$) (Table 2) and is the major form in the gas phase. A calculated transition state for the symmetry allowed 1,2-H shift from (**26**) to (**28**) (Scheme 4) involves the migrating hydrogen atom moving 59° out of the ring plane with a transfer angle at the hydrogen atom of 71° as in structure (**27**) ($R = \text{H}$). The activation barrier is 207 kJ mol^{-1} in the gas phase and is expected to be higher in a polar solvent since (**27**) is less polar than (**26**) $\langle 93\text{JA}2465 \rangle$. Since the tautomerism is a rapid process in solution and individual tautomers cannot be detected even at low temperatures, presumably a different mechanism with a lower activation barrier must be operating in solution. Calculations agree that the more polar 1H form is the dominant form in polar solvents $\langle 82\text{JST}(82)283, 85\text{JPC}460, 85\text{JCS}(F2)1555, 93\text{JA}2465 \rangle$, and that both forms should be present in about equal amounts in non-polar solvents. This has been observed for substituted 5-phenyltetrazoles by carbon-13 NMR and dipole moment measurements in $(\text{CD}_3)_2\text{SO}$ (ϵ , 49) and dioxane (ϵ , 2.2) $\langle 84\text{JCS}(P2)721 \rangle$. Gas-phase experimental measurements on tetrazole using *N*-methyl isomers as models have been carried out using microwave spectroscopy $\langle 74\text{JSP}(49)423 \rangle$ and photoelectron spectroscopy $\langle 81\text{ZN}(A)1246 \rangle$ and both techniques confirm the dominance of the 2H tautomer. The absence of a band at 12.8 eV which occurs in the photoelectron spectrum of 1*N*-methyltetrazole suggested that the 1H form of tetrazole was almost absent in the gas phase $\langle 81\text{ZN}(A)1246 \rangle$. A mass spectral study of 5-methyltetrazole and its ^{15}N -labeled derivatives established the 2H form (**28**; $R = \text{Me}$) as the dominant form in the gas phase $\langle 83\text{JCS}(P2)379 \rangle$.

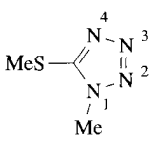
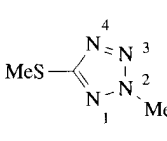
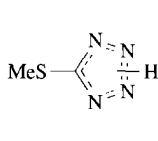


Scheme 4

(ii) In solution

Most of the experimental work on the annular tautomerism of 5-substituted tetrazoles has been carried out on solutions and a number of major studies are described in CHEC-I $\langle 84\text{CHEC-I}(5)791 \rangle$. Nitrogen-15 NMR spectra of 5-substituted tetrazoles and their *N*-1 and *N*-2-methyl isomers show

that tetrazoles exist predominantly as the 1H tautomer in solution <82JOC5132, 85BAP375, 85MRC166>. The ^{15}N -shifts from external MeNO_2 in $\text{DMSO}-d_6$ for the series of 5-methylthiotetrazoles are:

								
(29)			(30)			(31)		
N-1	158.0		82.2			N-1	} 101.2	
N-2	7.4		101.9			N-4		
N-3	-10.7		-1.8			N-2	} 5.7	
N-4	55.7		54.0			N-3		

These suggest $85 \pm 5\%$ of the 1H tautomer in DMSO <85BAP375>. Values of $90 \pm 5\%$ <85MRC166> and 99% <82JOC5132> for the parent tetrazole 1NH tautomer (**26**; $\text{R} = \text{H}$) in DMSO have been quoted from ^{15}N NMR shifts. The dipole moment of tetrazole in dioxane at 30°C was $4.88 \pm 0.05\text{D}$ and using 1,5- and 2,5-dimethyltetrazoles as models for the tautomers, the extent of the 1NH tautomer in dioxane was estimated as $78 \pm 2\%$ <82JST(82)283> and 85% <75BSF(2)1675>. The ^{13}C NMR shift of the tetrazole C-5 has been extensively used in tautomeric studies since it is about 8–10 ppm more deshielded in 2,5-disubstituted tetrazoles than in the 1,5-disubstituted isomers <84JCS(P2)721>. Using a statistical analysis of four parameters for 5-methylthiotetrazole, (**31**) ^{15}N shifts, the ^{13}C shift at C-5 and S-Me, and the ^1H shift at S-Me, a precision of 2% has been claimed in tautomeric estimates and the mole fraction of the 1NH tautomer of (**31**) was quoted as 0.8663 ± 0.0219 in DMSO <87BAP305>. The limits of the accuracy of these tautomeric assessments, however, are not clearly defined and there are few cases where different experimental approaches have been applied to the same substrate and models in the same solvent mainly because of solubility difficulties. Two such cases are 5-(*p*- MeOC_6H_4) CN_4H where the ^{13}C NMR measurements of the C-5 shift in the parent and *N*-methyl isomers gave a value of 64% 1NH tautomer in dioxane (at 70°C) and dipole moment measurements gave 72% (at 30°C); also 5-(*o,o*-dichlorophenyl)tetrazole where the corresponding values are 68% and 54%, respectively <84JCS(P2)721>. A good linear relationship of the tautomerism to the Hammett σ_p values for para-substituted 5-phenyltetrazoles shows that electron-withdrawing groups favor the 2NH tautomer, an effect which may arise from conjugation as in (**23**; $\text{R} = \text{H}$) <84JCS(P2)721>. The annular tautomerism of 5-(3-pyridyl) tetrazole, the nitrogen analogue of nicotinic acid, has been assessed by ^1H and ^{13}C NMR spectra using *N*-methyl isomers as models, including the compound (**25**) as a model for the possible pyridinium tautomer (**25a**). The normal 1NH form was the main tautomer (78%) in mixtures of D_2O and $(\text{CD}_3)_2\text{SO}$ <82JCR(S)122>.

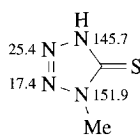
(iii) Solid state

CP-MAS ^{13}C NMR measurements with solid tetrazole (**26**; $\text{R} = \text{H}$) gave a C-5 shift of 144.0 ppm which is similar to that for 1-methyltetrazole (143.4) in $(\text{CD}_3)_2\text{SO}$ and suggests that the 1NH form is the major tautomer in the solid state <83H(20)1713>. This is supported by x-ray crystallography where intermolecular chains of tetrazole molecules have been detected in the crystal structures of tetrazole <74CSC321> and 5-trichloromethyltetrazole <87ZN(B)55>. These chain structures involve a hydrogen bridge between the 1N and 4N atoms of adjacent rings with the proton preferentially located at the N-1 site.

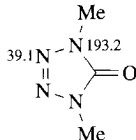
4.17.4.3.2 Ring substituent

Substituents containing active hydrogen atoms at C-5, such as HO, HS, and RNH, can theoretically exhibit a tetrazole–tetrazoline tautomerism. It is well established <84CHEC-I(5)791> that —OH and —SH groups exist predominantly and probably exclusively in the tetrazolin-5-one forms, for example (**32**) and (**34**).

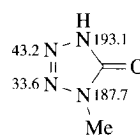
This has been further confirmed by ^{15}N NMR spectra which indicate $>95\%$ of the 5-one form with the tautomeric proton bonded to the N-4 atom <85MRC166, 86BCJ3263>. The ^{13}C NMR shift of C-5 in structure (**4**; $\text{R} = \text{H}$) also confirms the tetrazolinone form, being about 148–149 ppm for $\text{X} = \text{O}$ and about 163–165 ppm for $\text{X} = \text{S}$ in agreement with 1,4-disubstituted model compounds



(32)



(33)

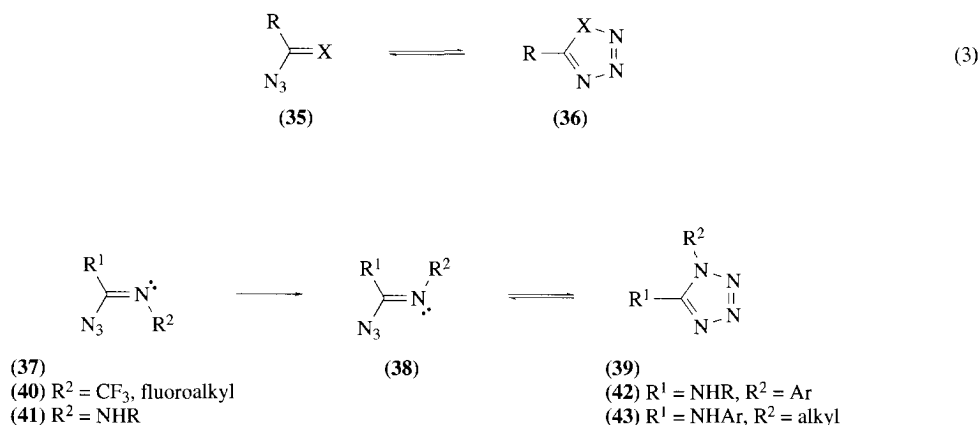


(34)

<84CHEC-I(5)791>. Amino groups at C-5 exist predominantly in the amino form unless the imino form is stabilized by a special intramolecular hydrogen-bonding interaction with the N-4 proton. For example *N*-substituted 5-nitro-aminotetrazoles exist even in aqueous solution in the nitrimino form <84KGS1569>. Carbon-13 NMR spectra of substituted 1-phenyl-5-aminotetrazoles and 1-substituted-5-phenylaminotetrazoles show tetrazole C-5 and phenyl C-1' shifts for the amino form only and these compounds exist exclusively in the 5-amino form in CDCl₃ <83M65>. It has been claimed that 5-aminotetrazole exists in the imino form in DMF and that separate NMR signals for both forms were seen in toluene and CCl₄ <92ZOR1767>. It has already been well established that 5-aminotetrazoles and 5-alkylaminotetrazoles exist exclusively in the amino form in DMSO and alcoholic solvents <77AHC(21)323>, this claim is surprising.

4.17.4.3 Ring-chain isomerism

The tetrazole ring (36; X = NR) may exist in equilibrium with an acyclic imidoazide form (35; X = NR). This is also the case for systems with X = O and S and the behavior of these provides a guide to some of the factors influencing the tetrazole case. When X is an oxygen atom the azido form (35) dominates and in general with strong electron-withdrawing groups on the imidoazide system cyclization to tetrazole is not observed <84CHEC-I(5)791>. A wide series of fluoroalkyl substituted imidoazides (40) which do not cyclize to tetrazoles has been reported <85IZV691, 85IZV700>. When X in (35) is a sulfur atom the system exists in the cyclic form (36) (Equation (3)) and with electron-donating substituents around the imidoazide structure (37) rapid ring closure to tetrazoles usually occurs in one of the main synthetic routes to tetrazoles (Section 4.17.9). A key stereoelectronic constraint on the cyclization is the required *cis* orientation of the imino lone pair and the azido group <80JCS(P2)535, 84CC913>. Thus a large range of imidoazides containing electron-rich substituents, for example hydrazonoyl azides (41) <92SL858>, do not cyclize easily to tetrazoles because they are in the wrong configuration (37) and are not easily isomerised to (38) (Scheme 5). Azides with substituents which lower the barrier to isomerization may give tetrazoles on heating if the azide has not decomposed or undergone other reactions <84BCJ539>. Higher temperatures favor the azido form (38) in the equilibrium with (39) and this ring opening is responsible for the Dimroth rearrangement of substituted 5-aminotetrazoles <82JHC943, 84JHC627> where 5-alkylamino-1-aryltetrazoles (42) rearrange into 5-arylamino-1-alkyltetrazoles (43) on heating at 180–200°C and both forms are present in the melt. The azido intermediate cyclizes onto the imino nitrogen with the strongest electron-donating substituent <54JA88>. For example nitroguanyl azide, N₃C(=NH)—NHNO₂, cyclizes away from the NO₂ group to give 5-nitroamino tetrazole in organic solvents <87KGS945>. The synthesis and cyclization of imidoazides is discussed in Section 4.17.9.



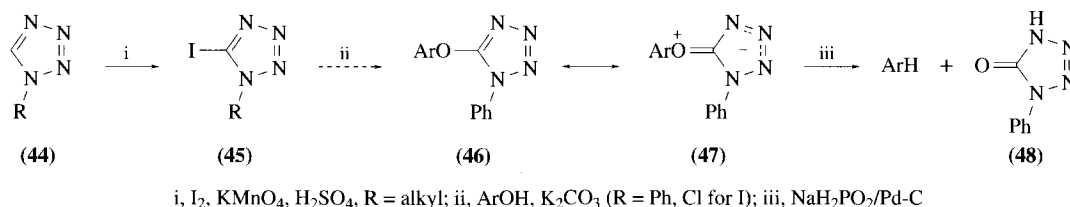
Scheme 5

4.17.5 REACTIVITY OF FULLY CONJUGATED RINGS

4.17.5.1 General Survey of Reactivity

4.17.5.1.1 Neutral tetrazoles

The neutral tetrazole molecule may undergo substitution at the N-H or 5-CH sites. Most studies on tetrazole systems involve compounds where one of these sites is already occupied by a substituent arising from the synthesis of the substrate. Despite the high nitrogen content and the presence of three deactivating pyridine-type nitrogens, the ring displays chemical aromaticity with Robinson retention of type in most of its normal substitution reactions. Significant thermal degradation reactions are, of course, to be expected for a ring with such high nitrogen content. Some main features of the general behavior of tetrazoles are illustrated in Scheme 6. Direct electrophilic substitution at C-5, for example iodination to give (45) <88KGS1699>, readily occurs but under acidic conditions where the reactive species is the 5-C-deprotonated ylide arising from initial N-4 protonation. Halides and particularly chlorides at C-5 are readily substituted by nucleophiles giving for example 5-aryloxytetrazoles (46) <84CHEC-I(5)791>. In these the vinyl resonance lies strongly into the tetrazole ring so that the difficult aryl-oxygen cleavage of aromatic carbon chemistry becomes easy with the oxygen being retained by the tetrazole <87JCS(P1)1069, 91CC1041>. Hence the reductive cleavage from (46) to (48) has become a standard method of removing OH groups from phenols. Main reactivity features such as electrophilic substitution at nitrogen atoms and thermal ring degradations are illustrated by Scheme 7. Thus treatment of a range of 5-substituted tetrazoles (49) with halides (50) in the presence of triethyl amine results in electrophilic substitution giving mixtures of the N-1 and N-2-substituted products (51) and (52) which are stable for R = Aryl, X = NAr <87BSB675, 88JCS(P1)1587>. Separate heating of compounds (51; X = NAr) gives ring opening to the azides (53) which lose HN₃ to give the triazoles (55). The compounds (51), depending on the substituents, may also lose N₂ giving an imido-yl nitrene which converts to a substituted 5-amino-1,2,4-triazole (55; R = NHR) <87BSB675>. Heating of the 2-hydrazono-yl-tetrazoles (52; X = NAr) results in N₂ loss giving the nitrilimines (54) which undergo Huisgen 1,5-electrocyclization <80AG(E)947> to the 4-amino-1,2,4-triazoles (56) <88JCS(P1)1587>. This reaction can be diverted to give 1,2,4,5-tetrazines (nucleophilic NH ring closure) by the presence of H⁺ or by acidic solvents <91JCR(S)272>.



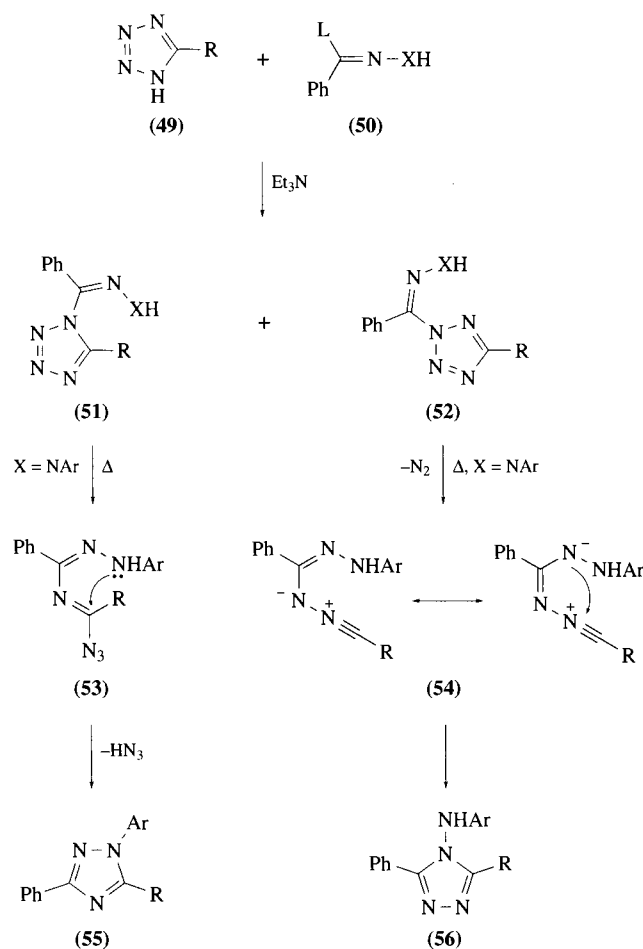
Scheme 6

4.17.5.1.2 Tetrazolate anions

The tetrazolic acids, R-CN₄H, are unique among the azoles since they are the full nitrogen analogs of the carboxylic acids. 5-Aryltetrazoles correspond to the series of benzoic acids and they display somewhat higher K_a values ascribed to higher resonance stabilization and better solvation of the tetrazolate anion <79JCS(P2)1670>. Hence tetrazolate anions are easily generated and are stable in hot alcoholic and aqueous solutions. They are more reactive than neutral tetrazoles towards electrophiles and alkylating agents and are often used in synthetic processes which are overall electrophilic substitutions on tetrazoles. This acidic property of 5-substituted tetrazoles has resulted in the use of —CN₄H as a replacement for —CO₂H in a wide range of biologically active molecules (Section 4.17.12).

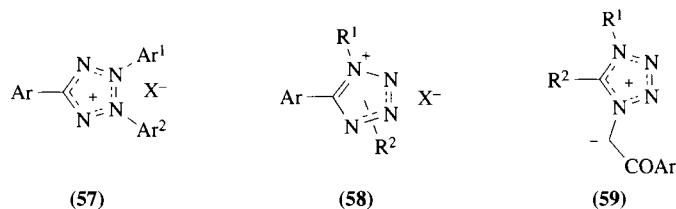
4.17.5.1.3 Tetrazolium cations

2,3,5-Trisubstituted tetrazolium salts (57) are the oxidation products of formazans. They have been used to produce tetrazolynyl radicals by controlled reduction <73AG(E)455>. N-Alkyltetrazolium



Scheme 7

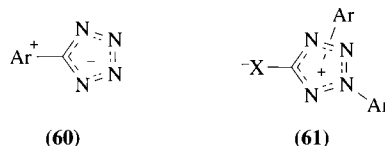
salts may have any of the structures represented in (58). Relatively little has been reported about their chemical behavior. If the substituent R² contains an active CH as in CH₂COAr, bases such as NH₃ may abstract a proton to give tetrazolium methanides such as (59) <86JCS(P1)1157, 93CB129>. The ammonia may also condense with the carbonyl group and give an imine which cyclizes at the tetrazolium C-5 to give new fused imidazo[1,2-*d*]tetrazoles. Nucleophilic attack by EtO⁻ on the tetrazolium salts (18) leads to the total destruction of the tetrazole system and the products are biphenyls <94JCR(S)216>.



4.17.5.1.4 Tetrazole ylide and tautomeric structures

Ylide compounds which incorporate the tetrazole ring may exhibit the anionic form as in structure (60) <82JCR(S)122, 87JOC5009> or the ring may exist in a tetrazolium form as in structures (61) and (59) <84JCS(P1)2545, 88TL491>. Structures of type (61) may undergo electrophilic attack on the exocyclic X⁻ site particularly when this is S⁻ or they may undergo dipolar cycloadditions <71CC490, 74CC639>.

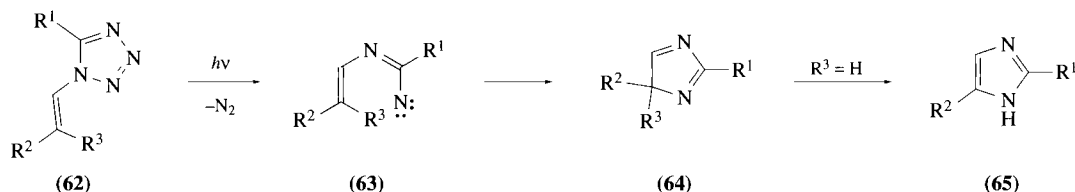
In the new structures of type (59) the reactive centre is the methanide site which behaves as a nucleophile. <86JCS(P1)1157, 92JCS(P1)1483> (Section 4.17.8). Tautomeric tetrazole–tetrazoline structures of general type (4; R = H) may show ambident reactivity with reactions occurring on the ring or the exocyclic X atom (Sections 4.17.6 and 4.17.7).



4.17.5.2 Thermal and Photochemical Reactions Involving No Other Species

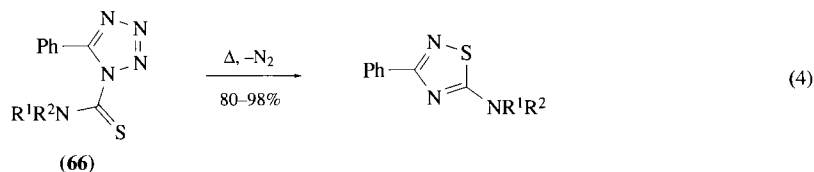
4.17.5.2.1 *N*-Unsubstituted and 1,5-disubstituted tetrazoles: fragmentations to nitrenes and carbenes

A new widely applicable route into substituted imidazoles has been developed from photochemical degradation of 1-alkenyltetrazoles (62) (Scheme 8) <82CC714, 83CC1082>. Evolution of N₂ gives *N*-vinylimidoyl nitrenes (63) which cyclize to the 4*H*-imidazoles (64) in good to moderate yields <87JCS(P1)1389, 91JCS(P1)335>. When R³ = H, a 1,5-shift in (64) results in aromatic imidazoles (65) <84JCS(P1)1933, 85JCS(P1)741>. The reaction has been developed to give a wide range of new imidazole derivatives including spiro-structures at C-4 in (64). When the vinyl double bond in (62) is part of a benzene ring the products are benzimidazoles and carbodiimides <84CHEC-I(5)791, 85JCS(P1)1471>.



Scheme 8

Pyrolysis of 1-(2-pyridyl)-5-aryltetrazoles in tetralin provides a nitrogen analog of the reactions in Scheme 8 and gives *s*-triazolo[1,5-*a*]pyridines <83IJC(B)117>. As shown in Scheme 7, 1-hydrazonoyltetrazoles (51) undergo thermal loss of HN₃ giving 60–90% yields of the 1,2,4-triazoles (55) <88JCS(P1)1587>. The corresponding oxygen analog, 1-oximinoyltetrazoles (51; X = O) display similar thermal behavior losing HN₃ on being heated under reflux in *p*-xylene and giving quantitative yields of 3,5-disubstituted-1,2,4-oxadiazoles <81BSB193>. Thermolysis of these 1-heteroacyl-type tetrazoles such as (51) <87BSB675> and the thiocarbamoyl derivatives (66) <92JPR283> may also result in N₂ eliminations and cyclization of the nitrene fragment (Equation (4)). Heating of the compounds (66) in chlorobenzene provides a new route to the 1,2,4-thiadiazole ring <92JPR283>. The thermolysis and photolysis of 5-aryl-1-(2'-aroylvinyl)tetrazoles gives a complicated mixture of products including imidazoles, pyrazoles, and products derived from solvent involvement <85CJC2601>.

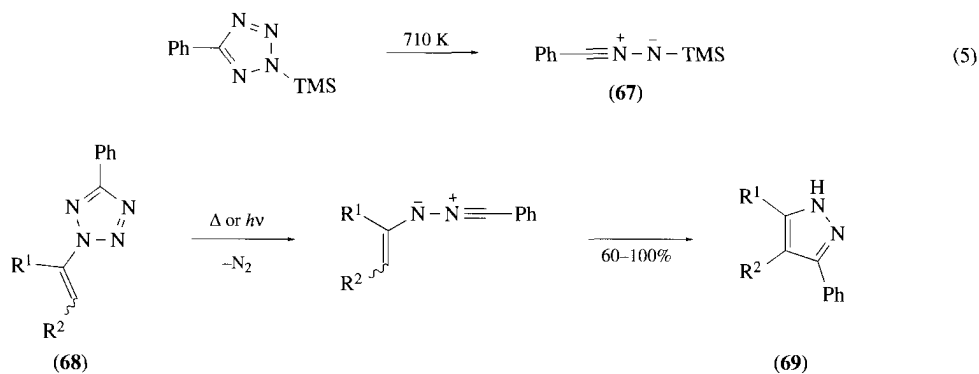


Flash pyrolysis of 1,4-bis(tetrazol-5-yl)benzene at 600°C has been explored as a possible route to the dicarbene, :CH–C₆H₄–CH:. The product was phenylethyne which carried a ¹³C label from the tetrazole C-5, confirming that a C₈H₆ species had been generated <87JA2534>. Thermal degradation of ¹³C-labelled 5-diazotetrazole has provided a source of atomic carbon for carbene reactions

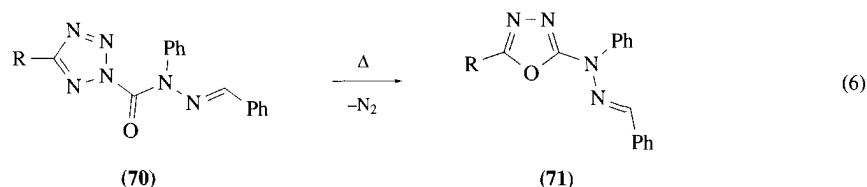
<79JA1303>. Flash vacuum pyrolysis of tetrazole and 5-substituted tetrazoles generates cyanamides (RNHCN), diazomethanes (RCHN₂) and carbodiimides (RN=C=NH) <85AG(E)56, 87TL617, 89CPH157>.

4.17.5.2.2 2,5-Disubstituted tetrazoles: fragmentation to nitrilimines

One of the best known reactions of tetrazoles is the thermolysis or photolysis of 2,5-disubstituted tetrazoles to give nitrilimines by loss of N₂, an example of which is shown in Scheme 7. The reaction is used not only for its synthetic potential but also as a source of nitrilimines for direct observation and exploration of their behavior. The first direct detection of a thermally generated nitrilimine was the species (67) produced by flash vacuum pyrolysis of 5-phenyl-2-trimethylsilyltetrazole (Equation (5)) <85AG(E)56>. Parent nitrilimine, HCNNH, has been generated by photolysis of tetrazole <96LA1041>. Bisnitrilimines have been observed from photolysis of bis(2-phenyl-5-substituted tetrazoles) in ethanol-ether glasses at 95 K <88JPR879, 88JPR887, 88ZC252>. The products from the photolysis of 2-phenyltetrazole in benzene under N₂ were phenylcyanamide (27%) and *C*-cyano-*C*-(*o*-anilino)-*N*-phenylhydrazone (53%) testifying to the complicated behavior of *C*-unsubstituted-*N*-phenyl nitrilimine at ambient temperatures in benzene <83CC610>. Photolysis of 2,5-diaryltetrazoles continues to be used as a source of nitrilimines for both synthetic and mechanistic studies of their cycloadditions with 2 π -dipolarophiles <88JPR406, 89JPR789>. Interesting new synthetic applications are those involving electrocyclizations and intramolecular cycloadditions. Examples are the synthesis of substituted pyrazoles (69) from 5-substituted-2-vinyltetrazoles (68) <91JCS(P1)329> and the formations of bicyclopiazolines when the alkenyl group is separated from the tetrazole by (CH₂)₃ <82JOC4256>. The earliest versions of the reaction involved unstable 2-acyltetrazoles generated *in situ* <60CB2106, 61JOC2372, 61CB1555, 65CB2966>. The 2-hydrazidotetrazoles (70) have been isolated and transformed to the oxadiazoles (71) (Equation (6)) <87JHC1233>. There is extensive literature on the elimination of N₂ from 2,5-disubstituted tetrazoles and the following reviews are recommended for access to the work of 1970s and earlier decades <77AHC(21)323, 80AG(E)947, 84CHEC-I(5)791, B-84MI 417-01>.



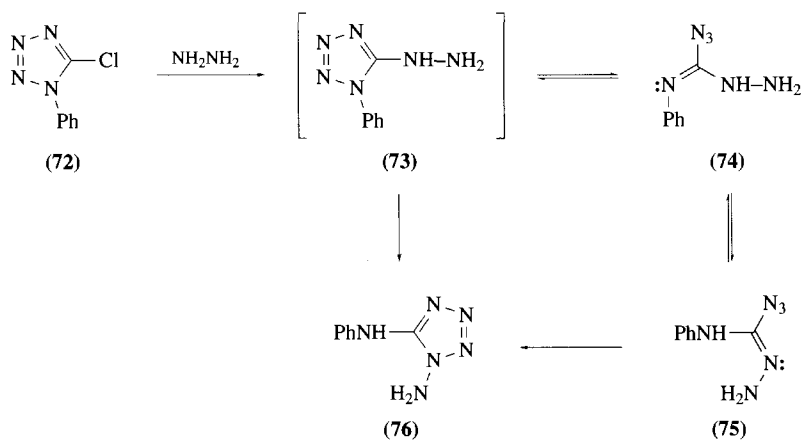
Scheme 9



4.17.5.2.3 Rearrangements

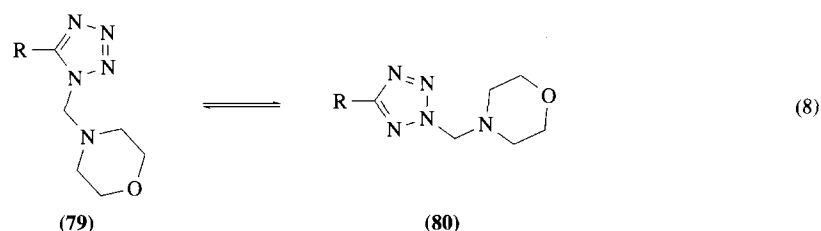
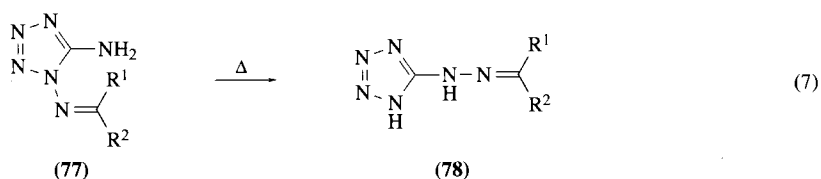
The imidoyl azide-tetrazole ring-chain isomerism of tetrazoles develops into a wide-ranging example of the Dimroth rearrangement in the thermal behavior of substituted 5-aminotetrazoles <84JHC627>. An example with 5-hydrazinotetrazoles is shown in Scheme 10 <88BSB543>. The reaction

involves ring opening to an azide, for example (74), which invariably cyclizes to the imino nitrogen carrying the most electron-donating substituent.



Scheme 10

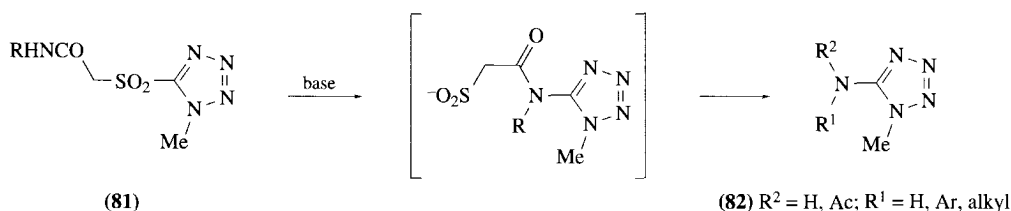
It has been observed with imines of 1,5-diaminotetrazoles (77) which rearrange thermally to the tetrazol-5-ylhydrazones (78) in a reaction which is strongly facilitated by electron-withdrawing R^1 and R^2 substituents (Equation (7)) <90CB1575>. The 1*N*-(α -alkylamino) tetrazoles (79) rearranged into an equilibrium mixture in which the 2*N*-isomers (80) (Equation (8)) were the main components in the solvents CDBr_3 , and toluene- d_8 <90T633>. Similar rearrangements were observed with substituted triazole systems. The rearrangement is an intermolecular process involving the stable tetrazolate anion and the iminium cation, $\text{CH}_2=\text{N}^+\text{R}_2$. Gas-phase thermal isomerisations of 1-methyl- to 2-methyltetrazoles have been reported <90MI 417-04>. The 1-substituted tetrazole ring is sufficiently electron deficient to undergo the Smiles rearrangement which in this case is an intramolecular nucleophilic displacement of a leaving group at the tetrazole C-5, for instance compounds (81) rearranged to the 5-substituted aminotetrazoles (82) on treatment with base (Scheme 11) <91CPB3331>. Examples of fragmentative rearrangements involving ring opening and loss of N_2 or HN_3 which convert the tetrazole to other azole rings are shown in Scheme 7. An extensive review of such reactions for azoles in general, including some examples with tetrazoles, has been published <93AHC(56)49>.



4.17.5.3 Electrophilic Attack at Nitrogen

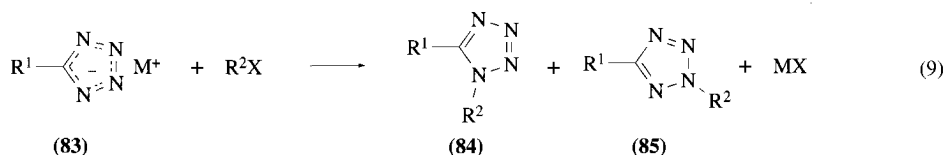
4.17.5.3.1 Alkylation of tetrazolate anion salts

Metal salts of 5-substituted tetrazoles (83) undergo ready alkylation on heating with alkyl halides in a wide range of solvents (Equation (9)). The products are mixtures of 5-substituted-1*N*- and 2*N*-



Scheme 11

alkyl tetrazoles (84) and (85). The relative proportion of the isomers depends on many factors including (i) the electronic and steric nature of the 5C-substituent, (ii) the alkylating agent, (iii) the medium, (iv) the cation and (v) the temperature. A methodology has been suggested for alkylation of azoles in which better control is expected if the deprotonation and nucleophilic displacement steps are separated and careful attention is paid to the individual reaction capabilities of the alkylating agent and the solvent chosen (90ACS1050). The results of extensive earlier studies of the alkylation of tetrazole anions have been summarized and tabulated (77AHC(21)323, 84CHEC-I(5)791). In general, electron-donating substituents at C-5 favor alkylation at N-1 while electron-withdrawing groups favor attack at N-2 and there are linear relationships of isomer distribution with Hammett σ -values for *para*-substituents on 5-phenyl rings (81JCR(S)174, 82ZOR1981). The reaction was insensitive to electronic effects of substituents on *para*-substituted benzyl halide alkylating agents but large steric effects on alkylating agents tend to favor N-2 alkylation (80JA2968). Two *ortho*-substituents in the phenyl ring of 5-phenyltetrazole oriented the reaction towards N-1 in contradiction to the expected steric blocking of the N-1 site. This has been explained by complete twisting of the rings which results in a facilitation of electrophilic attack at N-1 by complexation of the electrophile with the aryl π -system (81JCR(S)174, 81JCS(P1)390). Organic media generally favor N-2 alkylation while polar solvents favor attack at N-1. In general attack at N-2 which produces the less polar 2,5-disubstituted structure with low dipole moment, seems to be a softer orbital-controlled reaction relative to a harder charge-controlled reaction at N-1 which produces the 1,5-disubstituted tetrazole structure with high dipole moment. However, because of the wide variety of substrates, alkylating agents, and conditions used in these reactions, broad generalizations need to be tempered by the necessity to consider each alkylation in its own right (82ZOR1043, 92ZOR2349). Alkylations of tetrazolate anions and neutral tetrazoles are listed in Table 7.



4.17.5.3.2 Acylation and alkylation of neutral tetrazoles

(i) Basic conditions

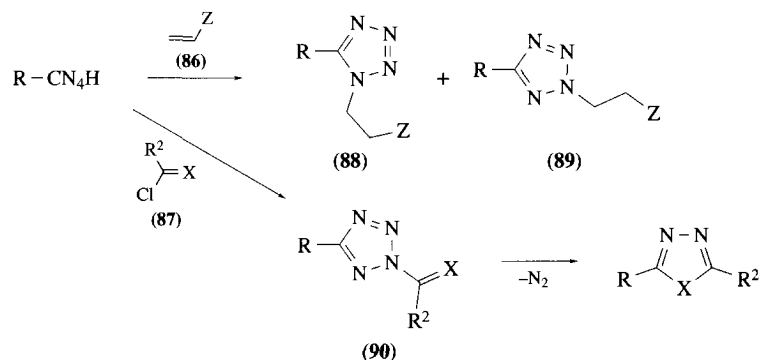
There is a wide range of electrophilic substitutions carried out on 5-substituted NH tetrazoles with reagents such as hydrazonoyl halides and oximinoyl halides (50) (Scheme 7) electron-deficient vinyl systems (86) and acyl halides (87) (Scheme 12) (Table 7). Invariably these reactions are carried out in the presence of excess Et₃N used to promote loss of halide or hydrogen halide (generating nitrilimines or nitrile oxides) and it is likely that these reactions involve the tetrazolate anion as the reactive tetrazole species. It has been established that triethyl ammonium tetrazolate salts are involved in reactions with benzonitrile oxide in CHCl₃ and a mechanism involving a concerted attack of tetrazolate anion on the carbon and the ammonium cation on the oxygen of the nitrile oxide has been proposed (85JCS(P2)403). From known steric effects for nucleophilic addition to nitrilium systems (79JA1988, 86JCS(P2)537) the imine lone pair should be *trans* to the incoming nucleophile and the products (51) and (52) should have the (*Z*)-structures shown (Scheme 7). The product isomer distributions are sensitive to both the substituents at the tetrazole C-5 and the

Table 7 Alkylations and electrophilic substitutions of 5-substituted tetrazoles.

Tetrazole type or 5-substituent	Electrophile	Main site (if any)	Ref.
HCN ₄ ⁻	Ar ₂ CHCl	N-1	90JMC416
ArNH-N=N-CN ₄ ⁻	MeI; aq. EtOH	N-1	84JCS(P1)1589
R—, Ar-CN ₄ ⁻	ClCH ₂ CN; dioxane		89ZOR1524
ArCN ₄ ⁻	BrCH ₂ CO ₂ Et; MeCN	^a	82ZOR1981
PhCN ₄ ⁻	CH ₂ =CH-COMe; MeCN, DMF	^a	87ZOR1082
ArCN ₄ ⁻	Me ₂ SO ₄ ; MeCN-H ₂ O	^a	82ZOR1043
RfCN ₄ ⁻	NOCl or ClCN; THF		89IC4629
ArCN ₄ ⁻	CH ₂ =CH-OAc	N-2	91JCS(P1)329
5-Me, 1-OH	CH ₂ =CHCOMe; MeCN	N-4	89IZV1619
ArCN ₄ H	CH ₂ =CH-Z; Pr ⁺ OH	N-2	89BSB277
Ar—, R-CN ₄ H	Ar-C≡N ⁺ -O ⁻ ; Et ₃ N, dioxane		81BSB193, 87BSB675
Ar-CN ₄ H	Ar-C≡N ⁺ -N ⁻ -Ar; Et ₃ N, EtOH		88JCS(P1)1587
Ar-CN ₄ H	Ar-C≡N ⁺ -O ⁻	^a	85JCS(P2)403
RO-CN ₄ H	ClSO ₂ Me or ClCN; THF	N-1	80JHC187
R—, Ar-CN ₄ H	R ₂ N ⁺ CH ₂ Ar		84KGS851
R—, ArCN ₄ H	MeN(NO ₂)CH ₂ Cl; THF/H ⁺		88ZOR2221
R, NHR, Rf, Ar	R'-OH; H ₂ SO ₄	N-2	90KGS1643
R, Ar	Me ₃ COH	N-2	90KGS1574
H, Ph	(Bu ⁿ Sn) ₂ O; EtOH	N-2	84JCS(P1)1933
Pyrid-3-yl	MeI, EtOH	N-2	82JCR(S)122
Ar-CN ₄ H	Ar'-C(Cl)=NAr ²	N-2 ^b	92ZOB194

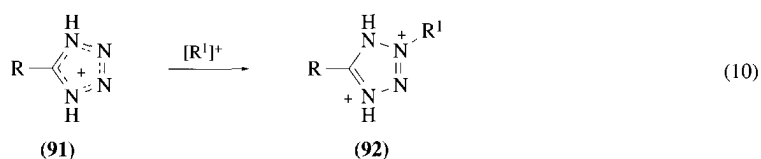
^aKinetics and mechanism. ^bProduct, 1,3,4-benzotriazepines.

acylating agent <81BSB193>. The Michael reactions of 5-substituted tetrazoles with electron-deficient vinyl systems (**86**) give the 2-alkylated products (**89**) in yields of about 50–80% <89BSB277, 91JCS(P1)329>. In a few cases low yields of the 1-alkyl derivatives (**88**) have also been reported <89BSB277>. Acylation of 5-substituted tetrazoles with acyl halides or acid anhydrides occurs at N-2 giving unstable products of type (**90**) (X = O) which may lose N₂ *in situ* and transform into oxadiazoles via nitrilimines and a Huisgen 1,5-electrocyclization <60CB2106, 61JOC2372, 67JOC3687>. *Ab initio* calculations on this type of transformation have been described <94JST(309)241>. Substitution at N-2 also occurs with isocyanates, isothiocyanates, thioacyl chlorides <61CB1555, 66ACS2795> and imidoyl chlorides <60CB2885>. The reaction of 5-aryltetrazoles with N,C-diarylimidoyl chlorides under phase-transfer catalysis has been developed as a route to 1,3,4-benzotriazepines. The imidoyl nitrilimine, formed by initial N-2 attack followed by N₂ elimination, underwent cyclization onto the *ortho*-position of the imidoyl *N*-phenyl ring rather than electrocyclization to the imidoyl nitrogen atoms which would have given a 1,2,4-triazole <92ZOB194, 93KGS907, 94ACS596>. Strong electron-donating substituents at C-5 may orient the acylation reaction towards N-1 and 5-alkoxytetrazoles were substituted at N-1 by BrCN and MeSO₂Cl to give derivatives which opened *in situ* to imidoyl azides, for example RO-C(N₃)=N-SO₂Me since the tetrazole form was destabilized by the strong electron-withdrawing group at N-1 <80JHC187>.

**Scheme 12**

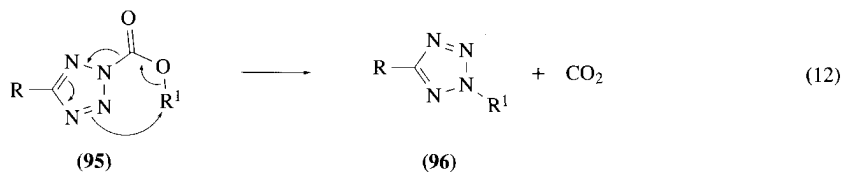
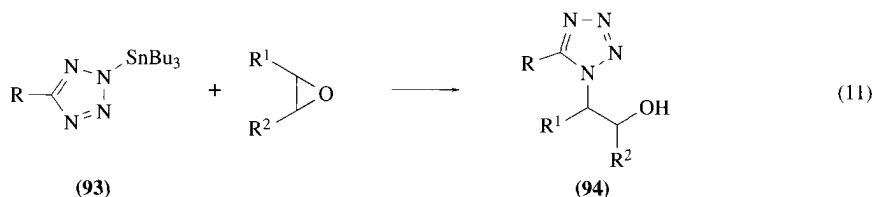
(ii) Acidic conditions

Direct alkylation of 5-substituted tetrazoles, RCN_4H , $\text{R} = \text{Ph, Me, CF}_3$, with *t*-butyl alcohol gave high yields of 2*N*-*t*-butyltetrazoles with a small amount of 1-*N*-*t*-butylation in the case of 5-methyltetrazoles <90KGS1574>. In concentrated H_2SO_4 5-substituted tetrazoles are protonated at N-4 (**91**) (Equation (10)) but they still react with cations at the N-2 lone pair giving a species represented as (**92**) which leads to high yields of 2,5-disubstituted products irrespective of the nature of the tetrazole 5-substituent. This approach has been used to alkylate a wide range of 5-substituted tetrazoles (**91**), $\text{R} = \text{alkyl, aryl, amino, trifluoroalkyl, vinyl}$, with substituted alcohols as sources of the cations R^1+ <88ZOR2221, 90KGS1643>. Electrophilic alkylation of 5-aryltetrazoles with Mannich reagents gave mixtures of 1*N*- and 2*N*-aminoalkylated products depending on the nature of the 5-substituent <84KGS851>.



(iii) Regiocontrol

Controlled substitution at N-1 has been achieved by blocking the N-2 position with a SnBu_3 group which is cleaved by HCl after the N-1 attack <84JCS(P1)1933, 85JCS(P1)741>. Thus high yields of the 1,5-disubstituted tetrazoles (**94**) were obtained from the substrates (**93**) (Equation (11)). A Michael reaction with propiolate esters gave mixtures of (*E*)- and (*Z*)-1-alkenyltetrazoles as the main products along with lesser quantities of the 2-alkenylisomers <85JCS(P1)741>. A limited preferential 2*N*-substitution has been achieved via the species (**95**) by treating cyano- or chloroalkylformates, $\text{X-CO}_2\text{R}^1$, with 1,5- or 2,5-disubstituted tetrazoles where the nitrogen substituent is TMS or SnBu_3 . Depending on the 5-substituent R group these may decompose by transferring R^1 onto the tetrazole N-2 with loss of CO_2 giving ratios of N-2 products to N-1 as high as 38:1 <90TL1925, 87MI 417-02>. However, the N-2:N-1 ratio was more normally in the range 2–5 and the alternative reaction of N_2 loss and Huisgen 1,5-electrocyclization to 2-alkoxyoxadiazoles became the main path with 5-aryl- and 5-alkoxyalkyltetrazoles <90TL1925>.



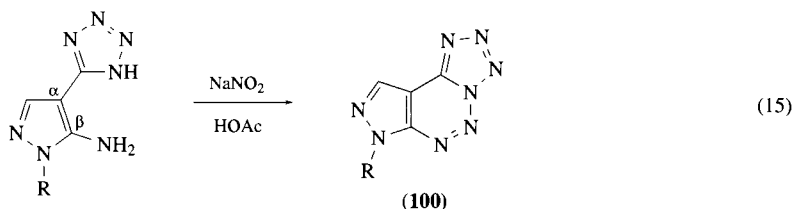
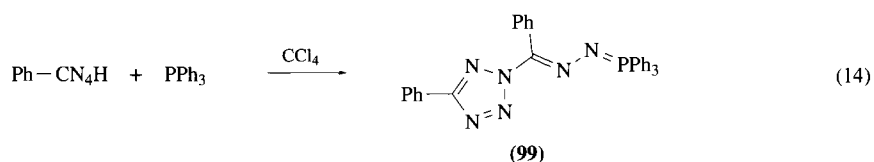
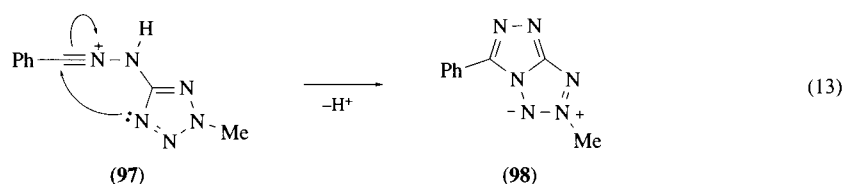
4.17.5.3.3 Protonation and quaternization

Theoretical and spectroscopic studies of the protonation of tetrazoles have been discussed in Sections 4.17.2.2 and 4.17.3. Protonation of 5-substituted tetrazoles, 1,5-disubstituted tetrazoles and 2,5-disubstituted tetrazoles in aqueous H_2SO_4 at H_2SO_4 concentrations up to 96% occurs at N-4 <82KGS1421>. The tetrazoles are weak bases with basic $\text{p}K_a$ values of about -3 to -4 <87AHC(41)187>. A basic $\text{p}K_a$ value of -3.0 has been measured for tetrazole in aqueous H_2SO_4 . Hammett relationships have been reported for the basic $\text{p}K_a$ values of 5-substituted tetrazoles

containing the acetic acid group $-\text{CH}_2\text{CO}_2\text{H}$ at N-1 and N-2, $\text{p}K_{\text{BH}}^+ = -1.53 \sigma - 3.26$, and $\text{p}K_{\text{BH}}^+ = -1.50 \sigma - 4.16$, respectively $\langle 82\text{KGS}1421 \rangle$. Basic $\text{p}K_{\text{a}}$ values of -3.25 for 2-methyl and -3.0 for 1-methyltetrazoles have also been reported $\langle 88\text{KGS}579 \rangle$. *N*-Methylquaternization of 2,5-diaryltetrazoles with dimethyl sulfate at 80°C occurred at N-4 giving high yields of the products **(18)** $\langle 94\text{JCR}(\text{S})216 \rangle$. *N*-Alkyl quaternization of 1-aryl-5-(2'-dimethylaminovinyl)-1*H*-tetrazoles with dialkyl sulfates and alkyl iodides also occurred at N-4 $\langle 89\text{JPR}885 \rangle$ but 1-methyl-5-vinyltetrazole was quaternized by dimethylsulphate at N-4 (60%) and N-3 (40%) $\langle 93\text{SA}(\text{A})135 \rangle$. Some 5-substituted-1-vinyltetrazoles also gave mixtures of *N*-methyl quaternization at N-4 (78–84%) and lesser quantities at N-3 $\langle 93\text{SA}(\text{A})135 \rangle$. *N*-Methyl quaternization of 1,5-dialkyltetrazoles with reagents such as $(\text{MeO})_2\text{SO}_2$, $\text{MeO} \cdot \text{SO}_2\text{F}$ and $\text{Me}_3\text{O}^+\text{BF}_4^-$ gave mixtures of quaternization at N-3 and N-4 the ratio of which depended on the tetrazole substituents and varied little with the alkylating agent. Quaternization of 1-methyl-5-alkyltetrazoles with Bu^iOH and HBF_4 gave *t*-butylation exclusively at N-3, away from the other substituents $\langle 87\text{LA}469 \rangle$.

4.17.5.3.4 Other electrophiles

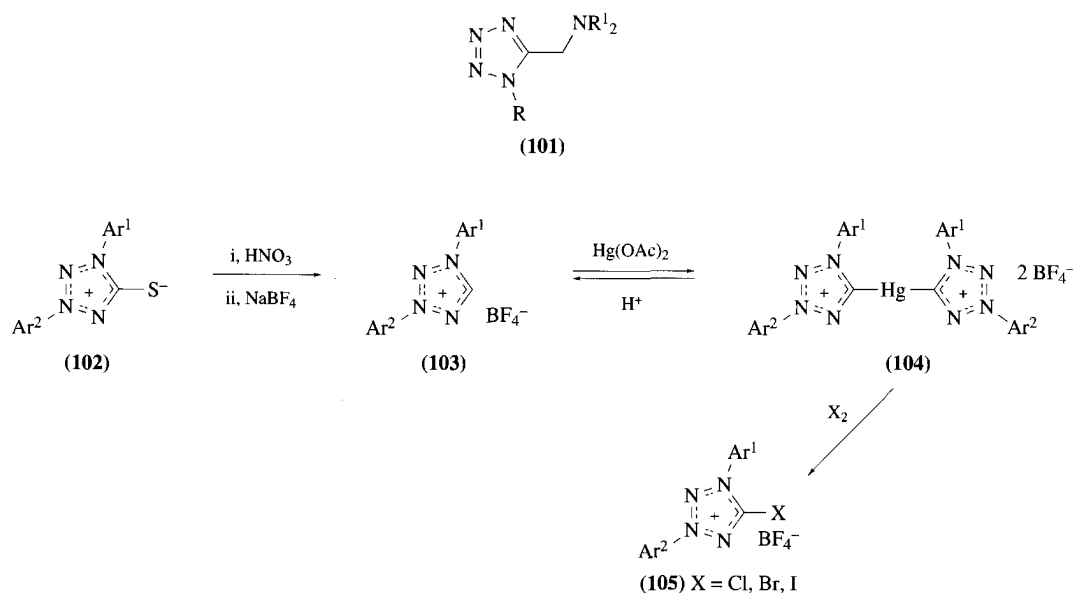
Intramolecular electrophilic attack, as in the species **(97)**, follows the intermolecular pattern and occurs at N-4 irrespective of whether the *N*-methyl group is at N-1 or N-2 (Equation (13)). The products from the species **(97)** are the meso-ionic fused triazolotetrazoles **(98)** $\langle 83\text{JHC}1629, 86\text{JCR}(\text{S})38 \rangle$. Treatment of 5-phenyltetrazole with triphenylphosphine and CCl_4 gave the species **(99)** along with HCl and some other phosphonium salts (Equation (14)) $\langle 81\text{ZOB}2462 \rangle$. A well-known oxidation of 5-substituted aminotetrazoles, RNHCN_4H , which gives isocyanides, $\text{R}-\text{NC}$, $\langle 84\text{CHEC-I}(5)791 \rangle$ when applied to 5-triazenyl tetrazoles did not give diazoisocyanides but rather diazocyanides $\langle 86\text{JCS}(\text{P}1)1101 \rangle$ (see Section 4.17.7.3.2). Active diazonium ions located at a β -position to a nitrogen unsubstituted tetrazole cyclize onto the N-1 position giving fused tetrazolotriazines **(100)** (Equation (15)) $\langle 89\text{LA}83 \rangle$.



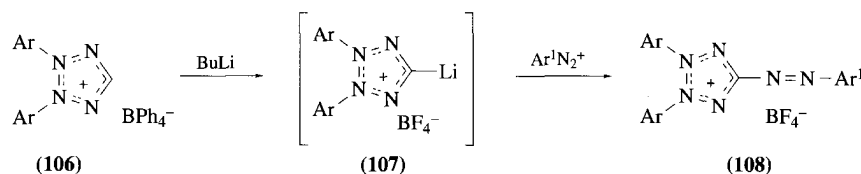
4.17.5.4 Electrophilic Attack at Carbon

1*N*-Substituted tetrazoles (**44**; R = alkyl, vinyl, aryl) undergo electrophilic iodination at C-5 to give the 5-iodo-derivatives **(45)** in yields of 55–75% on treatment with I_2 in acidic permanganate solution $\langle 88\text{KGS}1699, 92\text{MI} 417-04 \rangle$. Aminomethylation at C-5 giving the products **(101)** also occurs on treatment of the tetrazoles **(44)** with HCHO , HNR'_2 and acids such as HCl or $\text{CF}_3\text{CO}_2\text{H}$. This reaction did not occur readily with 2-substituted tetrazoles $\langle 85\text{KGS}564, 91\text{KGS}66 \rangle$. These reactions are considered to involve protonation at N-4 followed by deprotonation at C-5 giving a reactive

ylide which undergoes the electrophilic attack and as such they are not normal electrophilic aromatic substitutions. Treatment of compounds (**45**) with HgBr_2 and KOH in alcohol gave the bistetrazol-5-yl mercury derivatives in 40–85% yields (92MI 417-04). Oxidation of the mesoionic tetrazolium thiolates (**102**) (90JA333), and also the corresponding selenolates (78IZV1401), with concentrated nitric acid gives the 5-unsubstituted tetrazolium salts (**103**) (93CB1149) (Scheme 13). Treatment of these with mercuric acetate gives the bistetrazolium mercury salts (**104**) which represent essentially a metal-carbene trapping of the tetrazolium ylide species. Replacement of the mercury atom of (**104**) is readily achieved with halogens to give the 5-halotetrazolium compounds (**105**) (93CB1149) (Scheme 13). These new electrophilic reactions at the tetrazole C-5 arise from the lability of the 5-CH proton and they show the necessity of generating carbanionic character at C-5 before electrophilic attack can occur on this strongly π -deficient azole. Lithiation of neutral 1*N* alkyl substituted tetrazoles gave mainly C-5-lithiation with small amounts of lithiation at the 1*N* alkyl groups. Quenching with TMS-Cl allowed for silylation at C-5 (91JCS(P1)323). The 5-lithiotetrazolium salts (**107**) which are generated from the tetrazolium tetraphenylborides (**106**) also allow for ready addition of electrophiles such as D^+ , tosyl azide and aryl diazonium ions, the latter giving the products (**108**) (Scheme 14) (91AGE(E)1162). Proton removal from the tetrazole C-5 is discussed in Section 4.17.5.5.2.



Scheme 13



Scheme 14

4.17.5.5 Nucleophilic Attack on Tetrazoles

4.17.5.5.1 Attack at NH: acidity

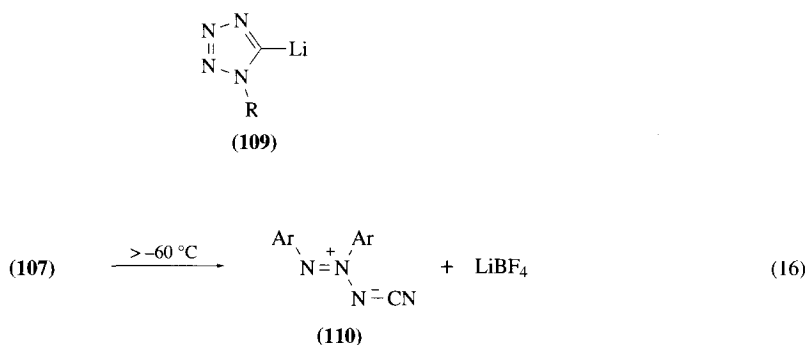
5-Substituted tetrazoles, RCN_4H , are the tetrazolic acids, the formal nitrogen analogs of the carboxylic acids, RCO_2H . The tetrazoles have acidic $\text{p}K_a$ values and steric characteristics similar to the carboxylic acid analogs (84CHEC-I(5)791). Hence there is a major applied interest in replacing $-\text{CO}_2\text{H}$ groups of biologically active molecules with $-\text{CN}_4\text{H}$ groups (Section 4.17.12). One differ-

ence between the $\text{—CN}_4\text{H}$ and $\text{—CO}_2\text{H}$ acid groups is the annular tautomerism of tetrazoles which is rarely studied for biologically active tetrazoles. For the tetrazole analog of nicotinic acid, 5-(pyrid-3'-yl)tetrazole, the main tautomer in aqueous DMSO is the 1NH form $\langle 82\text{JCR(S)122} \rangle$. The acidic $\text{p}K_{\text{a}}$ value of tetrazole in water is 4.89. Substituents at C-5 have effects generally similar to those for carboxylic acids. For example 5-methyltetrazole has $\text{p}K_{\text{a}}$ 5.56, $\text{CH}(\text{NO}_2)_2\text{CN}_4\text{H}$ has $\text{p}K_{\text{a}}$ 3.68 $\langle 87\text{ZOR254} \rangle$ and $\text{CF}_3\text{CN}_4\text{H}$ has $\text{p}K_{\text{a}}$ 1.14. Extensive tables of K_{a} values for 5-substituted tetrazoles are available $\langle 77\text{AHC(21)323, 79JCS(P2)1670, 84CHEC-I(5)791, 87AHC(41)187} \rangle$. In general, 5-aryltetrazoles are stronger acids than benzoic acids, for instance the K_{a} for PhCN_4H in 50% $\text{EtOH—H}_2\text{O}$ is 1.05×10^{-5} while that for benzoic acid is 0.17×10^{-5} . The increased acidity is ascribed to enhanced resonance stabilization in the 5-phenyltetrazolate anion relative to benzoate and to differing solvation of the ions $\langle 79\text{JCS(P2)1670} \rangle$. A review of the acidity of tetrazoles has been published $\langle 80\text{KGS867} \rangle$. Neutralization of tetrazolic acids with metal hydroxides gives stable metal tetrazolate salts.

The reaction of tetrazole with KBH_4 gave the first tetrazolylborate salt, potassium bishydridobis(tetrazol-1-yl)borate, $\text{K}^+ \cdot \text{H}_2\text{B}(\text{HCN}_4)_2^-$ $\langle 93\text{ZN(B)394} \rangle$.

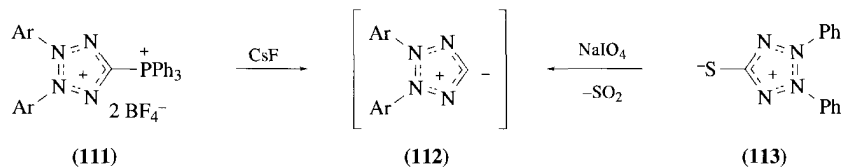
4.17.5.5.2 Attack at 5-CH: tetrazole carbanions and tetrazolium ylides

Base-induced D/H exchange readily occurs at the C-5 atom of nitrogen substituted tetrazoles via the carbanion. The rate of exchange was 10^5 times faster for 1-methyltetrazole than for the 2-methyl isomer in agreement with the general trend that ring protons α to singly bound nitrogens exchange much more rapidly than those β to such nitrogen atoms $\langle 72\text{JA5759} \rangle$. Treatment of 1-substituted tetrazoles with BuLi in THF at below -60°C gave stable compounds (**109**) which decomposed to lithium cyanamides and N_2 on warming $\langle 71\text{CJC2139} \rangle$. Tetrazolium salts with a 5-CH moiety such as (**103**) and (**106**) can readily lose the proton to give a tetrazolium ylide/carbene species (**112**) (which is involved in the D/H exchange at C-5 for nitrogen substituted tetrazoles under acidic conditions). Examples of these ylides have been trapped as lithium complexes (**107**) which were stable at -100°C allowing ^{13}C NMR spectra to be recorded. At -100°C in tetrahydrofuran the C-5 signal of (**107**; $\text{Ar} = p\text{-anisyl}$) appeared at 202.4 ppm showing a deshielding of 48 ppm relative to the corresponding salt (**106**). This deshielding is attributed to the weakening of the N—C σ -bonds and decreased π -electron density at the tetrazolium C-5 in the carbenoid species (**107**). Above -60°C the lithiotetrazolium salts (**107**) opened to the triazen-2-ium-1-ide species (**110**) (Equation (16)) $\langle 91\text{AG(E)1162} \rangle$. When the salts (**103**; $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$) were treated with base proton removal gave a tetrazolium ylide which opened to 1,3-diphenyl-3-cyanotriazene but which could also be trapped by coupling with p -(dimethylamino)benzenediazonium tetrafluoroborate $\langle 93\text{CB1149, 90JA333} \rangle$. Two further routes to the tetrazolium ylide (**112**) involve dephosphonation of the dicationic phosphonium-tetrazolium salts (**111**) and oxidative desulphurization of the tetrazolium-5-thiolates (**113**) (Scheme 15) $\langle 90\text{JA333} \rangle$. The species (**112**) generated by these methods also opened to the products (**110**) (Equation (16)). Theoretical calculations on the uncharged carbene (**114**) in comparison with other azole carbenes have led to the conclusion that it should not undergo spontaneous ring opening $\langle 85\text{JA4090} \rangle$.

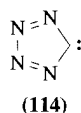


4.17.5.5.3 Nucleophilic addition and substitution at C-5

Chlorine and bromine atoms at C-5 in the 1,3-diaryltetrazolium salts (**105**) were readily replaced by nucleophiles such as OH^- , SH^- , SeH^- , $\text{NH}_2\text{Ph}/\text{NaHCO}_3$ and $\text{HC}(\text{CN})_2^-$ to give the corresponding



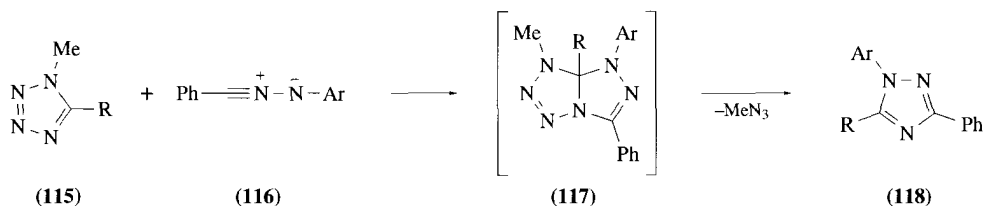
Scheme 15



mesoionic tetrazolium compounds in yields of 85–95% (93CB1149). Attack by the malononitrile anion on the tetrazolium salts (103) containing hydrogen at C-5 occurred at N-2 and resulted in fragmentation of the ring to the phenylhydrazone, $(\text{CN})_2\text{C}=\text{N}-\text{NHAr}^2$ and the cyanamide, Ar^1NHCN . This also occurred with an iodine atom at C-5 and in general substituents of low electronegativity directed the $\text{CH}(\text{CN})_2$ nucleophile to N-2 while substituents of high electronegativity, such as OR, at C-5 were replaced by the incoming nucleophile (93CB1149). The electron-deficient nature of the tetrazole ring facilitates the nucleophilic displacement of leaving groups at C-5 in normal nitrogen substituted tetrazoles. The reaction has been widely used in synthesis particularly with chlorine or bromine as leaving group and nucleophiles such as amines, hydrazines, alkoxides and phenoxides (77AHC(21)323, 84CHEC-I(5)791). There are few reports of the reactions of fully substituted tetrazolium salts with bases. Treatment of the trisubstituted tetrazolium salts (18) with alkoxide resulted in total ring degradation giving biaryls (94JCR(S)216). Tetrazolium salts may also be used as oxidizing agents and 2,3,5-triphenyltetrazolium chloride proved the most convenient oxidant for the conversion of α -ketol and enone derivatives of cyclohexanone into the corresponding diones (87TL4323). The reaction of 1,4,5-trisubstituted tetrazolium iodides with NaBH_4 gave Δ^2 -tetrazolines while 1,3,5-trisubstituted tetrazolium salts did not react with NaBH_4 (73BCJ1250).

4.17.5.6 Short-lived Reactive Species

There are few reports of the reactions of aromatic tetrazoles with short-lived reactive species. 1,5-Disubstituted tetrazoles (115) react with the nitrilimine 1,3-dipole (116) in benzene to give the 1,2,4-triazoles (118) in 60–70% yields (Scheme 16) (94JCR(S)196). The reaction involves a cycloaddition to give the species (117) which aromatizes by loss of MeN_3 . It is enhanced by electron-donating groups in the aryl substituent at the tetrazole C-5 and it is completely inhibited by the presence of two *ortho*-substituents in this 5-aryl group (89MI 417-02). 2-Methyl-5-substituted tetrazoles showed no reaction with the nitrilimine.



R = aryl, alkyl; Ar = *p*-NO₂C₆H₄

Scheme 16

4.17.6 REACTIVITY OF NONCONJUGATED RINGS

The main types of nonconjugated tetrazoline compounds are the 1,5- and 1,4-dihydroderivatives with the general structures (3) and (4). The structure (4) also includes systems which are tautomeric with the conjugated aromatic tetrazole ring. The only known tetrahydro-tetrazolines are the compounds (5) (Section 4.17.1.1).

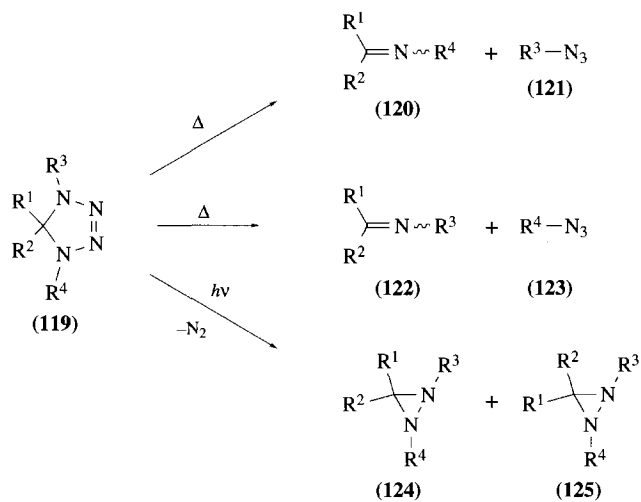
4.17.6.1 Substituted Nontautomeric 1,4-dihydrotetrazolines

4.17.6.1.1 Thermal and photochemical reactions involving no other species

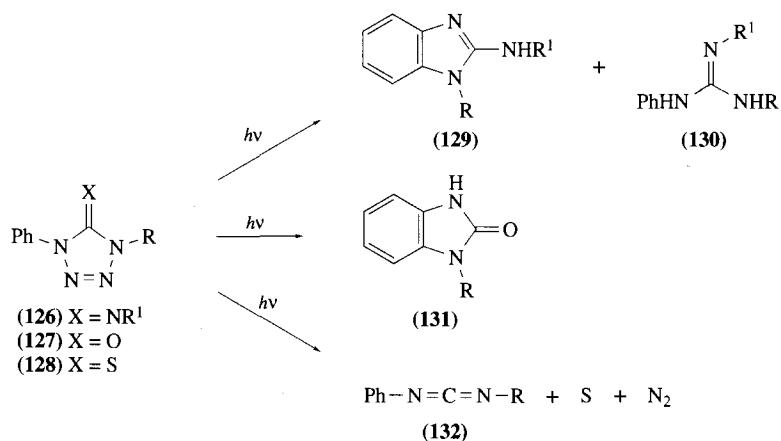
Thermolysis of substituted 1,5-dihydrotetrazolines (119) may result in N₂ loss or a cycloreversion to imines and azides (Scheme 17). The reaction pathway is controlled by the substituents at C-5. If one of the substituents at C-5 is aromatic cycloreversion to the imines and azides (120)–(123) predominates <87BSF525>. Photolysis at low temperatures leads to diaziridines (124) and (125) and if the C-5 bears two hydrogen atoms or one hydrogen atom and an alkyl group, thermolysis also leads to the diaziridines <87BSF525>. Irradiation of 5-iminotetrazolines (126) results in N₂ loss giving the benzimidazoles (129) as main products along with lesser quantities of guanidines (130). Deuterium atoms located on the 5-imino substituent (R¹) (Scheme 18) were completely scrambled over the possible positions in the products indicating equivalence of the N-1, N-4, and exocyclic nitrogen atoms during the reaction. The diradical species (133) has been postulated as the key intermediate <85CB2164>. Such a species has been directly detected from the photolysis of 1,4-dimethyl-5-methyliminotetrazoline in a butyronitrile matrix at –195°C <78JA1306>. Photolysis of the tetrazolinones (127) similarly gave the benzimidazolones (131) while photolysis of the tetrazolin-5-thiones (128) gave the carbodiimides (132) by extrusion of both N₂ and sulfur <85CB526>. With saturated substituents at the N-1 and N-4 positions of tetrazolin-5-one photolytic nitrogen evolution results in the formation of diaziridinones. <83CB3427, 84CHEC-I(5)791>. The photolytic method is superior to thermolysis for the synthesis of such hetero analogs of methylene cyclopropanes since the tetrazoline derivatives tend to be more thermally stable than the products. The use of these reactions for the synthesis of hetero cyclopropanes has been reviewed <80AG(E)276>. Ultraviolet irradiation of 1,4-disubstituted-5-alkylidene-1,4-dihydrotetrazoles (135) (obtained by deprotonation of the salts (134) with NaH) in deuterated hydrocarbon solvents at –60°C to 20°C gave the aziridine-2-imines (136) with the (*E*)-isomer predominating (Scheme 19). With different substituents at N-1 and N-4 in (135), equal amounts of both possible aziridines were obtained via a singlet diradical <88CB2117, 92CB2095>. The aziridinimines were photostable but at shorter wavelength they reverted to imines, R¹R²C=N-R⁴, and isocyanides, R³NC. Thermolysis of compounds (135) at 100°C in benzene also gave aziridinimines (80%) but these were thermally unstable at this temperature and cleaved *in situ* to imines and isocyanides <90CB1739>. Lower yields (ca. 18%) of spirotetrahydro-pyrimidino-tetrazolines, for example (137), were also obtained from secondary cycloadditions of the parent tetrazoline (135) to 1,3-diazabutadienes, derived from the biradical intermediates formed in the initial cleavage <90CB1739, 92LA581>.

4.17.6.1.2 Cycloaddition reactions

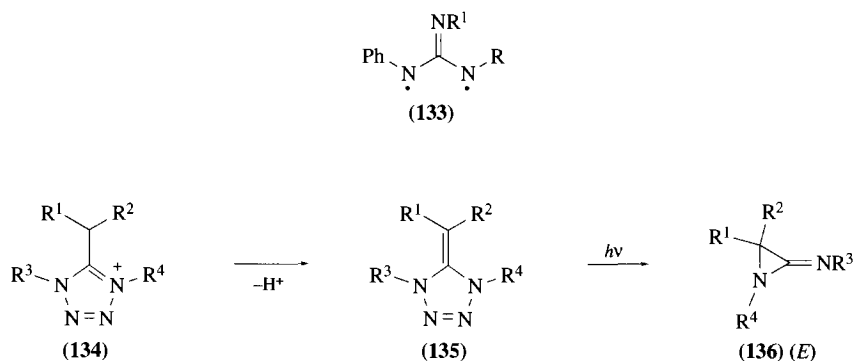
5-Alkylidene-1,4-dimethyltetrazolines (138) behave as electron-rich enamines for inverse-electron demand cycloadditions with electrophilic 4π-systems such as covalent azides (139). Cycloaddition reactions with alkyl and aryl azides at 0–20°C gave high yields of the spirotriazolines (141) <88CB1285>. These are formed from a nonconcerted two-step cycloaddition which is at the extreme of the 1,3-dipolar cycloaddition mechanistic range (Scheme 20). Remarkably, when R³ was strongly electron-withdrawing, some of the zwitterionic intermediates (140) were sufficiently stable for isolation in yields of 40–90%. An x-ray crystal structure was obtained for compound (140; R¹ = H, R² = Bu^t, R³ = MeSO₂) which was isolated in 52% yield and has m.p. 111–112°C <90AG(E)695>. There was a short distance, 258.5 pm, between the centres of negative and positive charge and the Bu^t group was oriented orthogonally to the plane of the tetrazoline ring causing steric inhibition of ring closure. Heating of the intermediates (140) in CDCl₃ gave the 1,2,3,4-tetrazine system (142) along with lesser yields of the tetrazolines (143) in a reaction which passed through the spirotetra-



Scheme 17

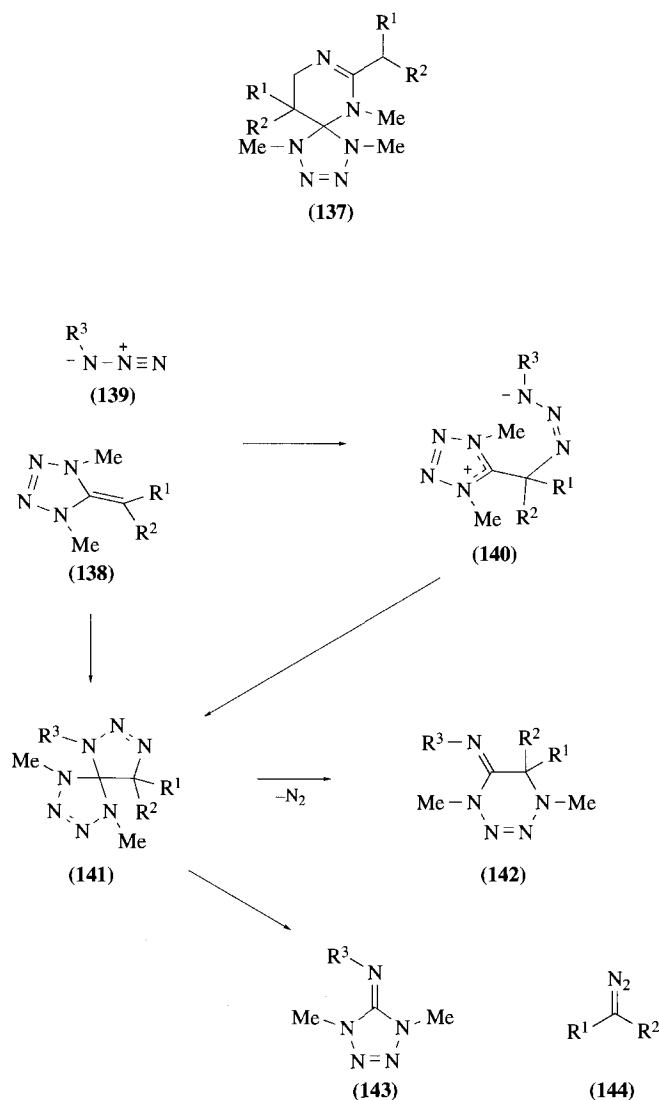


Scheme 18



Scheme 19

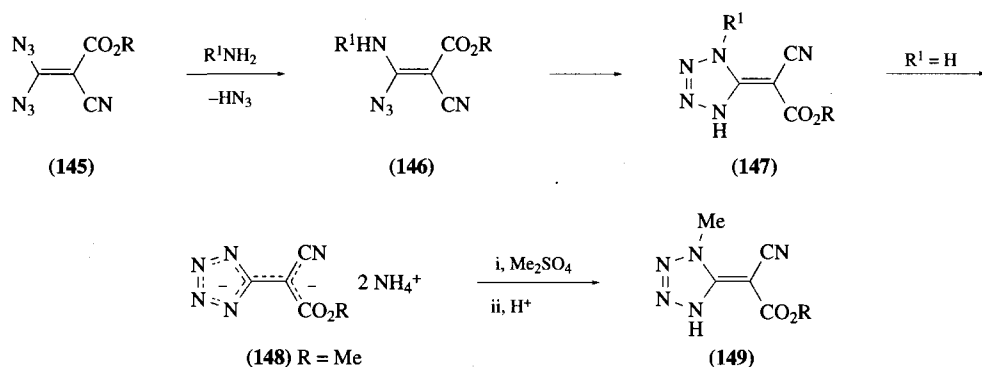
zoline compounds (141) <90AG(E)695>. In separate heating of stable spiro-tetrazoline derivatives (141), three modes of ring cleavage were observed. Two of these were cycloreversions to the iminotetrazolines (143) and the alternative corresponding iminotriazolines. The third mode was N₂ extrusion with a rare 1,2-N shift giving the 5-iminotetrahydro-1,2,3,4-tetrazines (142) <92CB2749>.



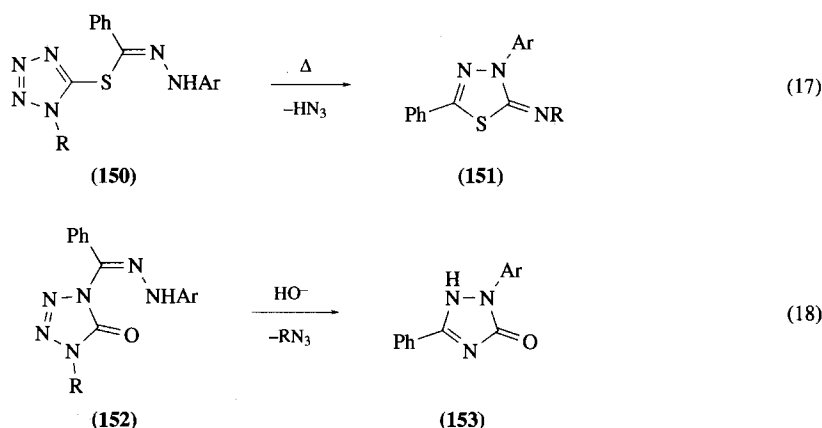
Scheme 20

4.17.6.2 Substituted Tautomeric 1,4-Dihydrotetrazolines

A range of potentially tautomeric tetrazolines (**147**) has been prepared from 3,3-diazo-2-cyanoacrylates (**145**) by treatment with substituted amines, hydrazines and hydrazides in CH_2Cl_2 at -25°C [87AG(E)1160]. In a number of cases the intermediate azides (**146**; $\text{R}^1 = \text{PhNH}$ and PhCONH) were stable [89CB519, 89CB969]. On heating in the presence of arylamines these undergo a base-catalysed rearrangement to the tautomeric tetrazolines (**147**) which exist in the 1,4-dihydrotetrazoline form and readily form stable salts (Scheme 21) [87AG(E)1160]. The parent molecule (**147**; $\text{R}^1 = \text{H}$) has also been prepared using ammonia and it readily gave a bis-ammonium salt (**148**) which was methylated at N-1 by dimethyl sulfate giving (**149**) [91JHC1863]. Among the more traditional tautomeric tetrazolines are those tetrazoles containing OH and SH groups at C-5. These exist predominantly in the tetrazolinone form. The oxygen compounds react almost exclusively on the N-4 nitrogen with electrophilic reagents such as electrophilic vinyl compounds [89BSB277]. Hydrazonoyl halides with Et_3N also react at N-4 giving the hydrazonoyltetrazolines (**152**) [93JCR(S)306]. In contrast, alkyl halides react almost exclusively on the exocyclic sulfur of tetrazolin-5-thiones [74JOC3770] as do hydrazonoyl halides which give (**150**) (Equation (17)). Heating of the hydrazonoyl derivatives (**150**) and (**152**) results in tetrazole fragmentation to the 1,2,4-triazoles (**153**) and the 1,3,4-thiadiazoles (**151**) (Equations (17) and (18)) [93JCR(S)306].



Scheme 21



Organotin halides also react with tetrazolin-5-thione anions at the sulfur atom giving 1-substituted 5-organotinthiotetrazoles <92JOM(430)25>. However, some electrophilic reagents may react with 1-substituted tetrazolin-5-thiones preferentially at the ring nitrogen. Thus phenylacetyl chloride gave acetylation at N-4 <74JOC3770> and hydroxymethylation also occurred at N-4 <64ZOB2517>. Acetylation of 1-alkyl tetrazolin-5-thiones with acetyl chloride has been reported to produce low yields of rare 1,2-dihydro-tetrazoline derivatives, 1-alkyl-2-acetyl-1*H*,2*H*-dihydrotetrazolin-5-thiones <74ZC16>. Acylation of the sodium salt of 1-phenyltetrazolin-5-thione with alkyl acid chlorides in benzene occurred on both the nitrogen and sulfur atoms giving mixtures of the products in yields which were dependent on the R group of the acid chloride <73ZC134>. Alkylation of an acidic solution of 1-methyltetrazolin-5-thione with excess ethereal diazomethane resulted in methylation at both sulfur and N-4 in the ratio 3:1 <85JOC2794>.

Ring-substituted 5-aminotetrazoles exist predominantly in the amino form. Reactions with electrophiles, however, may occur on either the exocyclic nitrogen or the ring nitrogen <84CHEC-I(5)791>. 1-Substituted 5-aminotetrazoles reacted with hydrazonoyl halides and Et₃N on the exocyclic amino nitrogen giving unstable products which rearranged *in situ* into 1,2,4-triazoles with loss of HN₃ <93JCR(S)306>. Alkylations of 1- and 2-alkyl-5-aminotetrazoles which give, respectively, 1,4-disubstituted-5-iminotetrazolines and meso-ionic 1,3-disubstituted 5-iminotetrazoline derivatives are well documented from the work of the 1950s <77AHC(21)323, 84CHEC-I(5)791>. Further reactions of amino groups and sulfur atoms at tetrazole C-5 are discussed in Section 4.17.7.

4.17.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO THE RING CARBON

4.17.7.1 General Survey

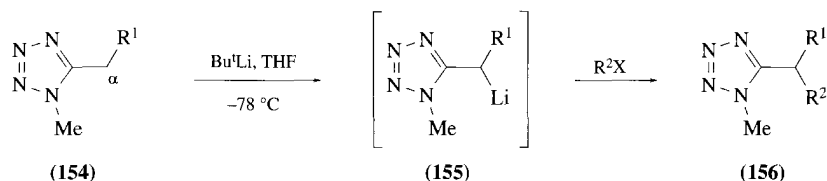
Substituents bonded to the tetrazole C-5 are situated at an amidine site in a strongly electron-deficient ring. The major influence of the ring is one of electron withdrawal with the three pyridine-type nitrogens overcoming the influence of the single pyrrole-type nitrogen. This electron-withdrawing effect is stronger for 1*N*-substituted tetrazoles (high dipole moment) than for 2*N*-substituted

derivatives (low dipole moment) in which there is a weak resonance electron-donating effect towards C-5. Substituents at C-5 behave normally. Nucleophilic displacement of leaving groups is facilitated by the electron-withdrawing ring and α -CH bonds show the expected acidity. Substituents with lone pairs are bonded strongly to C-5 because the heterovinyl resonance is enhanced by the nitrogen atoms of the ring (e.g., structure (47) (Section 4.17.5.1). The electron-withdrawing effect of the tetrazole ring on external substituents is, as expected, greater in tetrazolium salts.

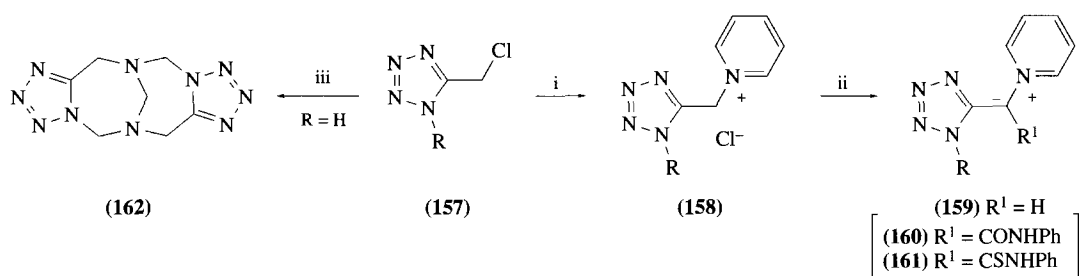
4.17.7.2 Substituents with Carbon Bonded to C-5

4.17.7.2.1 5-Alkyl, haloalkyl, carbonyl, and cyano groups

The α -CH site in 1-substituted-5-alkyltetrazoles (**154**) is not as reactive as might be expected for a location adjacent to such a high-nitrogen ring (Scheme 22). It undergoes metallation with *t*-butyllithium at -78° in THF and the intermediate is readily alkylated with electrophiles such as methyl iodide, cyclohexanone and aromatic and aliphatic aldehydes giving the products (**156**) in yields ranging from 16–90% (91JCS(P1)323, 93JOC1623, 96TL3655). In one case only, with benzaldehyde as electrophile and Et₂O as solvent, did the alkylation occur on the *N*-methyl group. However, with 2-methyl-5-alkyltetrazoles (**154**; Me at N-2) the comparable alkylation occurred on the 2*N*-alkyl group (93JOC1623, 94JOC773). The methylene group of 1-substituted-5-cyanomethyltetrazoles, (**154**; R¹ = CN), gave ready condensations with benzaldehyde, to give the C(CN)=CHPh substituent at C-5, and also coupling with PhN₂⁺·BF₄[−] to give a *C*-cyano-*C*-tetrazol-5-yl-*N*-phenylhydrazone (92ZOR1921). Displacement of chloride from 1-substituted-5-chloromethyltetrazoles with pyridine gives the pyridinium salts (**158**). These can be readily deprotonated to the ylides (**159**) which react with alkyl halides at the ylide carbon (Scheme 23) (76JCS(P1)909). On treatment with electrophiles such as phenyl isocyanate and phenyl isothiocyanate the ylides (**159**) gave the carbamoylated ylides (**160**) and (**161**), respectively (76JCS(P1)909). The compounds (**158**) were also used for the first synthesis of 1-substituted tetrazole-5-carbaldehydes (72LA(758)29) and their 2*N* substituted isomers were used as precursors for 2*N* substituted tetrazol-5-yl carbaldehydes (72LA(758)29, 75CB887, 81ZN(B)656). The parent unsubstituted tetrazole-5-carbaldehyde has been obtained from cyclo-additions of HN₃ with (EtO)₂CH·CN in pyridine followed by hydrolysis to the aldehyde which exists in a dimeric structure in the solid state (77CZ403). Treatment of the nitrogen unsubstituted 5-chloromethyltetrazole (**157**; R = H) with hexamethylene-tetramine also gave a novel dimeric tetrazole structure, the 1,3,6,8-tetrazecine system (**162**) (Scheme 23). This was also obtained from the reaction of 5-amino-methyltetrazole with formaldehyde (89LA689). An interesting reaction between the bis(tetrazol-5-yl)dichloromethanes (**163**) and trialkylphosphites in anhydrous benzene has been reported to give the products (**164**) (Equation (19)). Compound (**164**; R = Me₂CH) was formed in 82% yield and an x-ray crystal structure was obtained (91ZOR1790). A nitrile substituent at the tetrazole C-5 behaves normally and is readily hydrolyzed to amido and carboxylic acid groups (84CHEC-I(5)791). Addition of hydroxylamine to the nitrile at tetrazole C-5 gives an amidoxime substituent, —C(NH₂)=N-OH (76ZC90). 5-Cyanotetrazole, available in high yield (84CZ188), has been converted to 5-acetyltetrazole by Grignard addition and hydrolysis (92ZN(B)1803). A Grignard reaction of MeMgI with 2-phenyl-5-cyanotetrazole also led to the 2-phenyl-5-acetyltetrazole but ring degradation to AcN(Ph)CN occurred in the comparable reaction with 1-phenyl-5-cyanotetrazole (81CZ194). Carbonyl and particularly aroyl substituents at tetrazole C-5, introduced by oxidation of secondary alcoholic or methylene groups, behave normally. Only the acetyl group displays some unexpected behavior. The acetyl group of 1-phenyl-5-acetyltetrazole was displaced with NaOI to give 5-iodo-1-phenyltetrazole and on treatment with KCN or amines replacement by hydrogen occurred giving 1-phenyltetrazole (84CHEC-I(5)791). 1,4-Disubstituted tetrazolium salts with an active α -CH site at the ring C-5 are readily deprotonated to give ylide or ylidene structures which undergo normal addition and substitution reactions with electrophiles (Scheme 24) (91CZ331).

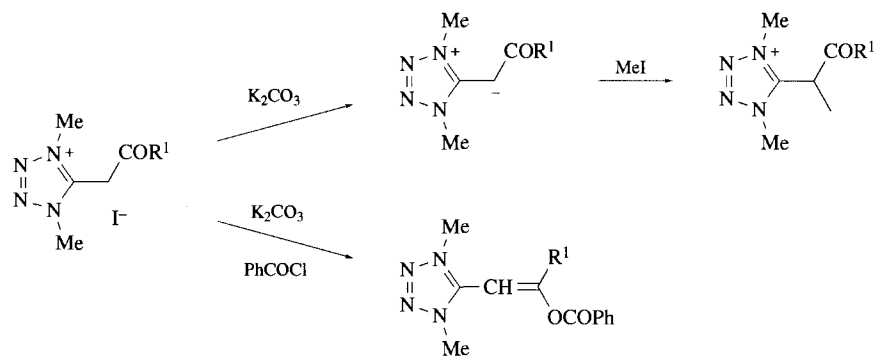
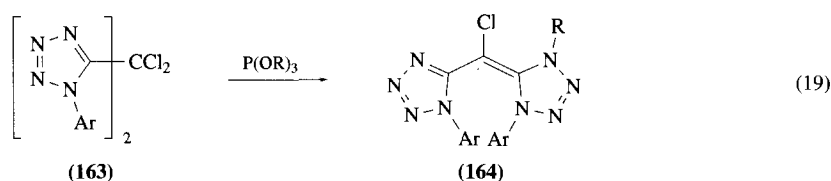


Scheme 22



Reagents: i, pyridine; ii, K₂CO₃·H₂O; iii, hexamethylenetetramine

Scheme 23

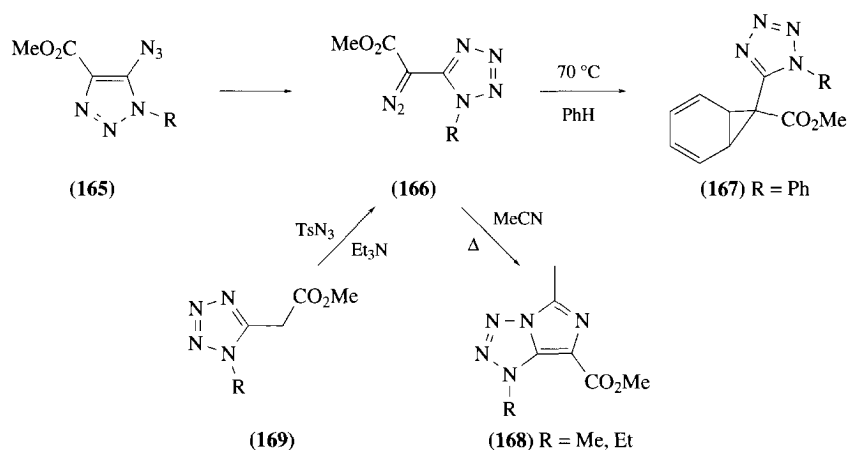


Scheme 24

4.17.7.2.2 5-Diazomethyl and vinyl groups

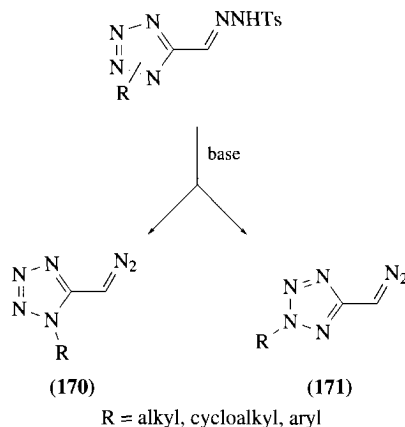
1-Substituted-5-(methoxycarbonyldiazomethyl)-tetrazoles (**166**) have been obtained by Dimroth rearrangement of the azidotriazoles (**165**) <83BSB913> and by diazo-transfer to the active methylene group in compounds (**169**) (Scheme 25) <88JHC1741>. On being heated in benzene and acetonitrile solvents, the diazo compounds (**166**) gave the new norcaradiene (**167**) <83BSB915> and the imidazotetrazoles (**168**) respectively, both from carbene attack on the solvent (Scheme 25) <88JHC1741>. The influence of the tetrazole substitution pattern on the behavior of the carbene intermediate derived from the tetrazole-5-diazomethyl systems was evident when the 2-*N*-R substituted isomers of (**167**) were in equilibrium with the ring-expanded cycloheptatriene form and the products (**168**) were replaced by 4-(2'-*N*-substituted tetrazol-5'-yl) oxazoles from cyclization of the acetonitrile carbon to the methoxycarbonyl oxygen rather than the tetrazole N-4 <88JHC1741, 89JHC729>.

In a comprehensive study of the comparative behavior of the 1*N*- and 2*N*-substituted 5-diazomethyl tetrazole systems (**170**) and (**171**), prepared via the Bamford-Stevens reaction (Scheme 26), Moderhack and Goos examined their reactions with (a) electrophiles and acids, (b) 2*π*-cycloaddition partners including benzyne, (c) nucleophiles, and (d) heat <87CB921>. Because of the stronger electron-withdrawing power of the 1,5-disubstituted tetrazole ring the series (**170**) were less reactive than (**171**) in cases (a) and (b) by factors in the range 10 to about 150. The order was reversed for cases (c) and (d) and the isomers (**170**) thermolysed about twice as rapidly as (**171**) at 70°C in benzene <88JHC1741, 87CB921>. In reactions with CN⁻ followed by H₃O⁺ the diazo group



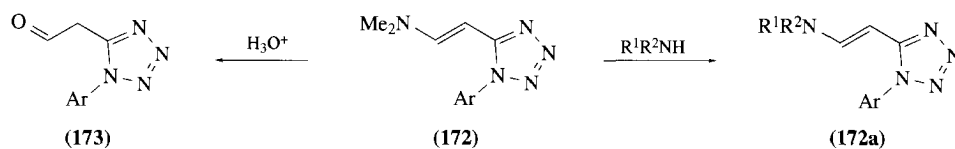
Scheme 25

was changed to $\text{CH}=\text{N}-\text{NHCN}$ and with OH^- the CHN_2 group was lost giving the 5-CH tetrazole <87CB921>.



Scheme 26

Among the 5-vinyltetrazole series the 1-aryl-5-(2-dimethylaminovinyl)-1H-tetrazoles (**172**) <88JPR963> represent stable derivatives of the unknown tetrazole-5-acetaldehydes (**173**) (Scheme 27). These aldehydes can be generated *in situ* from (**172**) and trapped as hydrazones or by condensations with diamines giving cyclic aminals <88JPR974>. Acid-catalyzed *trans*-aminations have also been carried out on the series (**172**) using a wide range of secondary amines, including 1,2-diamines which give bis-tetrazole products (e.g., (**172a**; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CH}_2\text{CH}_2\text{N}(\text{Me})\text{CN}_4-1-\text{Ar}$)) <88JPR981, 90JPR977, 94JPR79>. Polymerization of 5-vinyltetrazoles is commented on in Section 4.17.12.

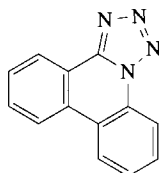


Scheme 27

4.17.7.2.3 5-Aryl substituents

In 1-aryl-5-(2'-halogenophenyl)tetrazoles the *ortho*-positions of both aryl rings are sufficiently close for photochemical or electrochemical bond formation to give phenanthrenotetrazoles (**174**)

<93JCS(P1)1557, 90JCS(P1)2995>. Directed metallation of the *ortho*-position of 5-phenyltetrazole has been observed on treatment with 3 moles of secondary butyllithium in tetramethylethylenediamine at -30°C and quenching with methyl iodide, acetaldehyde and acrolein gave the corresponding 5-*ortho*-substituted phenyltetrazoles without substitution on the ring nitrogens. Benzyl bromide, however, reacted at the tetrazole N-2 position and alkyl halides more complicated than MeI did not react <91TL6857>.



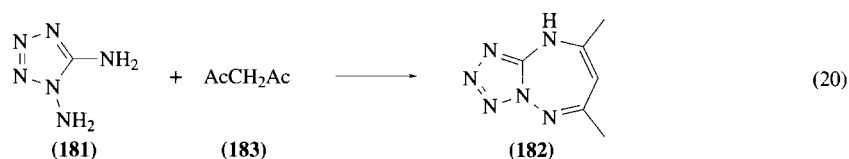
(174)

4.17.7.3 Substituents with Nitrogen Bonded to C-5

4.17.7.3.1 Substituted 5-aminotetrazoles: cyclocondensations

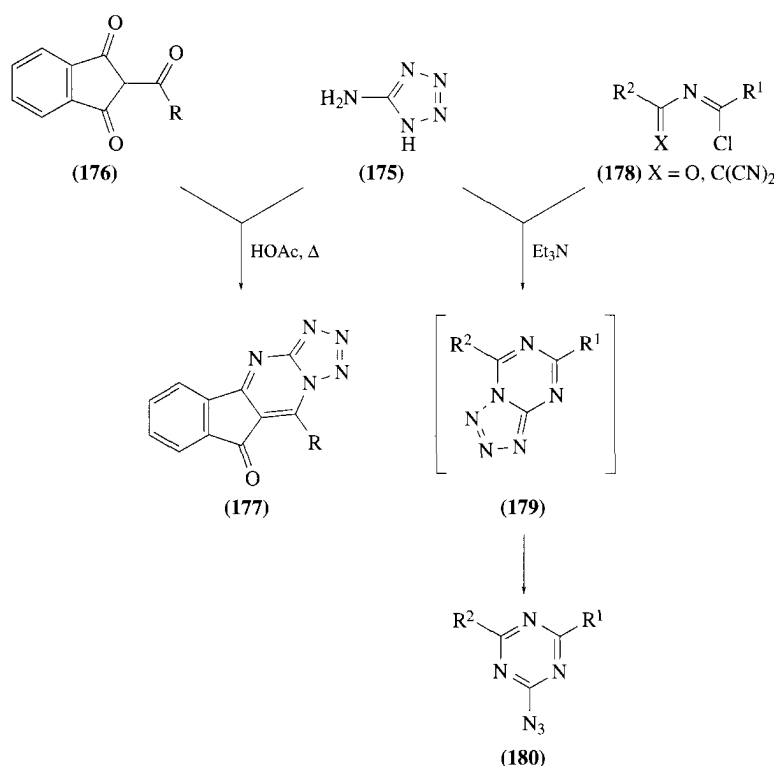
5-Aminotetrazole (175) is a central compound among the tetrazoles and it has played a major role in the development of tetrazole chemistry <77AHC(21)323, 84CHEC-I(5)791, B-84MI 417-01>. The participation of substituted 5-aminotetrazoles in Dimroth rearrangements involving tetrazole ring opening and ring closing has been discussed in Sections 4.17.4.3.3 and 4.17.5.2.3.

The difunctionality of 5-aminotetrazole facilitates cyclocondensations with 1,3-dicarbonyl compounds or other 1,3-difunctional substrates. Condensation of 5-aminotetrazole with 2-acyl-1,3-indanediones (176) in ethanol with catalytic HOAc gave the tetrazolo[1,5-*a*]pyrimidines (177) and the corresponding ring-opened azido isomers (depending on R) in yields of 38–63% (Scheme 28) <90S721>. A range of tetrazolo[1,5-*a*]pyrimidine derivatives has been synthesized in 50–98% yields from intramolecular self-cyclocondensation of 1- and 2-($\text{R}^1\text{C}(\text{O})\text{CH}_2\text{CO}-$)-substituted 5-aminotetrazoles and from condensations of 5-aminotetrazole with 1,3-difunctional compounds, $\text{R}^1\text{COCH}_2\text{COR}^2$ and $\text{R}^2\text{CO}-\text{C}(\text{R}^3)=\text{CH}-\text{Cl}$ <87UKZ319, 93JHC1267>. Cyclocondensation of 5-aminotetrazole with the carbimidoyl chlorides (178) gave the azido-*s*-triazines (180) in yields of 31–81% (Scheme 28) <85S311>. Cyclocondensation of 1,5-diaminotetrazole (181), prepared by PbO oxidation of $\text{NH}_2\text{NHCS}\cdot\text{NH}_2$ in DMF containing NaN_3 , with pentane-2,4-dione gave a 92% yield of the tetrazolotriazepine (182) (Equation (20)) <84KGS1683>. The amino groups in compound (181) display normal nucleophilic reactivity. The 5-amino group was monoacetylated by acetic anhydride while diacetylation occurred on the 1*N*-amino group. With aldehydes and ketones the 1*N*-amino group responded like a hydrazine and gave condensations to hydrazone-type products <84KGS1683>.



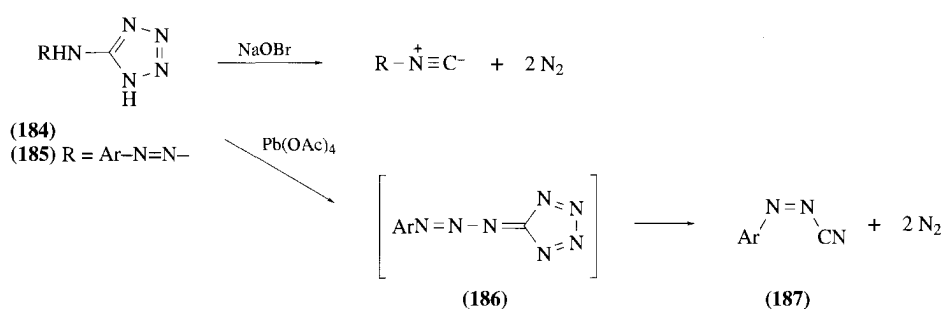
4.17.7.3.2 Substituted 5-aminotetrazoles: Reactions with electrophiles and oxidation

Oxidation of 5-substituted aminotetrazoles (184) provides an efficient synthesis of isocyanides in a reaction which proceeds through a pentaazafulvene intermediate from which two molecules of N_2 are extruded (Scheme 29) <76AG(E)113, 83OS(61)14>. Oxidation of the 5-triazenotetrazoles (185), however, gave diazocyanides (187) and the expected diazoisocyanides were not encountered. This led to the realization that literature claims of stable conjugated diazoisocyanides were incorrect and such compounds are unknown <86JCS(P1)1101, 87CC1210>. Acetylation of 1-substituted tetrazol-5-yltriazenes (188) with Ac_2O occurred on the nitrogen atom bonded to the tetrazole C-5 (Equation (21)). In the reactions of ring-substituted tetrazol-5-yltriazenes (188) with mercuric acetate and PhHgOH , the mercury(II) attacked the triazene nitrogen furthest from the tetrazole ring giving

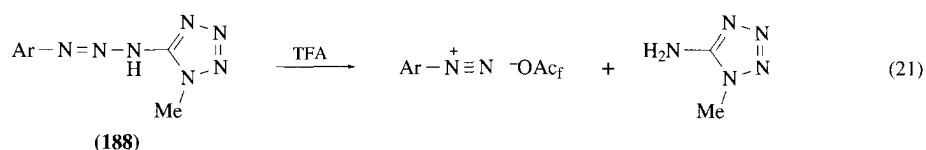


Scheme 28

bis(triazeno)mercury compounds <86JCS(P1)1101>. The triazenide anions of (188) were methylated at the same nitrogen atom furthest from the tetrazole ring <84JCS(P1)1589>. The strength of the vinyl resonance into the tetrazole ring (see Scheme 6) confers good leaving ability on the 1-substituted 5-aminotetrazole moiety and triazenes such as (188) have been developed as long-term bench-stable rapid sources of aryl diazonium ions. These can be generated when required by simple treatment with trihalogenoacetic acids <87JCS(P1)1039> which causes loss of 1-methyl-5-aminotetrazole after protonation thereby freeing the aryl diazonium ion.

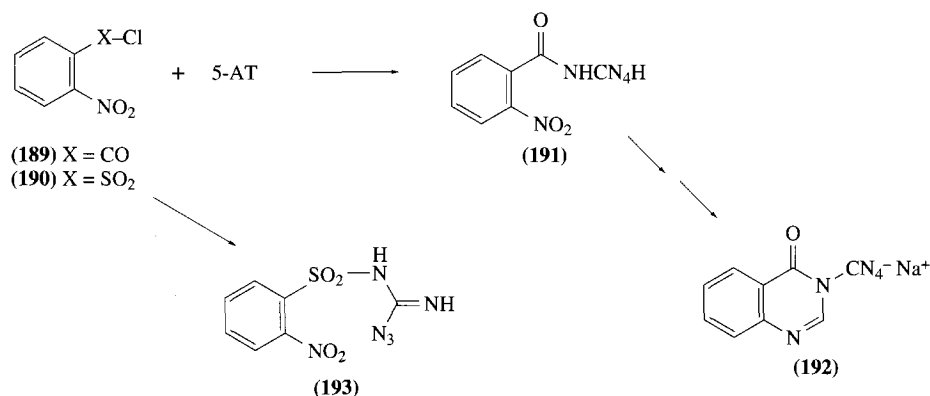


Scheme 29

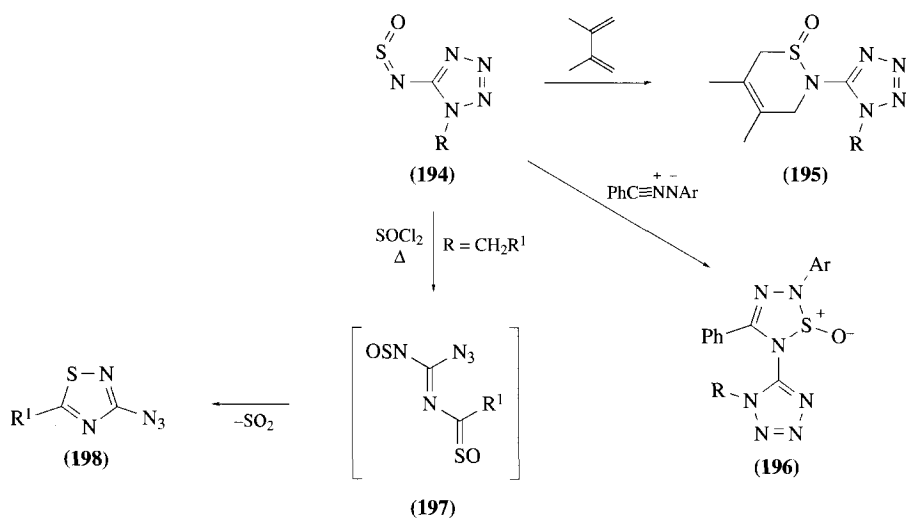


The amino group at tetrazole C-5 behaves as a normal nucleophile towards electrophilic acylating agents but acylation may also occur at the tetrazole N-1 or N-2 positions often giving ring degra-

dation to oxadiazole products <84CHEC-I(5)791>. Examples of the behavior of 5-aminotetrazole (5-AT) towards some electrophiles are shown in Scheme 30 for *ortho*-substituted phenyl acid halides. These reactions have been used in the synthesis of the antiasthma antiallergic agent, MDL-427, compound (192) <83USP4419357, 86JMC2403>. Both the benzoyl and sulfonyl halides (189) and (190) reacted with the 5-amino group giving the products (191) and (193), respectively. The azido form of the latter arose because of electron depletion around the imidoyl azide moiety <86JMC2403, 87JHC1531>. *ortho*-Substituted arylisocyanate reacted with 5-aminotetrazole at the ring N-1 position giving a kinetic product which rearranged to the 5-amidotetrazole form on heating <87JHC223>. Triethyl orthoformate, $\text{HC}(\text{OEt})_3$, reacted at the amino group of 5-aminotetrazole in hexane and after azeotropic removal of EtOH gave the imine, $\text{EtO}-\text{CH}=\text{N}-\text{CN}_4\text{H}$, in 95% yield <89JHC97>. 1*N*-Substituted-5-aminotetrazoles react with nitrilimines from hydrazonoyl halides and Et_3N at the 5-amino nitrogen giving unstable intermediates in which the tetrazole opens to an imidoyl azide and 1,2,4-triazoles are formed with loss of HN_3 <88JCS(P1)1587, 93JCR(S)306>. A mechanism invoking a cycloaddition of the nitrilimine 1,3-dipole to the 4,5 bond of the aminotetrazole has also been proposed for this reaction <87CB965>. Both 1- and 2-substituted-5-aminotetrazoles reacted with thionyl chloride in benzene to give the 5*N*-sulfinylaminotetrazole derivatives (194). The *N*-sulfinyl group displayed ready cycloadditions with butadienes and nitrilimines giving the products (195) and (196) in high yields at ambient temperatures (Scheme 31) <86CI(L)750, 89JCS(P2)1855>. When heated under reflux in *p*-xylene with an excess of thionyl chloride compounds (194) changed into the 3-azido-1,2,4-thiadiazoles (198) in a reaction thought to involve further sulfinylation of the 1*N*-alkyl group with tetrazole ring opening to the imidoyl azide (197) (Scheme 31) <86CC800, 88JCR(S)188>. Preparative electroreductions of some 5-nitroaminotetrazoles have been reported <92KGS944>.



Scheme 30

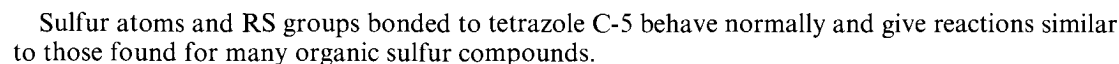


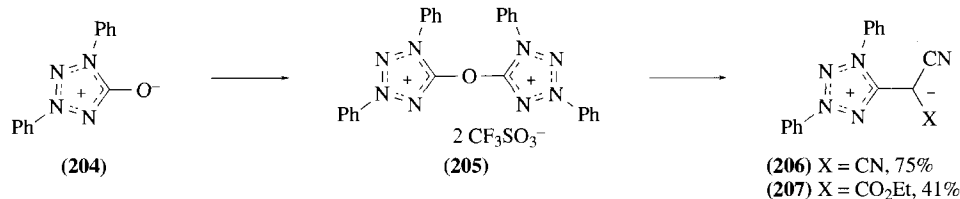
Scheme 31

Diazotization of 5-aminotetrazole with sodium nitrite and aqueous HCl gives tetrazole-5-diazonium chloride (**199**) which is dangerously explosive in the solid state or if it crystallizes out of solution, but kept in solution is an important synthetic intermediate in tetrazole chemistry <75CRV241>. It can be readily reduced to a hydrazine or the N₂ can be replaced by halogen, OH, or H <77AHC(21)323, 84CHEC-I(5)791, 84CHEC-I(5)822>. Removal of a proton gives the diazo form which has been used for a controlled generation of atomic carbon <74JA7830>. Theoretical studies of the diazoazole series suggest that 5-diazotetrazole should readily enter a cycloaddition transition state with electron-rich alkenes <90JCS(P2)1943>. The diazonium salt (**199**) couples with malonodinitrile under basic conditions to give the 3-azido-1,2,4-triazine derivative (**201**). This reaction formally involves a sequence of tetrazole ring opening, prototropic tautomerizations and intramolecular nucleophilic addition in the initial diazo product represented as (**200**) in Scheme 32 to illustrate the process although this particular species need not be an intermediate <84KGS557>. The hydrate of 5-[(diazomethyl)-azo]tetrazole, HN₄C-N=N-CH=N₂·H₂O, has also been reported and reduced to 5-hydrazinotetrazole and to tetrazol-5-yl diazomethanol, HN₄C-N=N-CH₂OH <92KGS1351>. In the earlier literature, ring-substituted 5-aminotetrazoles have been shown to undergo oxidative dimerization to azotetrazoles and diazotization to 5-nitrosaminotetrazoles or 1,3-bistetrazol-5-yltriazenes, depending on the diazotization conditions <75CRV241, 84CHEC-I(5)791>.



The most important use of tetrazoles with a nontautomeric oxygen group at C-5 is for deoxygenation of phenols as shown for compounds (**46**) Scheme 6. Kinetic and isotope studies have shown that the reaction is characterized by “burst kinetics” in which a steady state is controlled by the rate of release of the tetrazolone (**48**), with the process proceeding through intermediates of type (**202**) and (**203**) $\langle 87\text{JCS(P1)1069, 91CC1041} \rangle$ (Equation (22)). When these aryl ether cleavages are carried out electrochemically by cathodic reduction the products are mainly phenols and fragments from tetrazole degradation, which is the reverse of the catalytic chemical reduction $\langle 82\text{JCS(P2)391} \rangle$. The behavior of tautomeric oxygen-containing substituents has been discussed in Section 4.17.6.2. Earlier thermal Claisen-type rearrangements of allyloxy and alkoxy substituents at tetrazole C-5 have also been reviewed $\langle 84\text{CHEC-I(5)791} \rangle$. Treatment of the 1,3-diphenyltetrazolium oxides (**204**) with the anhydride of trifluoromethanesulfonic acid gave the ditetrazolium ether salts (**205**) which contain a leaving group at tetrazole C-5 (Scheme 33). Nucleophilic attack on the compounds (**205**) with the anions of malonodinitrile and ethylcyanoacetate gave the new substituted tetrazolium-5-methanides (**206**) and (**207**) in the yields shown $\langle 84\text{CL1045, 85JCS(P1)2439} \rangle$.

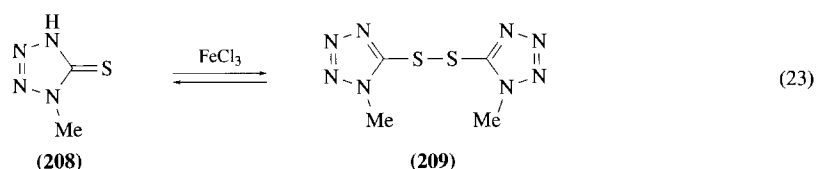




Scheme 33

4.17.7.5.1 The tautomeric SH substituent

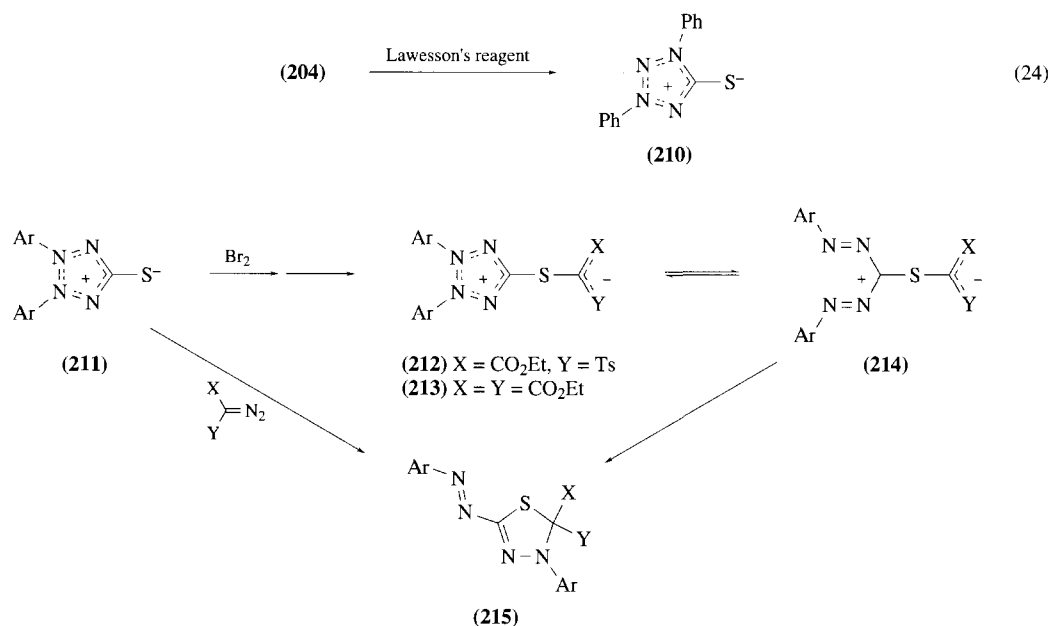
The reactions of tautomeric tetrazolin-5-thiones with alkylating agents and electrophiles are discussed in Section 4.17.6.2. The most common individual derivatives containing this group are the 1*N*-methyl and 1*N*-phenyl compounds. Mild oxidizing agents such as FeCl₃ convert the thiol compounds into ditetrazol-5-yl disulfides (209) and these are rapidly converted back to the parent thiones (208) along with some of the sulfinic acid derivative in aqueous solution at pH 7.39 (Equation (23)). At pH 1.25 (dilute H₂SO₄) cleavage of the disulfide was slow (*t*_{1/2} = 40 h) (85JOC2794). The aqueous chemistry of this system has assumed renewed importance due to an observed *in vitro* inhibition of an enzyme for the γ -carboxylation of the glutamyl residue of a model prothrombin precursor (83MI 417-01, 83MI 417-02). The high lability of the disulfide link in compound (209) facilitates rapid thiol–disulfide exchange reactions and disulfides such as (209) are effective agents for generating more stable disulfide linkages from other less acidic thiols (91JOC5475). Reactions of substituted epoxides with 1*N*-substituted tetrazole-5-thiones in DMF with LiBr as catalyst gave a 1,3-addition of the opened epoxide on the C=S bond with the oxygen attacking the tetrazole C-5 giving rise to spiro(oxathiolanedihydro-tetrazoles) (90JCR(S)126). Heating of compound (209) in nonpolar solvents in the presence of (*Z*)-alkenes causes isomerization of the alkenes to the (*E*)-forms in a reaction thought to involve tetrazol-5-yl sulfur radicals (89CAR(194)125). Earlier studies of rearrangements involving tetrazole ring migration in substituted 5-thiotetrazoles as well as protection of the 5-SH group and further experimental applications of tetrazole-5-thiones have been discussed (84CHEC-I(5)791).



4.17.7.5.2 Mesoionic tetrazolium-5-thiolates

A new route to 2,3-diphenyltetrazolium-5-thiolates (210) involves one-pot replacement of O[−] in (204) by heating with Lawesson's reagent in toluene (Equation 24) (88BCJ2977). This surpasses the older methods which involved alkylating the oxides (204) and replacing the alkoxy group with a sulfide or hydrogen sulfide anion (79JCS(P1)732, 83CPB1746). Complexation studies of the compounds (210) and (204) with molybdenum and iron carbonyls have been reported (93CB1157). The 2,3-diaryl tetrazolium-5-thiolates (211) are weak bases (Ar = Ph, basic p*K*_a = −1.73 at 25°C, measured in aqueous perchloric acid) which protonate on the sulfur atom (81JCS(P2)1534). The compounds form bromine adducts containing the leaving group, Br—S[−]—Br, on treatment with bromine in dry dichloromethane. *In situ* treatment of the bromine adducts with anions of active methylene compounds gave tetrazolium-5-thioylides such as compound (212) (Ar = Ph) which was isolated in 89% yield and had m.p. 125°C (88BCJ2979). In other cases, for example (213), the tetrazolium-thioylides rearranged into the 2-arylo-1,3,4-thiadiazolines (215) (Scheme 34) which were also obtained in 65% yield by treating the tetrazolium-5-thiolates (211) with diazo derivatives (88BCJ2979). Early cycloaddition reactions of compound (211; Ar = Ph), dehydrodithazone, with electron-depleted

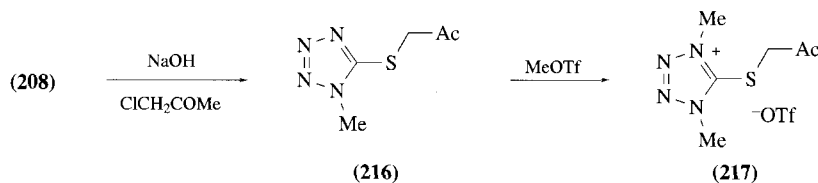
alkenes and ynamine dipolarophiles were reported to occur across the $\text{—N}^+=\text{C—S}^-$ moiety <71CC490, 74CC639, 77AHC(21)323>.



Scheme 34

4.17.7.5.3 S-alkyl substituents

Successive alkylation at sulfur followed by quaternisation at N-4 in 1-methyltetrazol-5-thione gave the series (216) and (217) which are active as transglutaminase inhibitors (Scheme 35) <91EUP411894>. Lability in the alkyl-sulfur bond of these systems can render the 1*N*-substituted-5-thiotetrazole moiety as an effective leaving group thus allowing alkyl transfer onto active centres. Benzylic and allylic groups have been transferred to *O*-silylated ketones and ester enolates from the sulfur atom of the 1*N*-phenyl-5-thiotetrazole in the presence of silver triflate <90TL265>. Basic cleavage of the R—S bond in 1-phenyl-5-alkylthiotetrazoles depends also on the R group fragment <85JOC980>.



Scheme 35

4.17.7.6 Halogens

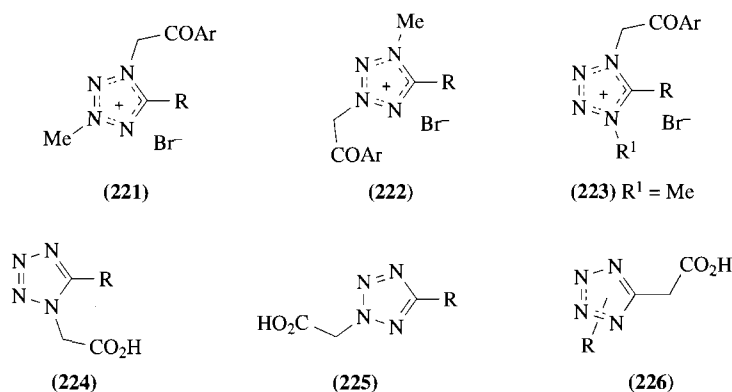
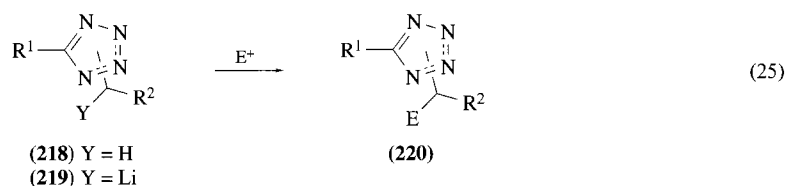
Halogen atoms at the tetrazole-5-position are readily displaced by better nucleophiles because of the electron-depleted character of the ring. The nucleophilic displacement was much more rapid with 1-substituted-5-bromotetrazoles than with the 2-substituted isomers <84CHEC-1(5)791>. These reactions are often best carried out by warming the halotetrazole in the neat amine or hydrazine when these are liquid. Synthetic uses of the reaction are shown in Schemes 6 and 10. New routes to 5-halotetrazole derivatives have been found <95JO6468>

4.17.8 REACTIVITY OF SUBSTITUENTS AT RING NITROGENS

Substituents bonded to tetrazole ring nitrogens behave similarly to those bonded to the tetrazole C-5 and the tetrazole ring mainly behaves as a passive electron-withdrawing group when influencing their behavior. The tetrazole ring exerts a stronger electron withdrawing effect on substituents at the ring nitrogens than it does on substituents at the ring carbon.

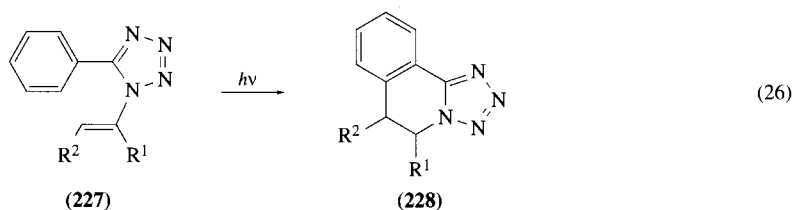
4.17.8.1 Methyl and Methylene Substituents Bonded to Ring Nitrogen

Treatment of either 1*N*- or 2*N*-alkyl-5-substituted tetrazoles with *t*-butyllithium at -78°C in tetrahydrofuran gave colored solutions of α -lithioalkyltetrazoles (**219**) which were stable up to -23°C and possibly higher (Equation (25)) <90SL413, 91JCS(P1)323>. Quenching the species (**219**) with a series of electrophiles, including D_2O , aldehydes, ketones, nitriles, TMS-Cl and Me_2SO_4 , allowed an introduction of the electrophilic entity at the α -position giving the products (**220**) in high yields. In these reactions, the 2-alkyltetrazoles were more acidic than the 1-alkyl isomers. With a hydrogen atom at C-5, the lithiation occurred at this site <91JCS(P1)323>. No direct lithiation at the *ortho*-position of the 5*C*-aryl group was encountered with the nitrogen substituted species (**218**) but with 5-aryl nitrogen unsubstituted tetrazoles, lithiation at the *ortho*-position of the 5*C*-phenyl ring occurred in some cases <91TL6857> (Section 4.17.7.2.3). It is also of interest that for the compounds (**154**), lithiation occurred at the 5-alkyl group rather than the *N*-alkyl group but with the 2*N*-methyl isomers of (**154**) lithiation occurred on the 2*N*-methyl group <93JOC1623>. The acidity of methylene protons bonded to tetrazole nitrogens is greatly increased if they are also bonded to $\text{C}=\text{O}$ and if the tetrazole ring is quaternized. Moderhack *et al.* have prepared a wide series of the salts, (**221**)–(**223**). The $\text{p}K_{\text{a}}$ values for the series for $\text{R} = \text{H}$, $\text{Ar} = \text{Ph}$ were: (**221**), 8.98; (**222**) 8.45; and (**223**), 9.64. These values also agreed with the relative rates of H/D exchange in these compounds <86JCS(P1)1157>. Proton removal from the salts (**221**) and (**222**) with aqueous K_2CO_3 gave the corresponding tetrazolium ylides as stable yellow to red solids, even when $\text{R} = \text{H}$, but the series (**223**) proved problematic giving tetrazole ring degradations on treatment with aqueous base <85CZ432>. However, with higher homologs of the 1*N*-substituent or with electron-withdrawing substituents in the Ar group the ylides from (**223**) were eventually generated as unstable oils <92JCS(P1)1483>. The reactive center in these tetrazolium *N*-ylides is the exocyclic methanide site, $-\text{CHCO}$, which behaves as a nucleophile. Interestingly, when ammonia was used as the base for deprotonation of (**223**), the products were mainly fused imidazotetrazolines from imine formation at the carbonyl group <93CB129>. In the series of tetrazolylacetic acids (**224**)–(**226**), the acidity of the carboxylic acid groups are comparable to those of haloacetic acids and the inductive σ constants for the tetrazol-1-yl, tetrazol-2-yl and tetrazol-5-yl groups were reported as 0.65, 0.62 and 0.41, respectively, from $\text{p}K_{\text{a}}$ values of the series (**224**–**226**; $\text{R} = \text{Me}$, Et, Ph, NH_2) <82KGS264>.



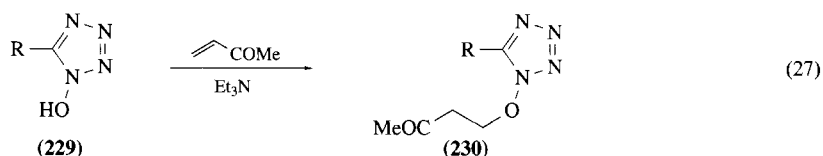
4.17.8.2 Substituents with Unsaturated Carbon Bonded To Ring Nitrogen

The presence of a —C=X ($\text{X} = \text{O}, \text{NR}, \text{S}$), bonded to a tetrazole ring nitrogen, has a destabilizing influence on the ring and the main reactions of these systems involve thermal tetrazole ring degradations and transformations into other heterocyclic systems. Many examples of such systems have been described herein, for example compounds (51), (52), (66), (70), (90), (95) and (152). The best known such reaction is where the acyl group is bonded to tetrazole N-2 and loss of N_2 gives a 1,3/1,5-dipole which undergoes a Huisgen 1,5-electrocyclization to a 1,3,4-oxadiazole, 1,3,4-thiadiazole, or a 1,2,4-triazole (see Section 4.17.5.3.2) <80AG(E)947>. The structure (197) represents the behavior of a C-sulfinyl group at the tetrazole N-1. Tetrazole rings with vinyl or aryl groups bonded to ring nitrogens are more stable but if heated to appropriate temperatures they also undergo ring transformations, for example see Scheme 8. *N*-Vinyltetrazoles undergo polymerization and copolymerization processes which are influenced by both the tetrazole inductive effect and the conjugation effect between the ring and the vinyl substituent <88MAC1363>. Interaryl ring coupling can be achieved between the *ortho*-positions of the 1*N*-aryl and 5*C*-aryl substituents giving products such as (174) <90JCS(P1)2995>. In the irradiations of 1-vinyltetrazoles which gives imidazoles (Scheme 8) tetrazoles which contain a 5-phenyl ring (227) also exhibit photocyclization to (228) as a competing reaction which is highly solvent dependent (Equation (26)) <82CC714>.



4.17.8.3 Substituents with Oxygen or Nitrogen Bonded to Ring Nitrogens

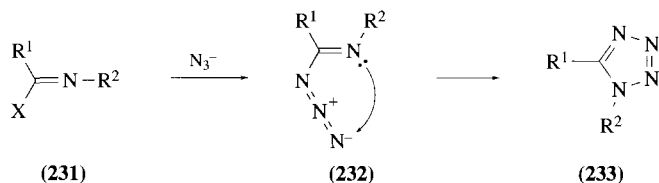
Hydroxy groups bonded to the tetrazole N-1 position (229) appear to be deactivated by the electron-withdrawing power of the ring. Methylation with MeI , Me_2SO_4 or CH_2N_2 occurs almost exclusively on the exocyclic oxygen but methylation with $\text{Me}_3\text{O}^+\text{BF}_4^-$ gave mixtures from methylation at ring nitrogens as well as the exocyclic oxygen <84IZV181, 92IZV1619>. Compounds (229; $\text{R} = \text{Ar}$) were unreactive in Michael reactions and gave low yields of products (230) in reactions with methyl vinyl ketone in EtOH at $40\text{--}50^\circ\text{C}$. Reactions with dimethyl acetylenedicarboxylate (DMAD) gave complicated mixtures of products due to secondary reactions involving the initial mixture of adducts <89BSB277>. 1-Aminotetrazoles behave like 1,1-disubstituted hydrazines and give nucleophilic addition or addition-elimination reactions at the NH_2 group with aldehydes, sulfonyl halides and isocyanates <84CHEC-I(5)791>. Rearrangements and condensation reactions of some 1-aminotetrazole derivatives are discussed in Sections 4.17.5.2.3 and 4.17.7.3.1. Aldehyde imine (or hydrazone) derivatives of 1-aminotetrazoles are readily cleaved to the 1-aminotetrazole derivatives in glacial acetic acid <83KGS841>. The reaction of acyl halides with 1-aminotetrazoles results in acylation at both the 1-amino group and the ring N-4 position and gives rise to substituted 1,3,4-oxadiazoles <66CB850, 84CHEC-I(5)791>.



4.17.9 SYNTHESIS

The traditional routes are still the main synthetic avenues to tetrazoles. Improvements in these are continually being developed and the increasing use of trimethylsilyl azide as a safer and organically soluble source of azide is a significant development. This section in particular needs to be taken as complementary to the corresponding section in CHEC-I.

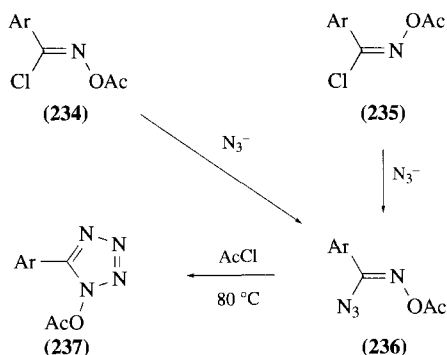
4.17.9.1.1 From imidoyl azides



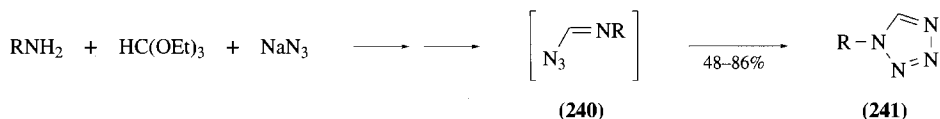
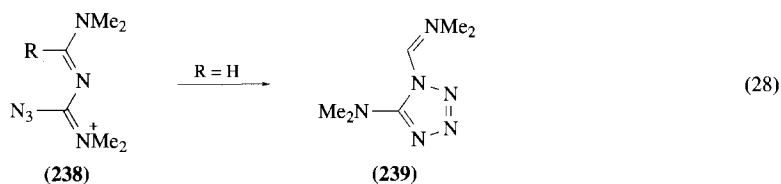
Scheme 36

The (*Z*)-halides (**234**) reacted with N_3^- with retention while the (*E*)-halides (**235**) underwent inversion on treatment with azide ion and both gave the same product, the (*Z*)-azide (**236**) (Scheme 37). Heating of (**236**) with acetyl chloride at 80°C was required to achieve the nitrogen inversion to the (*E*)-form necessary for spontaneous cyclization to the tetrazole (**237**) (Scheme 37) <84CC913>. The behavior of the imidoyl azides (**238**) also depended on the ease of isomerization (Equation (28)). With R = H the tetrazole (**239**), which hydrolysed to the 1-NH compound, was readily formed but when R was ArCH_2 , 1,2,4-triazinium-1-imides were formed <85CC1522>. Many hydrazoneyl azides (**231**; X = N_3 ; $\text{R}^2 = \text{NHAr}$) do not readily cyclize without catalysts for similar stereoelectronic reasons <84BCJ539, 92SL858>. A widely applicable synthesis of 1-substituted tetrazoles (**241**) involves the reaction of primary amines with triethyl orthoformate and NaN_3 in hot acetic acid which passes through the imidoylazide intermediate (**240**) (Scheme 38). The use of hydrazones (e.g., $\text{PhCH}=\text{N}-\text{NH}_2$) in this reaction gives 1-aminotetrazole derivatives <83KGS841, 85KGS1422, 85KGS1521, 90KGS1528>. The series of compounds (**242**)–(**245**) are further examples of imidoyl azides which remain in the acyclic form under normal conditions. The compounds (**244**) changed to carbodiimides, $\text{R}^1\text{N}=\text{C}=\text{N}-\text{R}^2$ (73–83%) on being heated at 270–300°C <85IZV700> but the azides (**245**) cyclized to 5-nitraminotetrazole on being heated in organic solvents <87KGS945>. The species (**246**) the carbon analog of (**242**) and (**243**) is not known and attempts to prepare it by treating the corresponding imidoyl chloride with LiN_3 or by addition of HN_3 to the keteneimine, $\text{Me}_2\text{C}=\text{C}=\text{NTs}$, gave in both cases Me_2CHCN and TsN_3 , testifying to the fact that aliphatic imidoyl halides may give complicated reactions with azide ion <83BSB79>. A traditional route to imidoyl azides involves converting amides to imidoyl chlorides which are then treated with azide ion. A more efficient one-pot version of this route into tetrazoles has been developed by treating the amide with PPh_3 , trimethylsilyl azide and diethyl azodicarboxylate in THF at ambient temperatures under N_2 .

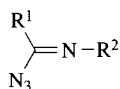
<91JOC2395> (entry 11, Table 8). An alternative simple one-pot conversion of amides to tetrazoles employing trifluoromethane sulfonic anhydride and sodium azide at 20 °C has also been reported <93S767> (entry 13, Table 8). Tetrazoles have also been obtained from imido azides generated by treatment of *N*-(4-dimethylaminophenyl)nitrones, $\text{Ar-N}^+(\text{O}^-)=\text{CHR}$ (R, electron withdrawing) with HN_3 (Table 8, entry 12). Treatment of amidines, $\text{R-C}(=\text{NPh})\text{-NR}_2^+$, as their acetate or methyl sulfate salts with NaN_3 in acetic acid under reflux gave 45–65% yields of 1-Ph,5*R*-tetrazoles <85KGS566>. Imido azides have also been generated by treatment of 2,4,6-triaryl-1,3-oxazinium salts with azide ion <85CJC86> (Table 8, entry 15). Further examples of tetrazole systems synthesized by the imido azide route are listed in Table 8.



Scheme 37



Scheme 38



(242) $\text{R}^1 = \text{SMe}$; $\text{R}^2 = \text{Ts}$

(243) $\text{R}^1 = \text{NMe}_2$; $\text{R}^2 = \text{Ts}$

(244) $\text{R}^1 = \text{CF}_3$, C_2F_5 ; $\text{R}^2 = \text{CF}_3$

(245) $\text{R}^1 = \text{NHNO}_2$; $\text{R}^2 = \text{H}$

(246) $\text{R}^1 = \text{Pr}^i$; $\text{R}^2 = \text{Ts}$

4.17.9.1.2 Tetrazoles from 1,1-diazo compounds

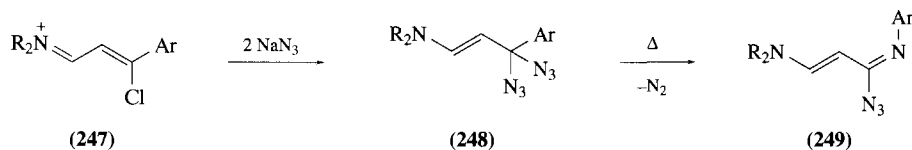
Heating of *gem*-diazido compounds leads to 1,5-disubstituted tetrazoles in a reaction which has been considered to involve a 1,2-C → N shift either in an azido nitrene intermediate or concomitant with N_2 loss from one of the azide groups to give an imido azide intermediate (e.g., (249)) which cyclizes (Scheme 39) <84CC338, 88JPR963>. The thermal conversion of diazidomalonates to tetrazoles has been shown to involve a complicated chain process with an intermolecular methyl transfer <85JOC3710>. The chemistry of geminal vinyl diazides (145) has been extensively developed by

Table 8 Synthesis of tetrazoles.

No.	R ¹	R ²	Reagent/ Condition	Yield (%)	Ref.
Part A: Tetrazoles (233) via imidoyl azides (232) from precursor (231) (Scheme 36)					
1	Ph	CH=C(Me) ₂			83CC1082
2	Ar	NHSO ₂ Ph		6–15	84BCJ539
3	Ar	CH ₂ P ⁺ Ph ₃ Cl [−]			88ZOB2465
4	(1-ArN ₄ C)-CH ₂	Ar			86ZOR200
5	Ph	S=C-N(CH ₂ CH ₂) ₂ O		60	86ZC70
6	Ar'-N-CO-Ar ²	Ar'		55–70	87S823
7	CH ₂ X	OH			92IZV1619
8	Ar	N=CHAr		31–36	92ZOR1024
9	CO ₂ R	NHPh		25–71	92SC309
10	Ph	S=C-NR ₂		15–50	92JPR283
11	4'-Me-1,1'-biphen-2'-yl	CH ₂ CH ₂ CN		44	91JOC2395
12	CONH-Ar or CN ₄ R'	<i>p</i> -C ₆ H ₄ NMe ₂		10–61	77JHC757
13	alkyl	alkyl		27–72	93S767
14	ArCOCH ₂ ; ArCHCN	alkyl, Ar		60–79	88S453
15	Ar	Ph-CO-CH=C(Ph)			85CJC86
Part B: Tetrazoles from nitriles and azides (R ¹ , Scheme 42)					
16	Ar, alkyl		Me ₃ Al, TMS-N ₃ , PhMe, 80°C	71–98	93TL8011
17	Ar, (CH ₂) _n CN		R ₂ SnO; TMS-N ₃ , PhMe	60–98	93JOC4139
18	Biaryl		Me ₃ SnN ₃ ; PhMe	85	91JOC2395
19	R'CH ₂		Me ₂ NH·HN ₃ , range of solvents	80–90	92KGS1214
20	(NO ₂) ₃ C; F(NO ₂) ₂ C		H ₃ O ⁺ ·NaN ₃ ; TMS-N ₃	72–79	81JHC1477
21	<i>o</i> -FC ₆ H ₄		NaN ₃ , HOAc, BuOH	70	93JOC5023
22	N=C—		HN ₃ , pyridine, NaHCO ₃	95	84CZ188
23	N≡C—; —C ₂ N ₂ S(CN) ^a		[Ph ₃ PNPPh ₃] ⁺ ·N ₃ [−]	96	90ZN(B)77
24	Cl ₃ C; C ₆ H ₄ CN		Schiff base, Co(III)N ₃	< 30	87ZN(B)55

^a3-Cyano-1,2,4-thiadiazole and 3-cyano-1,2,5-thiadiazole.

Saalfraank *et al.* Replacement of one of the azido groups with NH₃ or RNH₂ gives the aminovinyl azides (146) (Scheme 21). These are readily converted by bases such as Et₃N to salts of the substituted 4,5-dihydro-1*H*-tetrazol-5-ylidenes (147) which can then be freed by treatment with acid (89JOC4356, 91CB595) (see Section 4.17.6.2). Another route into these types of tetrazoles involves displacement of MeS[−] from ketene *S,N*-acetals, RRC=C(NHR)-SMe, with NaN₃ (Table 8, entry 14) (88S453). Treatment of benzophenone dimethylacetal with 2 moles of trimethylsilyl azide and catalytic SnCl₄ gave 1,5-diphenyltetrazole (57%) via a 1,1-diazido intermediate (83S500). 1-Hydroxymethyl tetrazoles have similarly been obtained from α -hydroxyacetophenones bearing electron-donating substituents in the phenyl ring (84S683). A number of fused tetrazolo carbohydrates have been reported from the photolysis of benzyl- and acetyl-protected glucopyranosylidene diazides (94TL89).

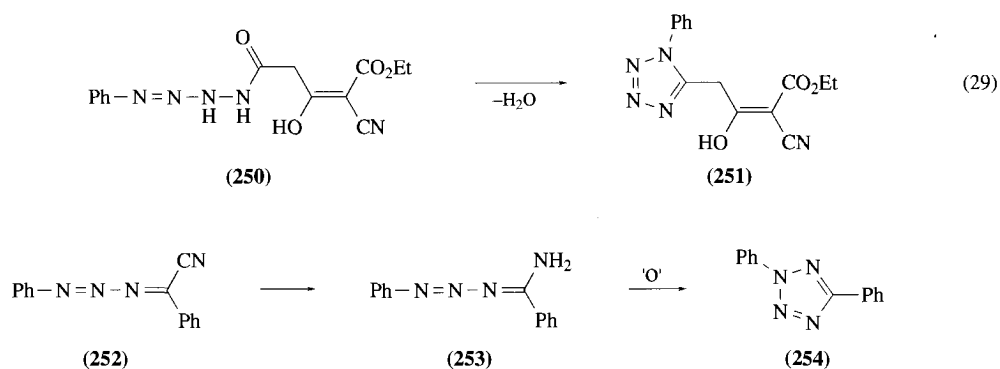


Scheme 39

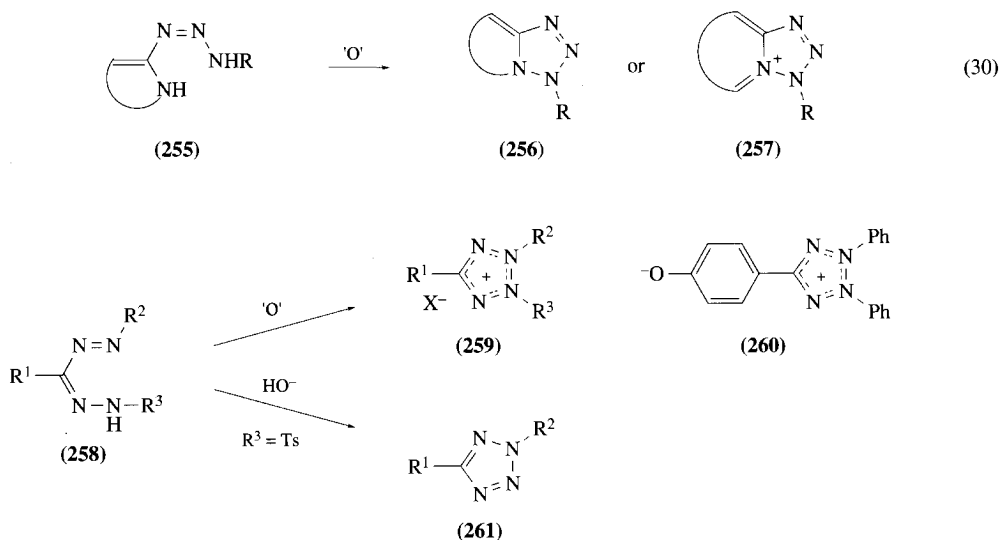
4.17.9.1.3 Tetrazoles from cyclization of tetrazenes, triazenes, and formazans

Acyclic systems other than imidoyl azides which may be cyclized to tetrazoles include substituted tetrazenes, —C—NH—N=N—NH—, some triazenes —N—C—NH—N=N—, and formazan derivatives, —N=N—C=N—NH— (84CHEC-I(5)791). Tetrazenes with an α -carbonyl group are obtained from the coupling of aryl diazonium salts with hydrazides (e.g., compound (250)) dehydration of which gave the tetrazole (251) in 80% yield (Equation (29)) (83S478). Examples of triazene systems which have been oxidatively cyclized to tetrazoles are compound (253), obtained by displacement of cyanide from (252) (90JOC3351, 90JOC3362), and compounds containing the unit

(255) which give fused azolotetrazoles (256) <83JHC1629, 87CB1375> or tetrazoloazinium salts (257) <86T5415> depending on the substrate (Scheme 40; Equations (29) and (30)). Triazenes of type (253) are not at present practical precursors for tetrazole synthesis due to difficulties with their own synthesis combined with low yields of tetrazoles and mixtures from their oxidation reactions <90JOC3362>. Oxidation of formazans (258) with a wide range of oxidizing agents is the standard route to the tetrazolium salts (259). The use of interphase catalysis with KMnO_4 in CHCl_3 with 5% aqueous HCl has given the series (259; $\text{R}^1 = \text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{substituted phenyl}$) in 70–80% yields after conversion of the anion to iodide for ease of isolation <88ZOR225>. The use of *p*-methoxyphenyl groups at C-5 in the systems (259) allowed for cleavage of the methoxy group followed by deprotonation of the resulting phenol to give the first examples of meso-ionic tetrazolium phenolates (260) <87TL4289>. When the formazans (258) contain an arylsulfonyl group on one of the nitrogens, treatment with strong base gives a Bamford–Stevens-type reaction providing an excellent route to 2,5-diaryltetrazoles (261) (Scheme 41) <76BCJ1920, 84JHC797>.



Scheme 40



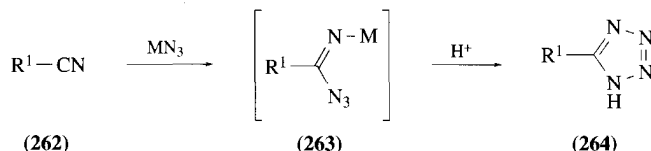
Scheme 41

4.17.9.2 Formation of Two Bonds from 3 + 2 Atom Components

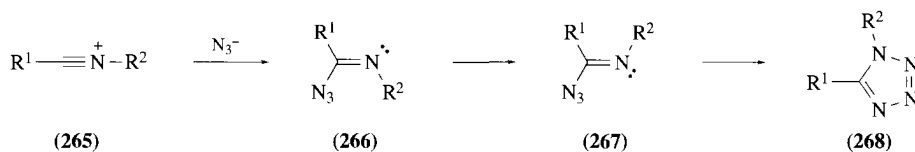
4.17.9.2.1 Addition of azide ion and metal azides to nitriles and nitrilium ions

The addition of azide ion to nitriles remains the main synthetic route to 5-substituted tetrazoles. The distinction between this approach and the imidoyl azide route (Section 4.17.9.1.1) is blurred

since imidoyl azides are probably intermediates in these reactions also. Typically, nitriles (**262**) are treated with HN_3 generated *in situ* from acid and sodium azide. The use of sodium azide in acetic acid–butanol mixtures under reflux for about 50 h was an effective early procedure developed by Herbst *et al.* <57JOC1142>. The reaction has also been promoted by the use of ammonium chloride and ammonium azide salts at 120°C <58JA3908>. Since this work, interest has focused on procedures for lowering the temperature and shortening the time required and the use of dipolar aprotic solvents such as DMF proved beneficial. The reaction probably involves a complexed imidoyl azide (**263**) which undergoes rapid nitrogen inversion and ring closure to the tetrazole which is subsequently freed by acid (Schemes 42 and 43). Nucleophilic addition of azide ion to nitrilium ions gives the intermediates (**266**) (Scheme 43). These also undergo rapid nitrogen inversion to (**267**) with spontaneous ring closure to (**268**) (Scheme 43) <80ACR448>. However, the possibility that the reaction of azide ion with the nitrile triple bond could be a concerted cycloaddition is still open but the weight of opinion appears to be against it and semiempirical and *ab initio* calculations favor the two-step mechanism <94JST(312)11, 95JST(343)149>. Approaches to the nitrile/azide reaction have employed the use of metal azide complexes and trimethylsilylazide to avoid HN_3 . Examples are summarized in Table 8 (Part B). The reaction of azide ion with nitrilium salts has been improved by using *N*-methyl nitrilium trifluoromethanesulfonate salts in dry nitromethane which gives >90% yields of 1-methyl-5-substituted tetrazoles <93JCR(S)4>. Tetrazole syntheses involving the reaction of HN_3 with nitrilium ions include the Beckmann reactions of oximes in the presence of azide ion <83JCR(S)18> and the Schmidt reaction of ketones with excess hydrazoic acid (Scheme 44) <84CHEC-1(5)791>. Since the first report by Schmidt of the reaction of HN_3 with carbonyl compounds in the presence of mineral acids <23AG511> there has been an interest in this reaction for the synthesis of tetrazoles (Scheme 44) <87CJC137>. The reaction, which may also proceed via diazido intermediates, has provided a range of steroidal tetrazoles by ring expansion of cyclic α,β -unsaturated ketones using excess HN_3 and more recently trimethylsilylazide in the presence of trimethylsilyl triflate <91JCS(P1)2657>. The use of Lewis acids such as SnCl_2 with TMS-N_3 gave good yields of 1,5-disubstituted tetrazoles from acetals of simple ketones via diazido intermediates <83S500, 84CL455, 84S683, 88S106> and the 1-fattyalkyl 5-vinyltetrazole (**269**) has been obtained in 66% yield by treatment of $\text{Me}(\text{CH}_2)_{13}\text{CO-CH=CHCO}_2\text{Me}$ with excess HN_3 in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <84MI 417-02>. High yields of 1,5-disubstituted tetrazoles have been obtained from both aromatic and aliphatic ketones in a Schmidt reaction using excess NaN_3 with titanium(IV) chloride and acetonitrile as solvent <93S1218>. Tetrazole synthesis by acid-catalyzed addition of azide ion to isocyanides, a reaction also involving nitrilium ions, has been discussed in <69TL5081, 84CHEC-1(5)791>.



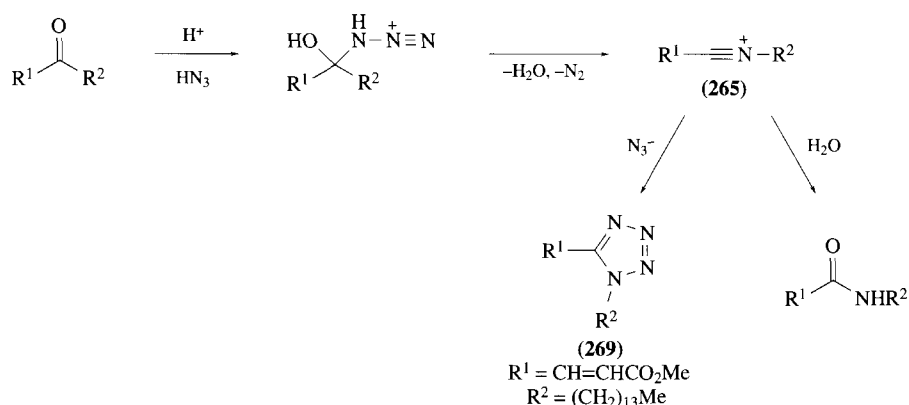
Scheme 42



Scheme 43

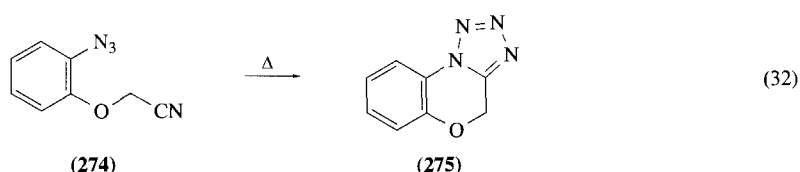
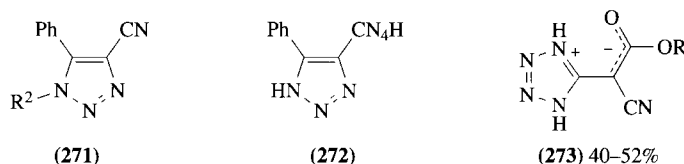
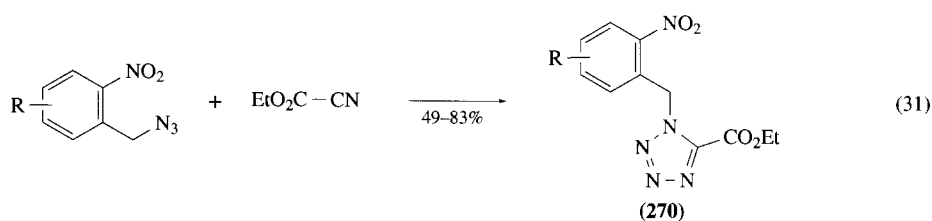
4.17.9.2.2 Cycloaddition of organic azides to $-\text{C}\equiv\text{N}$ systems

The 1,3-dipolar cycloaddition of organic azides with nitriles could give rise to two regioisomers. Since organic azides are Type II 1,3-dipoles on the Sustmann classification (approximately equal HOMO–LUMO gaps between the interacting frontier orbital pairs) the reactions could be dipole HOMO or LUMO controlled and the regioselectivity should be determined by the orbital coefficients for the dominant HOMO–LUMO interaction. Such systems show U-shaped kinetic curves in their



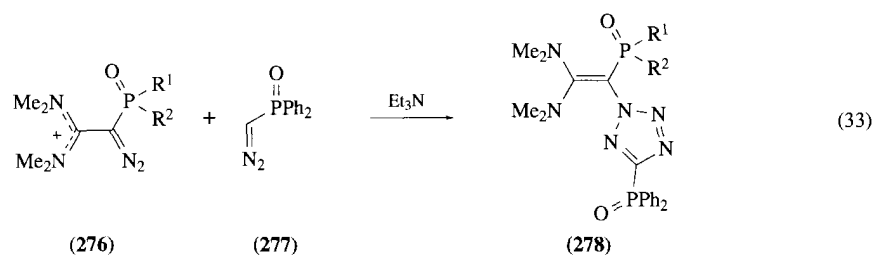
Scheme 44

response to substituent effects and the reactions are usually enhanced by all substituents (B-84MI 417-03). Hence mixtures of tetrazole isomers might be expected from such reactions. Experimentally these reactions are difficult and require forcing conditions. They have been observed mainly with strong electron-withdrawing groups on the nitrile in which case the products are 1,5-disubstituted tetrazoles. A series of *ortho*-nitrobenzyl azides gave good yields of the tetrazoles (270) when treated with ethyl cyanoformate in a pressure bomb at 145°C for 5–6 h (Equation (31)) (85JHC333). Polyfluoroalkyl nitriles also reacted with alkyl azides at 130–150°C to give 1,5-disubstituted tetrazoles in yields ranging up to 95% (62JOC2085). The reaction between trimethylsilyl azide and nitriles gave the 2-substituted tetrazoles but due to the lability of the TMS group these may not be the first-formed products (68CB743). On heating the phenyl acetylenic nitrile, $\text{Ph}-\text{C}\equiv\text{C}-\text{CN}$, with aryl and alkyl azides, R^2N_3 , at 110°C in toluene for 20–140 h the compounds (271) were formed in 35–52% yields. The same reaction with $\text{Al}(\text{N}_3)_3$ at 65°C gave (271; $\text{R}^2 = \text{H}$) (36.5%) and (272) (52.2%) (84ZOR142). The tetrazolium-5-(2-cyanoacetate) ylides (273) were obtained by stirring $\text{CH}(\text{CN})_2\text{CO}_2\text{R}$ with trimethylsilyl azide in chloroform at ambient temperatures for 72 h (93S873). Intramolecular cycloadditions of organic azides and nitriles are experimentally easier reactions, a feature which is mainly due to the favorable entropy factor as shown by the easy thermal conversion of the azide (274) to the tetrazole (275) (Equation (32)) (83JCR(S)202). *N*-Methyl nitrilium salts prepared from nitriles and methyl triflate, gave cycloadditions with methyl azide at 0–5°C which produced 1,4-dimethyltetrazolium salts (92LA581).



The reactions of covalent azides with $-\text{C}=\text{N}-$ systems have been discussed (77AHC(21)323,

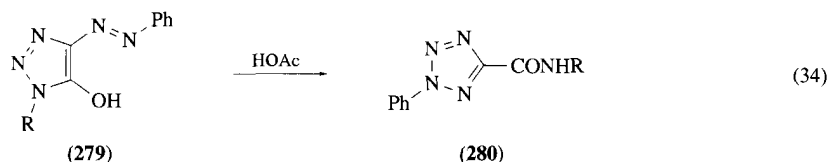
84CHEC-I(5)791). Organic azides add across the —N=C— bond of isocyanates to give 1,4-disubstituted tetrazolin-5-ones <73JOC675>. There are few examples of cycloadditions of organic azides with imine systems but aryl azides containing strong electron-withdrawing groups undergo cycloadditions with aldehyde hydrazones under basic conditions to give 2,5-disubstituted tetrazoles along with the arylamine fragment <68JHC565, 68T3787, 80MI 417-02>. This reaction was first reported by Dimroth and Merzbacher <07CB2402, 10CB2899>. The reactions of HN_3 and organic azides with isothiocyanates are complicated and give mainly 1,2,3,4-thiatriazoles and other sulfur heterocycles <74JA3973, 77JOC1159, 84CHEC-I(5)719>. Covalent metallic azides such as trialkyltin azides add across the —N=C— bond and it has been shown that the products are 5-tinhiotetrazoles arising from tin migration and not 1,4-disubstituted tetrazol-5-thiones as previously thought <92JOM(430)25>. The new substituted 2-vinyl-5-phosphoryltetrazoles (**278**) have been obtained from the formamidine substituted (diazomethyl)phosphoryl compounds (**276**) and the phosphoryldiazomethanes (**277**) (Equation (33)) in an interesting reaction. An x-ray crystal structure has been reported on compound (**278**; $\text{R}^1 = \text{R}^2 = \text{Ph}$) <85CB2105>. Base-induced dimerization of α -diazoketones has been used to prepare 5-benzoyl-2-phenacyltetrazoles in earlier work <69CJC3997>.



4.17.10 TETRAZOLES FROM TRANSFORMATIONS OF OTHER RINGS

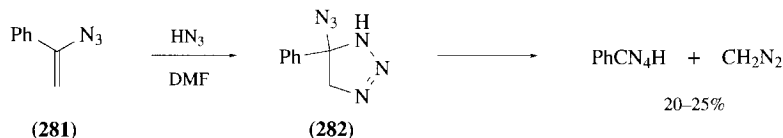
4.17.10.1 Tetrazoles from 1,2,3-Triazoles

Most transformations of lower azoles into tetrazoles involve azido substituents with the exception of the rearrangements of substituted 5-amino-1,2,3,4-thiatriazoles. 5-Azido-1,2,3-triazoles with a CO_2Me group at C-4 rearranged at 50–70°C in organic solvents into the 5-diazoester substituted tetrazoles (**166**) (Scheme 25). The reaction is enhanced by conjugated electron-withdrawing R substituents at the triazole N-1. The CO_2Me group at the triazole C-5 appears to be essential and with aryl groups at C-5 nitrogen evolution and ring opening to triazenes occurred <85T4621, 88T3617, 89T749, 90BSB213, 90BSB281>. Tetrazoles of type (**166**) are obtained in 60–75% yields from these reactions in solvents such as chloroform, benzonitrile and acetonitrile <89T749>. Treatment of 5-azido-1,2,3-triazole with NaH in DMSO gave an anion which rearranged to the 5-diazomethyl-tetrazole anion and this could be methylated to give N-methyltetrazoles <88CC1144>. The 1,2,3-triazoles (**279**) with a phenylazo group at C-4 rearranged into 2-phenyl-5-carboxamido tetrazoles (**280**), on recrystallization from acetic acid (Equation (34)) <58ACS1236>. The 5-azido-1,2,3-triazoline (**282**), generated by heating α -styryl azide (**281**) with $\text{NaN}_3\text{—HOAc}$ in DMF on a steam bath for 72 h, underwent a retro 3 + 2 elimination of diazomethane and gave low yields of 5-phenyltetrazole in the first transformation of an azidotriazoline to a tetrazole (Scheme 45) <90SL349>.



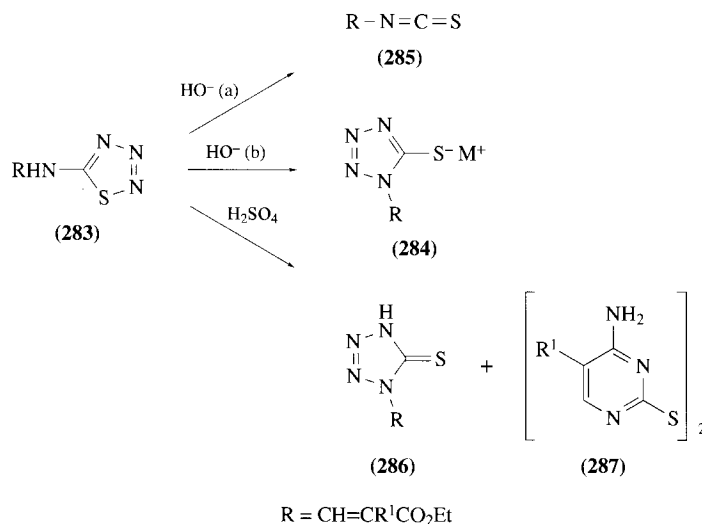
4.17.10.2 Tetrazoles from Other Azoles

Treatment of 5-substituted amino-1,2,3,4-thiatriazoles (**283**) with aqueous base results in competitive rearrangement to 5-thiotetrazoles (**284**) and fragmentation to isothiocyanates (**285**) and



Scheme 45

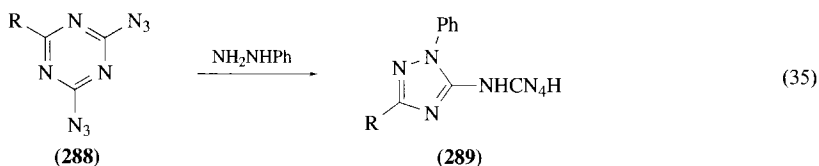
azide ion (Scheme 46) $\langle 57\text{CJC}832, 67\text{JOC}3580 \rangle$. The use of solid $\text{Ba}(\text{OH})_2$ suspended in toluene containing HMPA or the use of strontium metal (avoiding OH^-) has given 80% yields of tetrazole sulfur-metal complexes from this reaction and the degradation path (a) was found to be due to excess OH^- . In these types of reactions the nature of the counterion complexation to the azole anion is of major importance $\langle 92\text{CC}1152 \rangle$. The ring transformation has also been achieved under acidic conditions with the substrates (**283**; $\text{R} = \text{CH}=\text{CR}'\text{CO}_2\text{Et}$) which gave low yields of tetrazoles (**286**) accompanied by the disulfide (**287**) (Scheme 46) $\langle 93\text{JPR}190 \rangle$. Flash vacuum pyrolysis of 5-phenyl-3-azido-1,2,4-oxadiazole, which gives benzoyl cyanide, is considered to pass through a transient benzoyl pentaazafulvene species which fragments to the isocyanide (see Scheme 29) $\langle 82\text{TL}121 \rangle$. Earlier work on base promoted ring transformations of some oxygen azole systems to tetrazoles has been discussed in $\langle 84\text{CHEC-I}(5)791 \rangle$. Diazotizations of 3-amino-4-azido-furazan with NaNO_2 in $\text{AcOH}-\text{Et}_2\text{O}$ gave the sodium salt of 1-hydroxy-5-cyanotetrazole (51%) $\langle 88\text{KGS}1666 \rangle$.

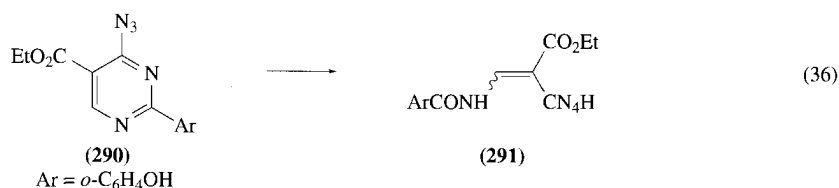


Scheme 46

4.17.10.3 Tetrazoles from Azines

A number of azido azine systems display transformations into tetrazoles with degradation of the azine ring. Thus heating of the diazido *s*-triazines (**288**; $\text{R} = \text{MeO}, \text{EtO}, \text{NH}_2$) with hydrazine or phenylhydrazine in ethanol gave the 5-triazolylaminotetrazoles (**289**) (Equation (35)) $\langle 93\text{MC}49 \rangle$. The 4-azido pyrimidine derivative (**290**) underwent spontaneous solid phase transformation into the tetrazole (**291**) in the dark at room temperature (Equation (36)) $\langle 93\text{MC}61 \rangle$. A similar type of transformation occurred on treatment of 4-chloro-5-nitropyrimidines with sodium azide in DMF giving products of type (**291**; NO_2 for CO_2Et) $\langle 94\text{TL}103 \rangle$.





4.17.11 PREFERRED ROUTES TO TETRAZOLE CLASSES

In the synthesis of particular tetrazole types, there is often only a limited choice as to the route but choices do exist in the use of reagents and solvents.

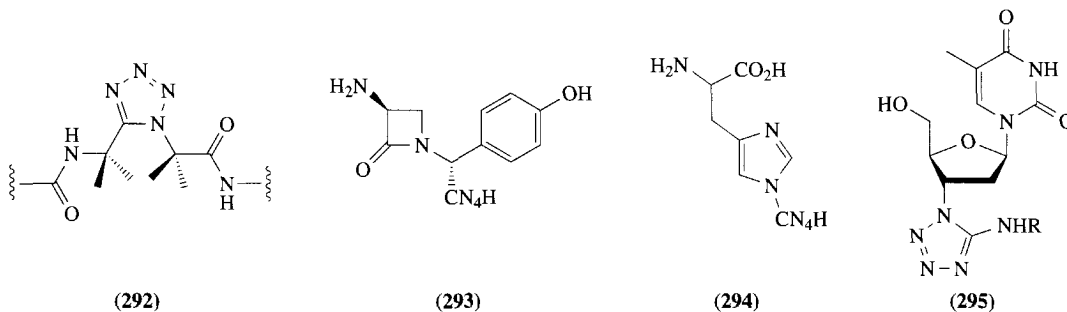
The main route to 5-substituted tetrazoles is via the nitrile/azide reaction (Section 4.17.9.2.1) (Schemes 42 and 43). 1-Substituted tetrazoles are available from isocyanides and HN₃ under acid catalysis <69TL5081> and also by a new route from primary amines triethyl orthoformate and NaN₃ in acetic acid <90KGS1528> (Section 4.17.9.1.1). 1,5-Disubstituted tetrazoles are available from imidoyl azides (Section 4.17.9.1). In the future amides and ketones which are halogen free may be the preferred precursors and the methods developed by Duncia *et al.* <91JOC2395> and Thomas <93S767> for one-pot conversions of amides to 1,5-disubstituted tetrazoles could become the main routes. The most common 2,5-disubstituted tetrazoles are 2,5-diaryl derivatives (**261**; R¹, R² = aryl) and the best entry to these is via the Bamford–Stevens reaction of formazans prepared by coupling aryl diazonium salts with arylsulfonylhydrazones of aromatic aldehydes (Scheme 41) <73CL1071>. 2-Substituted tetrazoles are best prepared either by direct 2*N*-substitution of tetrazole (Section 4.17.5.3) or by decarboxylation of 2-substituted 5-cyano or carboxy tetrazoles <76ZC90>.

4.17.12 APPLICATIONS AND SPECIAL COMPOUNDS

4.17.12.1 Tetrazole Modifications and Mimicry of Biological Molecules

The tetrazolic acid group, —CN₄H, has similar acidity to the carboxylic acid group, —CO₂H, and is almost isosteric with it. Of the two, the tetrazolic acid group is metabolically more stable and hence replacement of CO₂H groups by CN₄H groups in biologically active molecules is an area of major interest. It has been found that when a 1,5-disubstituted tetrazole is incorporated into a peptide link (e.g., (**292**)) in place of a *cis*-amide, 88% of the conformations of the normal peptide are still allowed <88JA5875>. A number of tetrazole peptide analogs incorporating this tetrazolo-peptide link (**292**) have been prepared <87JOC2051, 87MI 417-03>. Analogs containing a terminal tetrazolate species in place of carboxylate competed effectively with the normal peptide for the secondary binding site of carboxypeptidase A <87MI 417-03>. New examples of tetrazole analogs of amino acids including the 3-aminocardicinic acid derivatives (**293**) have been reported <90TL1755>. The tetrazole ring has been used to modify the heme environmental structure of myoglobin by incorporating the *N*-tetrazol-5-yl histidine unit (**294**) in which the tetrazole ring was formed from the *N*-cyano compound and azide ion. The presence of the tetrazole ring caused the heme plane to tilt by 0.8° and the pyrrole nitrogen plane by 4.8° and an x-ray crystal structure of the modified heme has been reported <91JA1826, 93MI 417-01>. The 3'-tetrazolo-3'-deoxythymidines (**295**) have been prepared from 3'-azido-3'-deoxythymidine (**295**; N₃ in place of tetrazole), which is the only approved drug for AIDS treatment. The azido group was converted to the 5-substituted amino tetrazole moiety via a phosphine imine, Ph₃P=N—, which was in turn converted to a carbodiimide by treatment with isocyanate (RNCO), and then subjected to addition of HN₃ in toluene <92S358>. A variety of tetrazolyl nucleosides have been prepared from glycosylazides <86LA1736>. Tetrazoles have found a role as activators of phosphoramidite monomers in the coupling reaction of the phosphoramidite with the free 5'-hydroxy function of an immobilized oligonucleotide, which is the essential step in the synthesis of deoxyoligonucleotides <84JOC4951, 87MI 417-04, 87TL3643, 88MI 417-03, 93JCS(P1)2291>. Three special features of the tetrazole are involved: (i) the acidic tetrazole protonates the nitrogen of the phosphorus–nitrogen bond in the phosphoramidite, (ii) the tetrazolate anion thereby generated is nucleophilic enough to displace the amine giving a phosphorus bonded to the tetrazole-1 position, and (iii) the tetrazole is then a good enough leaving group to allow for the subsequent formation of the new phosphorus–oxygen bond <88MI 417-03>. The tris(tetrazolyl enolate)

iron(III) complexes (**10**) (Section 4.17.1.2) are metalloporphyrin analogs. They have been used for aerobic epoxidation of alkenes with molecular oxygen in the presence of isobutyraldehyde as an electron source in a process analogous to cytochrome P-450 <93TL6033>.



4.17.12.2 Drug Applications

The earlier medicinal applications of tetrazoles have been reviewed <B-80MI 417-03, 84CHEC-I(5)791> and a tabulation of biologically active tetrazoles has been provided <77AHC(21)323>. As judged by the number of patent claims and publications, interest in the medicinal applications of tetrazoles continues to grow rapidly. A selected outline is provided in Table 9. The medicinal effects of replacing $\text{—CO}_2\text{H}$ groups by tetrazole are not predictable and need to be assessed in each case. Medicinal activity may be enhanced, reduced or eliminated.

4.17.12.2.1 Antihypertensive activity; angiotensin II antagonists

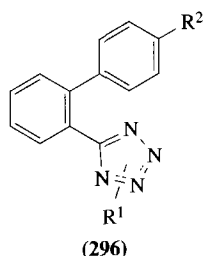
A wide range of tetrazole derivatives has been patented for antihypertension activity and as angiotensin II receptor antagonists. These are claimed to be useful for treating congestive heart failure and preventing cardiac hypertrophy (Table 9, entries 1–17). Among the active compounds, the *ortho*-tetrazolyl-substituted biphenyl structure (**296**) is prolific. Some synthetic routes to this general type of system are shown in entries 18 and 21 in Table 8. Two routes to the compound known as DuP532, a potent angiotensin II receptor antagonist, have been described, one of which is suitable for large-scale synthesis <93JOC4642>. Many of the active structures (**296**) have a substituted imidazole as R^2 including DuP532 but a variety of R^2 substituents in (**296**) may also be found in these molecules (Table 9). A range of other tetrazolyl substrates, including 3-(tetrazol-5'-yl)thiophenes and 2-(*ortho*-tetrazol-5'-ylphenyl)furans have also been claimed as antihypertensive agents <92EUP510812, 92EUP514192>.

4.17.12.2.2 Antiallergic activity

The tetrazole ring features in a range of antiallergic substances which act by inhibiting the allergic histamine release (Table 9, entries 18–22, 32, 34, 39). Examples of these structures include the series (**192**), (**297**) and (**298**). Usually with these compounds, the antihistamine effect is greater for the tetrazole analog than for the carboxylic acid counterpart. A new synthesis of compound (**192**) (MDL-427) has been reported (Scheme 30) <89JHC97>. In the tetrazolylpyrazine series, (**298**), the activity is greatly increased if a spacer group, —CONH— or —NHCO— is placed between the pyrazine and the tetrazole substituent <90CPB201>. 2-Tetrazolylpyridine analogs of (**298**); and nitrogen analogs of the chromone system (**297**) are also active <83JMC1499>, 3-(tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones show high levels of antiallergic and bronchodilator activity <82JMC864>.

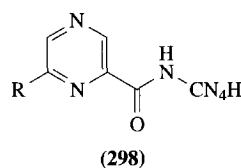
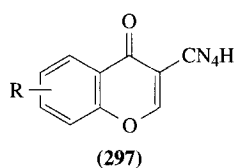
Table 9 Applications of tetrazole derivatives.

No.	Application	Tetrazole structure/tetrazole containing molecular type	Ref.
1	Angiotensin II (A-II) antagonist	(296) R ² , substituted imidazol-1-yl	93JOC4642
2	Hypertension, heart failure	(296) R ² , substituted imidazol-1-yl	93USP5218125
3	A-II antagonist	(296) R ² , substituted imidazol-1-yl	93EUP547514
4	A-II antagonist	(296) R ² , O-quinoxaline	93JMC2335
5	Hypertension, atherosclerosis	(296) R ² , R-imidazol-1-yl	93EUP535463
6	A-II, blood pressure	(296) R ² , CH ₂ -indole	93USP5212195
7	A-II antagonist	(296) various	93JAP0532661
8	Hypertension, heart failure	(296) R ² , CH ₂ -pyrrolo	93EUP539086
9	A-II antagonist	(296) R ² , CH ₂ -4-N-1,2,4-triazole	93JMC2558
10	A-II, hypertension	(296) R ² , CH ₂ -N-pyrimidine	93EUP547442
11	A-II antagonist	(296) R ² , acylimidazol-1-yl	93USP5219856
12	Hypertension	2-(<i>o</i> -CN ₄ H)-phenylbenzofuran	92EUP514192
13	Hypertension	3-(tetrazol-5-yl)thiophenes	92EUP510812
14		(296) R ² , CHO, alkyl	93EUP550313
15	A-II antagonist	(296) R ² , R-imidazol-1-yl	93EUP535465
16	A-II antagonist	(296) R ² , CH ₂ OR; CH ₂ NR	93EUP540356
17	A-II antagonist	2-(tetrazol-5'-yl) indoles	93EUP547556
18	Antiasthma, antiallergy	(192)	86JMC2403
19	Antihistamine	(298)	90CPB201
20	Antiallergic	Pyrimidobenzothiazole	82JHC864
21	Antiallergic	2-Pyridinecarboxamidotetrazole	83JMC1499, 88JAP63150277
22	Antiallergic	(297)	77JMC141, 93JCR(S)462
23	Antiulcer agent	Pyrido [1,2- <i>a</i>]pyrimidinones	93MIP9304065
24	Muscarinic, analgesic	1,5-Di(fatty alkyl)tetrazole	93USP5200419
25	Muscarinic	Quinuclidine-3-tetrazole	92JMC1280
26	Anticonvulsant	5-(Decahydroisoquinolinyl ethyl)tetrazole	93JMC2046
27	Anticholesterol	Substituted 3-(tetrazol-5-yl) 1,3-butadienes	92MI 417-03
28	HMG-CoA reductase inhibitor	Substituted 3-(tetrazol-5-yl) 1,3-butadienes	92BMC1085
29	Anticholesterol	5-(Amidoalkyl) tetrazoles	93MIP9304052
30	Leukotriene antagonist	Tetrazolyl-aromatic thioethers	89EUP298583
31	Leukotriene antagonist	Tetrazolyl-2-quinolinyl methoxy aryl ethers	90JMC1186
32	Antiallergic	N-thiazolyltetrazole carboxamides	89EUP321115
33	Inflammation inhibitors	ArOCH ₂ -tetrazole	90USP4945099
34	Antiallergic	ArCH=CHCONHCN ₄ H	90EUP384450
35	Bronchodilators, TXA ₂ receptor antagonists	5-Alkenyltetrazoles	90EUP352083
36	Monoamine oxidase inhibitors	5-Heteroaryl tetrazoles	89FRP2631827
37	Drug fungicides	5-Aryl-1-substituted aminomethyl tetrazoles	89CZP261442
38	Antihypertensives	(296) (R ¹ = H; R ² = CH ₂ X)	88EUP291969
39	Antiallergic	Phenoxymethylphenyltetrazole	88EUP288305
40	Leukotriene antagonist	ArO-(CH ₂) ₄ CN ₄ H	85EUP132367
41	Antiviral activity	H ₂ PO ₃ CH ₂ CN ₄ H	85MI 417-01
42	Angiotensin II antagonist	Biphenyl tetrazoles	93MI 417-02
43	Antiinflammatory	Indanylmethyl tetrazoles	85MI 417-02

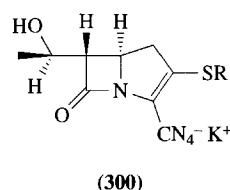
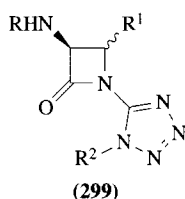


4.17.12.2.3 Antibiotic and other drug activity

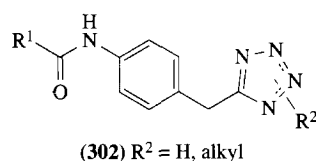
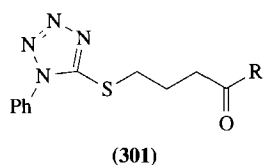
Azetidin-2-ones with general structure (299) have been synthesized from the reaction of 5-aminotetrazole with amino acid esters <84TL911> and from addition of glycine enolates to *N*-(tetrazol-5-yl)imines <84TL3849>. A number of these compounds displayed moderate to potent



activity against a variety of bacteria. Conversion of the C-3 carboxyl group of the penam antibiotic amoxycillin to a tetrazol-5-yl group resulted in increased β -lactamase stability and enhanced activity against many bacterial strains $\langle 76AAC132 \rangle$. A total synthesis of a series of the 3-(tetrazol-5-yl)carbapenems (**300**) has been reported. A major difficulty centered on protection and deprotection of the tetrazole ring and a new tetrazole protecting group, (((*p*-nitrobenzyl)carbonyl)oxy)methyl, was successfully used $\langle 84JA1808 \rangle$. The 1-substituted-5-thiotetrazole group has been incorporated into a series of 1,2-disubstituted carbacephem antibiotics $\langle 93SL139 \rangle$.



A range of tetrazole derivatives has been explored for antituberculous activity and the disulphide (**209**; Ph for Me) showed significant activity comparable to that of *p*-aminosalicylates $\langle 85MI 417-03 \rangle$. The 1-phenyltetrazole-5-thio group is also present in the antiulcer agents (**301**) and compound (**301**; R = cyclohexyl) is the most potent $\langle 89CPB958 \rangle$. A wide range of compounds with the tetrazol-1-yl acetic acid structure (**224**) has been claimed as aldose reductase inhibitors for treatment and prevention of diabetes complications $\langle 93EUP528277, 93JAP0543574 \rangle$. The tetrazole derivatives (**302**; R¹ = perfluoroalkyl) represent a new structure which is active against the noninsulin-dependent diabetes mellitus (NIDDM). Following the withdrawal of biguanides in 1977, these are the first examples of oral antidiabetics not containing thiazolidinedione or sulfonylurea units. Glucose lowering activity depended on the length of the perfluoroalkyl substituent R¹ and was retained when the tetrazole *N*-substituent R² was H, Me, or benzyl either at N-1 or N-2 $\langle 89JMC11 \rangle$. Examples of other medicinally active molecules containing the tetrazole ring are listed in Table 9 (entries 23–43). These include antiulcer agents, analgesics, muscarinic agents, anticonvulsants, anticholesterol agents and reductase and acyltransferase inhibitors. Also a new series of tetrazol-5-methylsulfonamides has been claimed for antihypocholesterolemic activity $\langle 93USP5239082 \rangle$.

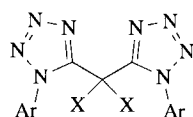


4.17.12.3 Other Biological Applications

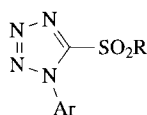
4.17.12.3.1 Agriculture

The main uses for tetrazoles in agriculture are as plant growth regulators, herbicides and fungicides. With compounds which affect plant growth, small changes in structure can give rise to either growth stimulation or inhibition. The bis(tetrazolyl)dichloromethane (**303**; Ar = *o*-MeC₆H₄) acted as a growth inhibitor for oats and lettuce while compound (**304**; Ar = *p*-BrC₆H₄) acted as a stimulant for growth $\langle 88MI 417-04 \rangle$. Some 1*N*-substituted-5-(tetrazol-5'-yl)imidazoles have been patented as growth inhibitors for cereals and soya bean $\langle 86GEP3514116 \rangle$. A number of 1-aryltetrazole-5-thio derivatives display fungicidal activity including 1-aryltetrazole-5-sulphones (**305**) which are active against *Plasmopara viticola* $\langle 89CAT263, 90MI 417-05 \rangle$. The tetrazole-5-thio group when bonded by the

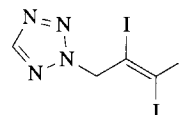
sulfur atom to C-5 of a 3-chloro-1,2,5-oxadiazole ring has been patented as a pesticide and fungicide <88GEP3640153> and 1*H*-tetrazole has been added as a stabilizer to other active pesticides <90GEP4009141>. A number of 5-alkenyltetrazoles including fatty alkenyltetrazoles <91MI 417-03> and the 5-(aminovinyl)tetrazole series (172) (Scheme 27) <89EGP268692> have been claimed as pesticides, fungicides and growth regulators. A range of 1*N*-substituted tetrazol-5-yl ethers are claimed as active herbicides <85EUP149269, 88JAP63174977>. For example, 1-(3-trifluoromethylphenyl)-5-phenoxy-1*H*-tetrazole, when applied as a soil drench or a foliar spray, controlled a wide range of weeds <85EUP149269>. Substituted *m*-(tetrazol-5-yl)phenol ethers have also been patented as herbicides <85GEP3427606>. A number of 1,5- and 2,5-disubstituted tetrazole systems with an R-CH₂ group at C-5 and/or a ring nitrogen are active as agricultural and drug fungicides and among these the 2*N*-(triiodoallyl) tetrazole (306) was particularly potent <84EUP107859, 87JMC552>.



(303) X = Cl
(304) X = H



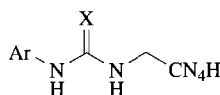
(305)



(306)

4.17.12.3.2 Sweeteners

Tetrazole surrogates of carboxylic acids have been extended into the area of artificial sweeteners <90JPS826, 91MI 417-04>. As with many biological responses involving tetrazoles, the property was enhanced or reduced relative to the corresponding carboxylic acid. With some tetrazolyl guanidines (307; X = NR) potencies of up to 30000 times that of a 2% sucrose solution were discovered while with others, depending on R and Ar, no sweetness was encountered. Further understanding of structure-activity relationships in the complicated phenomenon of sweetness has arisen from comparisons of the series (307) with the carboxylic acid analogs <90JPS826>. A range of the tetrazolyl guanidines (307; X = NR) has been patented as sweeteners <89EUP299533>.



(307) X = O, S, NR

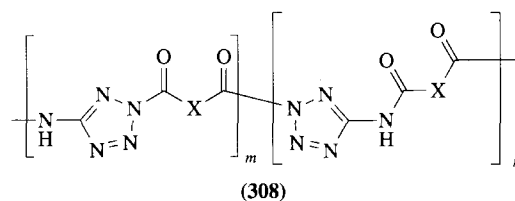
4.17.12.4 Nonbiological Applications

4.17.12.4.1 Photography and photoimaging

5-Substituted tetrazoles are added to silver halide photographic materials as stabilizers to prevent fogging during storage <87EUP241107, 88JAP6340140>. Substituted 1-aryl-5-thiotetrazole derivatives are used as additives for silver halide color photographic materials. They cause improved sharpness, better color grain and color reproduction <89JAP01142722>. Widely different substituents are employed on the tetrazole-5-sulfur atom including substituted naphthalenes <86EGP238281> and substituted pyrroles <89EGP267816>. The reduction of tetrazolium salts is also used for intensification of silver images in photographic materials <90MI 417-06>. 5-Substituted aminotetrazoles as additives are useful for stabilizing images and preventing peppers (small high-density dot stains) on lithographic printing plates <84JAP5948763> and also for stabilizing copper images on silver-free photoimaging materials <85MI 417-04>. 5-Aminotetrazole has been used for stabilizing silver photographic images <90EUP371359>.

4.17.12.4.2 Polymers

Free-radical copolymerization of 1-vinyltetrazole with styrene, methyl methacrylate and acrylonitrile has been studied following earlier reports that homopolymers of 1-vinyltetrazole are insoluble, nonfusible materials (87MI 417-05, 88MI 417-05). In the thermal degradation of poly-5-vinyltetrazole and poly(2-*t*-butyl)-5-vinyltetrazole, the tetrazole rings are degraded first. At slow heating rates, the 2,5-disubstituted tetrazole polymer evolves N₂ from the ring, giving a nitrilimine in a normal ring degradation (91MI 417-05) but at higher heating rates a second degradation path involves a competing removal of the *t*-butyl group (91MI 417-05). Poly-5-vinyltetrazole degrades by loss of HN₃ or ring opening to an imido-yl azide followed by N₂ evolution (90MI 417-07). A number of tetrazole polymers with general composition (308) were obtained by condensation of 5-aminotetrazole in *N,N*-dimethylacetamide with bis(acid chlorides), ClCO—X—COCl, in which X was a vinylene or *p*-phenylene group (85KGS1690).



4.17.12.4.3 Explosives and fuels

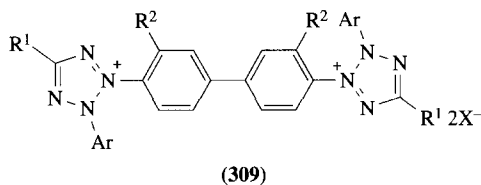
There has been a long interest in tetrazoles as components of explosives and rocket fuels (84CHEC-1(5)791). New areas of application include the use of tetrazole derivatives as fuel additives to increase octane ratings and the use of tetrazoles for explosive rapid expansion of air-bags with safe nonpoisonous nitrogen dominated gas mixtures. Thus a number of explosive mixtures containing 20–40% by weight of 5-aminotetrazole with various oxidizers and some other reducers have been patented as inflator gas generators with emphasis on the high nitrogen content and nontoxic nature of the gases produced (90JAP02225389, 90JAP02184590, 92USP5084118). Addition of 5-alkyl and 1,5-dialkyltetrazoles at 500 ppm to diesel fuel gave increased fuel performance and the tetrazoles were about 30% more effective than alkyl nitrate additives (86USP4632674). Fatty amido derivatives of 5-, 1- and 2-aminotetrazoles have been patented as anticorrosion additives for gasoline–ethanol fuel mixtures (84USP4445907).

5-Nitrotetrazole and azotetrazole, as well as a wide variety of their metallic salts, continue to be developed as the main constituents of detonators and primers in combination with oxidizers such as KClO₃, NaClO₄ and others (85FRP2555985, 86USP4566921). Because of these applications, the combustion reactions and mechanisms of tetrazole derivatives have received considerable attention. (Section 4.17.4.2). Rapid thermolysis of 1,5- and 2,5-diaminotetrazoles involves two competitive pathways, one giving HCN, NH₃, and N₂ and the other giving NH₂CN, NH₃, and N₂ (91MI 417-06). The burning rate of 5-substituted tetrazoles is controlled by Hammett σ -values of the 5-substituents (91MI 417-02). Several tetrazole derivatives including 5-amino-1-vinyl-tetrazole, poly(5-vinyltetrazole) and copper complexes of tetrazoles are reported to undergo self-propagating thermolysis (85DOK(29)824).

4.17.12.4.4 Miscellaneous applications

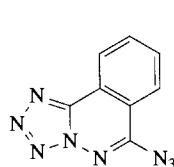
The ditetrazolium salts (309) have been patented for use in electrochromic electrodes which are used in display devices (89JAP01230026) and tetrazolium salts have also been developed for cell bioassays for neurotoxins active on voltage-sensitive sodium channels (93MI 417-03). Tests for inhibition of corrosion of zinc and brass carried out on 5-aminotetrazole showed it to be ineffective relative to other azoles (86MI 417-01). A number of tetrazoles including the 5-amino, 5-methyl, and 5-phenyl derivatives have been separately incorporated into surfactants used for corrosion inhibition with copper in water (91MI 417-07). Photopolymerizable resin compositions which are highly resistant

to heat and chemicals are made up of, (a) a thermoplastic binder, (b) a crosslinkable ethylenic monomer, (c) a photoinitiator, and (d) a tetrazole derivative. These resins are used for coating metal and other surfaces. A number of preparations have been patented <84JAP59125726, 90JAP0216566>.

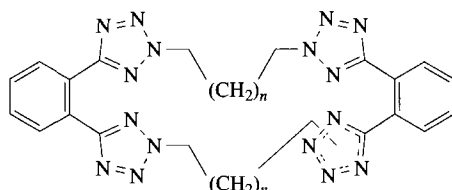


4.17.12.5 Special Tetrazole Compounds

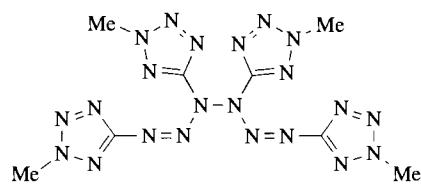
Tetrazole compounds synthesized by natural systems are very rare. Compound **(310)** has been isolated as a toxic metabolite of the dinoflagellate *G. breve* which has been implicated in the production of toxic red tides along the Gulf Coast of Florida. Its x-ray crystal structure has been reported <85AX(C)1199>. The tetrazole ring has begun to appear in macrocycles, a range of ditetrazolophanes have been reported by Ried and co-workers <88T3399, 88CZ385, 89LA497, 89CZ384>. A number of tetratetrazolomacrocycles including tetratetrazolophanes such as **(311)** and the N-1, N-2-isomers have been described <92CC1481, 94JCR(S)148>. Studies of the metal-complexing capabilities of these systems are ongoing and an x-ray crystal structure of compound **(311)** ($n = 6$) shows the tetrazole azo linkages on the inside of the cavity <94UP 417-01>. Finally, the tetratetrazolyhexazan **(312)** should probably be classified as a special compound, it is thermally stable but shock sensitive <82JCR(S)183>, with the potential to decompose to 11 molecules of N_2 , four methyl radicals and four atomic carbons it should have prospects as a fuel additive.



(310)



(311)



(312)

4.18

Oxatriazoles

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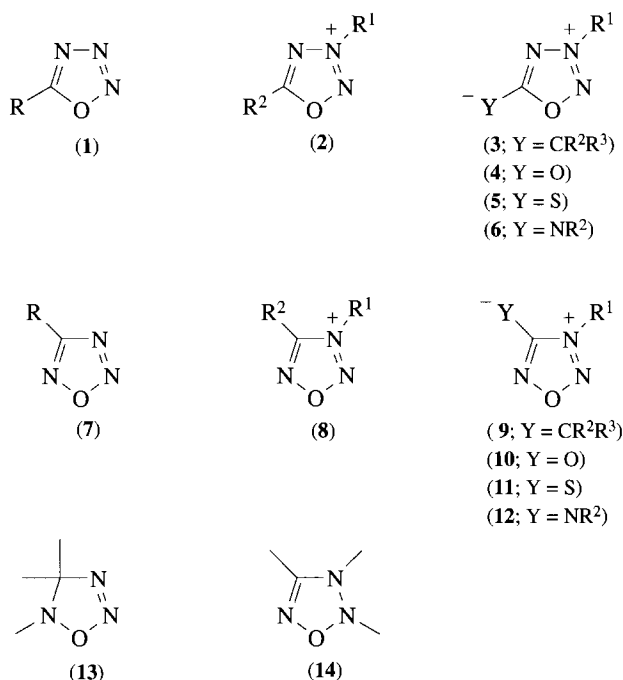
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4.18.1 INTRODUCTION

Two types of nuclei with an oxygen and three nitrogen atoms are possible, namely 1,2,3,4-oxatriazoles (**1**) and 1,2,3,5-oxatriazoles (**7**). The neutral aromatic species have not yet been reported but 1,2,3,4-oxatriazolium salts (**2**) and mesoionic species (**3**)–(**6**) are known. 1,2,3,5-Oxatriazolium salts (**8**) and mesoionic compounds (**9**)–(**12**) are not yet known but 1,2,3,5-oxatriazolines (**13**) and (**14**) have been reported. The two types of oxatriazoles will be discussed in two separate sections.

4.18.2 1,2,3,4-OXATRIAZOLES

The synthesis of mesoionic oxatriazoles was reported as early as 1896 <1896CB2161>, but the structure was first proved in 1964 <64JCS906>. The original method of preparation is still in use, but alternative procedures have been developed. Activity in the field peaked in 1979 and in the period



1980–1994 a limited number of publications have appeared. The mesoionic species possess pesticidal and herbicidal properties and they can display hypotensive, antiplatelet, fibrinolytic, thrombolytic, or bronchiolytic activity.

The mesoionic compounds can be named in several ways. The systematic name for structure (4) is a 3-substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide. Similarly, structure (5) is named a 3-substituted anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide, and structure (6) a 3-substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide. Frequently used names for structure (4) are 3-substituted 5-hydroxy-1,2,3,4-oxatriazolium hydroxide inner salt (*Chemical Abstracts*), 3-substituted 1,2,3,4-oxatriazol-5-ylidene oxide, or 3-substituted 1,2,3,4-oxathiazol-5-olate. For practical purposes, the term mesoionic 1,2,3,4-oxatriazol-5-one is often used. Analogously, (5) and (6) are named mesoionic 1,2,3,4-oxatriazol-5-thione and mesoionic 1,2,3,4-oxatriazol-5-imine, respectively.

4.18.2.1 Theoretical Methods

4.18.2.1.1 Neutral aromatic 1,2,3,4-oxatriazoles

While the neutral 1,2,3,4-oxatriazoles (1) still await synthesis, some of their properties have been predicted by theoretical calculations. AM1 calculations combined with a principal component analysis loading data from other related heteroaromatics have been used to estimate geometric characteristics, aromaticity, energy of formation, and ¹⁵N chemical shifts <90JPR885>. The oxatriazoles (1) and (7) and the 1,2,3,5-thiatriazoles, which also have not been prepared, are calculated to be in the group with the lowest classical and magnetic aromaticity.

4.18.2.1.2 Mesoionic 1,2,3,4-oxatriazoles

For 3-methyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (4; R¹ = Me) electron populations, charge densities, and orbital energies, and dipole moment have been calculated by using different semiempirical CNDO/2 methods and *ab initio* calculations (PEMCSCF) at different levels <89IJQ465>. The π -electrons are found to be highly delocalized and the compound is highly polar.

The best calculation method indicates that N-2 is slightly positive while N-3 and N-4 are electron rich. The methyl carbon is nearly neutral. Resonance diagrams of the calculated primary configuration and the secondary structure give information about bond orders and orbital overlap.

4.18.2.2 Experimental Structural Methods

The cyclic structure of the mesoionic 3-substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) has been established through their dipole moments, mass spectra, x-ray spectra, and ^{13}C and ^{15}N NMR spectra.

4.18.2.2.1 NMR spectroscopy

The ^1H NMR signals from substituents give no inherent information about the ring system but the ^{13}C , ^{14}N , ^{15}N , and ^{17}O chemical shifts and the linewidths of the ^{14}N signals of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; $\text{R}^1 = \text{Ph}$) and 3-phenyl-anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide (**5**; $\text{R}^1 = \text{Ph}$) are characteristic and of diagnostic value (Table 1) <91BAP265>. The unambiguous assignment of the nitrogen signals was made by ^{15}N labeling of N-2. The ^{14}N NMR spectra give information about the charge distribution since positively charged nitrogen atoms give rise to narrow ^{14}N signals <88MRC1012>. The ^{15}N chemical shifts are related to those of similar mesoionic compounds by simple additivity rules. The spectra confirm the mesoionic structure and rule out alternative open-chain valence tautomers. The ^{13}C NMR shifts indicate that the phenyl and the oxatriazole rings are coplanar in (**4**; $\text{R}^1 = \text{Ph}$) and (**5**; $\text{R}^1 = \text{Ph}$). ^1H Chemical shifts for substituents in anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide (**5**) <79JCS(P1)732> and anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide (**6**) <79JCS(P1)736, 92MIP9213847, 94MIP9403442> have been reported.

Table 1 Carbon-13, nitrogen-14, nitrogen-15, and oxygen-17 chemical shifts (δ , ppm) of 1,2,3,4-oxatriazolium salts (**2**) and mesoionic 1,2,3,4-oxatriazoles (**4**).^a

Compound	O-1	N-2	N-3	N-4	C-5	Exocyclic O
(2 ; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{OEt}$)		22.3 (broad)	-62.9 (500)	-101.4 (broad)	188.7	
(4 ; $\text{R}^1 = \text{Ph}$)	360 (400)	-8.8 (905)	-71.6 (50)	-154.8 (865)	166.2	220 (100)
(5 ; $\text{R}^1 = \text{Ph}$)	398 (400)	12.9 (1200)	-64.5 (70)	-107.5 (1200)	193.4	

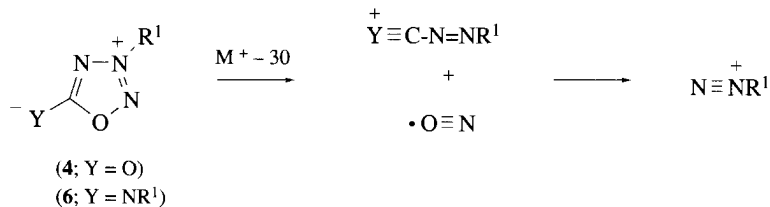
^aLinewidth of nitrogen-14 signals are given in parenthesis.

3-Phenyl-5-ethoxy-1,2,3,4-oxatriazolium tetrafluoroborate (**2**; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{OEt}$) has been analyzed by ^1H , ^{13}C , ^{14}N , and ^{15}N NMR spectroscopy in CDCl_3 <88MRC1012> and acetone- d_6 (Table 1) <91BAP265>. The ^1H NMR signals from substituents do not give specific information about the ring system, but the position of ^{13}C , ^{14}N , and ^{15}N NMR signals from the ring atoms are characteristic of the structure. The ^{13}C NMR data reveal that the phenyl and the oxatriazole rings are coplanar. The ^{14}N NMR spectra give information about the charge distribution since positively charged nitrogen atoms give rise to narrow ^{14}N signals <88MRC1012>.

4.18.2.2.2 Mass spectroscopy

The fragmentation of anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) and anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) in the mass spectrum follows the pattern characteristic

of mesoionic azoles <79JCS(P1)747> and is shown in Scheme 1. No molecular peak is observed in EI spectra <79JCS(P1)747, 83CC1388>. Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) give an additional peak of low intensity from the RO⁺ ion.



Scheme 1

4.18.2.2.3 IR spectroscopy

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) exhibit a strong C=O absorption at 1780–1805 cm⁻¹ <64JCS906, 79JCS(P2)533, 80JCS(P2)1437>. Thus, 3-aryl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**) with Me, Cl, NO₂, OMe or F substituents in the aryl group give rise to an absorption at 1785–1805 cm⁻¹ <82JMC1503, 83CC1388>. IR spectra recorded at higher resolution revealed that two C=O absorptions may be present in the 1790–1840 and the 1775–1795 cm⁻¹ ranges, respectively <81KGS1682>. The more electron-attracting the substituents on the phenyl ring, the further both absorptions are shifted to higher wave number. Signals in the 1515–1540 cm⁻¹ range have been attributed to a C=N bond and these signals shift to decreasing wavenumbers the more electron-attracting the substituents of the phenyl ring.

3-Substituted anhydro-5-thio-1,2,3,4-oxatriazolium hydroxides (**5**) display a strong C=S absorption at 1365–1375 cm⁻¹ <74JCS(P1)645>, while anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) show a strong C=N absorption at 1675–1680 cm⁻¹ <79JCS(P1)741>.

Hydrochlorides derived from 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) give rise to a characteristic C=N absorption at 1700–1720 cm⁻¹ <92MIP9213847>. In some cases a second absorption appears at 1730–1745 cm⁻¹. IR data for a series of anhydro-5-acetylamino-1,2,3,4-oxatriazolium hydroxides (**6**; R² = Ac) and anhydro-5-sulfonylamino-1,2,3,4-oxatriazolium hydroxides (**6**; R² = SO₂R) have been reported <92MIP9213847, 94MIP9403442>. The anhydro-5-acetylamino-1,2,3,4-oxatriazolium hydroxides (**6**; R² = Ac) display C=O absorptions below 1700 cm⁻¹, indicating that the carbonyl groups are highly polarized.

4.18.2.2.4 UV spectroscopy

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) are usually colorless. 3-Phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; R¹ = Ph) shows UV absorptions at λ_{max} = 203 nm (log ε = 4.06) and 268 (4.07) <81KGS1682>. The wavelength of the signals is influenced by substituents in the phenyl group <64JCS906> and in some cases only the 203 nm signal is observed <81KGS1682>. 3-Substituted anhydro-5-thio-1,2,3,4-oxatriazolium hydroxides (**5**) are yellow. The 3-phenyl substituted compound (**5**; R¹ = Ph) gives absorptions at 259 nm (4.34) and 394 nm (3.42) <79JCS(P1)732>. 3-Substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) are red. The 3,5-diphenyl substituted compound (**6**; R¹ = R² = Ph) absorbs at 265 nm (4.49) and 410 nm (3.40) <79JCS(P1)732>.

A series of 3-aryl-substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydrochlorides (**2**; R¹ = Ar, R² = NH₂) exhibited characteristic UV absorptions in the 265–300 nm range <92MIP9213847>.

4.18.2.2.5 Dipole moment

The dipole moment of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; R¹ = Ph) in benzene solution is 6.19 D (1 D = 3.336 × 10⁻³⁰ C m), a value close to that calculated for the 5-methyl analogue (Section 4.18.2.12) <81KGS1682>. Electron-attracting substituents in the phenyl group decrease the dipole moment.

The dipole moment of 3-phenyl-anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxide (**5**; $R^1 = \text{Ph}$) is 6.83 D. For substituted phenyl derivatives values in the range 5.1–7.9 D have been reported <79JCS(P1)736>. The dipole moment of 3-phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide (**6**; $R^1 = R^2 = \text{Ph}$) is 5.4 D. Values between 4.2 and 6.3 were found for derivatives substituted at the phenyl groups. With the same substituent at N-3, the dipole moment decreases in the series $5\text{-S} > 5\text{-O} > 5\text{-NR}$, a trend observed for other mesoionic azoles <78JCS(P1)600>.

4.18.2.2.6 X-ray crystallography

The structures of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**15**) and 3-phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide (**16**) (Figure 1) have been analyzed by x-ray diffraction methods. These compounds show the same structural features as those of the isoelectronic sydnone <76AHC(19)90>. Thus the central 5-membered ring is planar; the ring C—O bond length in (**15**) is relatively long; the exocyclic C—O bond in (**15**) and the exocyclic C—N bond in (**16**) correspond to a normal double bond. The two N—phenyl bond lengths in (**16**) (143.7 nm and 140.2 nm, respectively) indicate that there is only small, if any, conjugation between the two phenyl rings and the mesoionic ring.

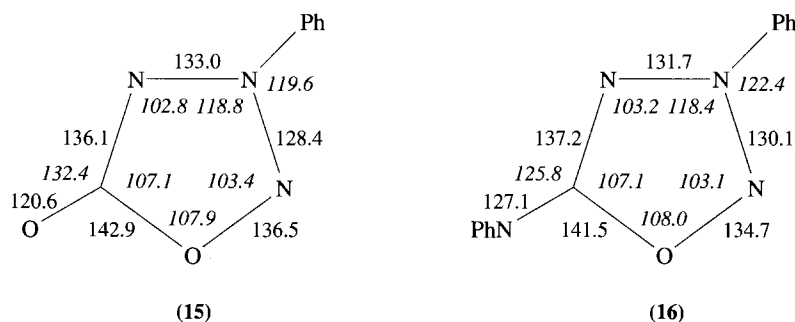


Figure 1 Bond lengths (nm) and bond angles (degrees; in italics) of mesoionic 1,2,3,4-oxatriazoles.

4.18.2.3 Thermodynamic Aspects

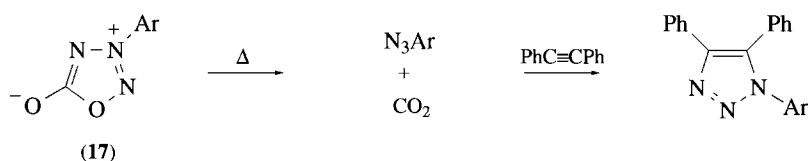
The mesoionic 1,2,3,4-oxatriazoles are crystalline, polar compounds which are usually recrystallized from methanol. Melting points are mid-range, frequently from 100°C to 150°C.

The basicity of 3-aryl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; $R^1 = \text{Ar}$) has been determined, $\text{p}K_{\text{BH}}^+$ being in the range 1.37–1.78 <82JCS(P2)701>. A $\text{p}K_{\text{a}}$ value of 6 has been estimated for anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide (**6**; $R^1 = \text{Ph}$, $R^2 = \text{H}$) <72ACS858>.

4.18.2.4 Reactivity of Fully Conjugated Rings

4.18.2.4.1 Thermal reactions and 1,3-dipolar cycloadditions

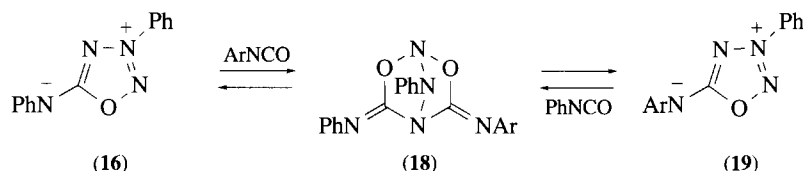
Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) are relatively stable at elevated temperatures under neutral and salt-free conditions. However, prolonged heating of (**17**) in the presence of lithium chloride gives rise to elimination of carbon dioxide with formation of an azide which can be trapped by 1,3-dipolar cycloaddition to an alkyne (Scheme 2) <68CB536>.



Scheme 2

The stability of 5-substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) depends on the nature of the substituent R^2 and decreases from very stable to moderately stable compounds in the order $RSO_2 > RNHCO > RCO > R$ <94MI 418-01>.

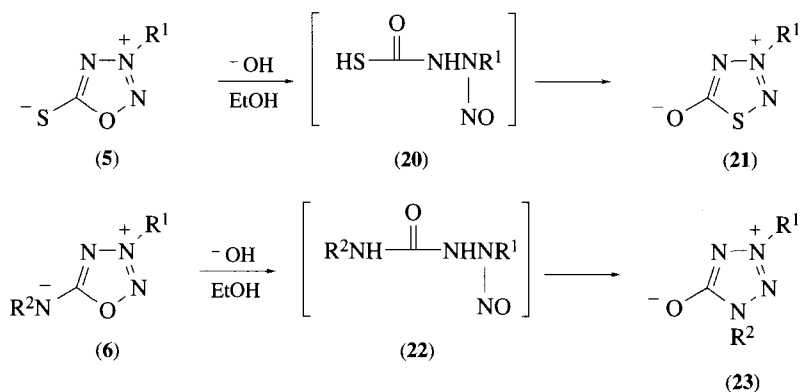
Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) and anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides (**5**) do not act as 1,3-dipoles <79JCS(P1)732>. However, anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxides (**16**) react with aryl isocyanates with exchange of the exocyclic aryl group <79JCS(P1)736>. This process can be explained in terms of a 1,3-dipolar cycloaddition to give (**18**) which then eliminates phenyl isocyanate producing (**19**) (Scheme 3).



Scheme 3

4.18.2.4.2 Rearrangements

Anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides (**5**) rearrange to anhydro-5-hydroxy-1,2,3,4-thiatriazolium hydroxides (**21**) in nonaqueous (alcoholic) basic solution <76CC306, 79JCS(P1)732>. Under similar conditions, anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) rearrange to 1,3-disubstituted anhydro-5-hydroxytetrazolium hydroxides (**23**) (Scheme 4) <1896CB1686, 29CB1449, 71ACS625>.



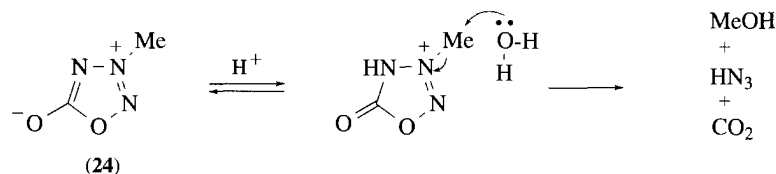
Scheme 4

The mechanism of these rearrangements is not known but it may be similar to that observed for other mesoionic species and follow the course shown in Scheme 4 <79JCS(P1)732>. However, intermediates other than (**20**) and (**22**) are conceivable.

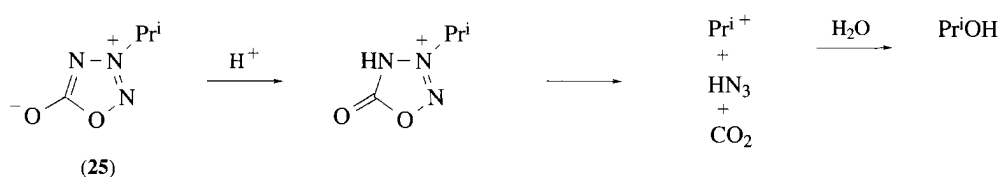
4.18.2.4.3 Hydrolysis

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) decompose on heating in strong acids <32G912, 56JA5124>. The 3-alkyl substituted compounds produce carbon dioxide, azoimide (HN_3), and the alcohol corresponding to the 3-substituent. The 3-aryl substituted analogues produce carbon dioxide and aryl azide. In some cases the initially formed aryl azide decomposes further to anilines under the conditions of the reaction <82JCS(P2)701>. Kinetic studies indicate that 3-methyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**24**) reacts via a bimolecular A-2

mechanism (Scheme 5). The corresponding 3-isopropyl compound (**25**) reacts via a unimolecular A-1 mechanism (Scheme 6), while the 3-ethyl and 3-aryl substituted analogues react by a bimolecular mechanism in which proton transfer seems to be partly rate limiting at low acidities and a unimolecular mechanism at higher acidities <76JOC3040, 79JCS(P2)533, 80JCS(P2)1437, 82JCS(P2)701>.



Scheme 5

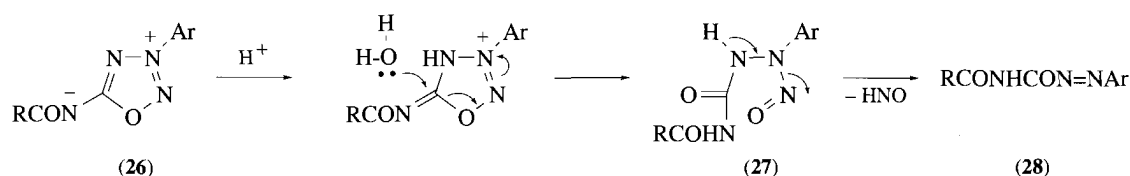


Scheme 6

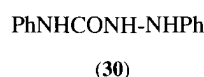
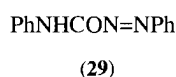
For 3-aryl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**; $R^1 = \text{Ar}$) the rate of hydrolysis is dependent not only on acidity but also on the nature of the acid and the ionic strength <82JCS(P2)701>. Although the kinetics of the hydrolysis of 3-substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) is known, detailed mechanistic aspects, such as the migration of aryl groups from N-3 in (**4**; $R^1 = \text{Ar}$), remain unexplained.

3-Phenyl-anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide (**5**; $R^1 = \text{Ph}$) behaves similarly toward acids and is also hydrolyzed by strong aqueous base, producing phenyl azide <79JCS(P1)732>.

3-Substituted anhydro-5-acylamino-1,2,3,4-oxatriazolium hydroxides (**26**) are transformed to azo compounds (**28**) by treatment with strong aqueous hydrochloric acid <94MI 418-01>. The mechanism shown in Scheme 7 has been suggested but it was not possible to isolate the intermediate (**27**) and it is not known whether it eliminates hyponitrous acid to give the azo compound (**28**) or is oxidized prior to elimination of nitrous acid. 3-Phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide (**16**) reacted similarly to give the azo compound (**29**) <29CB1449>. In addition, a minute amount of the corresponding 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**15**) was isolated <71ACS625>. 3-Phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide (**16**) reacts with hydrogen sulphide to give the hydrazo compound (**30**) corresponding to the azo compound (**29**) formed upon hydrolysis <71ACS625>.



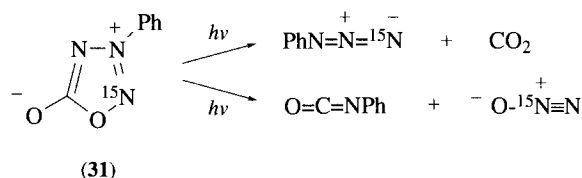
Scheme 7



4.18.2.4.4 Photolysis

Photolysis of 3-cyclohexyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; $R^1 = \text{cyclo-C}_6\text{H}_{11}$) in the presence of water yields cyclohexanone <70CC1591>. In the absence of water,

3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**31**) produces phenyl azide and phenyl isocyanate $\langle 79T409 \rangle$. 3-Phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**31**) labeled at the 2-position with ^{15}N gives rise to phenyl azide labeled at the 3-position and labeled N_2O (Scheme 8) $\langle 79T409 \rangle$. This indicates that the phenyl group migrates in the course of the reaction, but the mechanism is unknown.



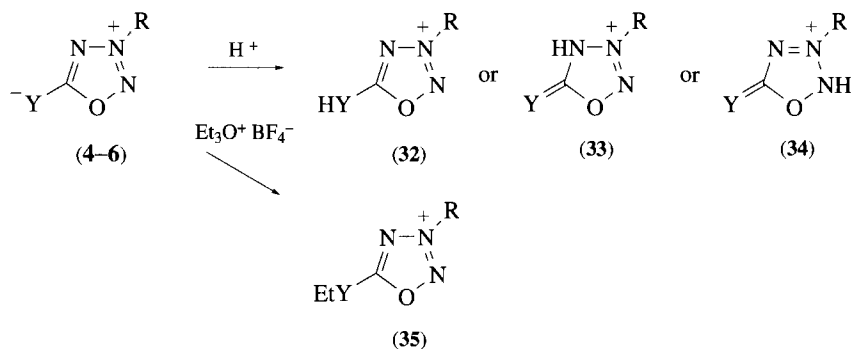
Scheme 8

4.18.2.4.5 Oxidation and reduction

A mixture of the azo and the hydrazo compounds (**29**) and (**30**) is formed when 3-phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide (**16**) is treated with zinc and acetic acid $\langle 29CB1449 \rangle$.

4.18.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) are weak bases $\langle 82JCS(P2)701 \rangle$, but the corresponding salts have not been isolated. There are three possible sites of protonation leading to the structures (**32**–**34**; $\text{Y} = \text{O}$) but it is not known where protonation actually occurs (Scheme 9).



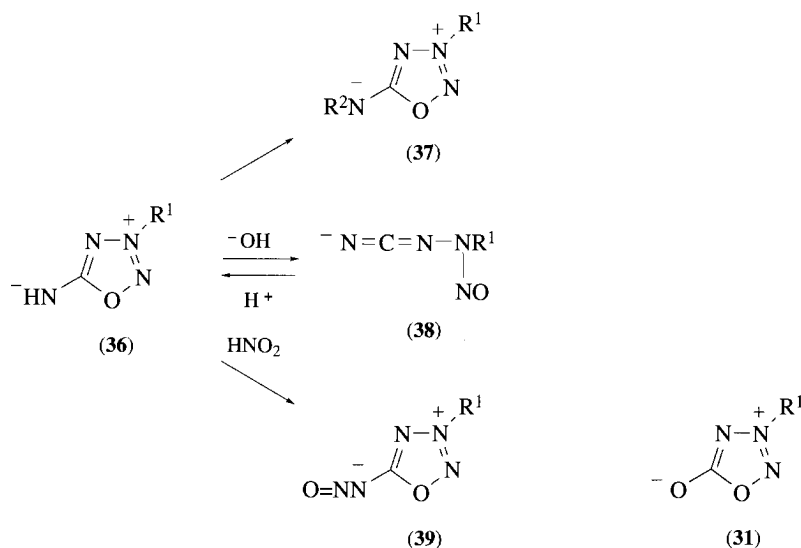
Scheme 9

Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) are alkylated by triethyloxonium tetrafluoroborate to give 5-ethoxy-1,2,3,4-triazolium tetrafluoroborates (**35**; $\text{Y} = \text{O}$) $\langle 88MRC1012, 91BAP265 \rangle$. Anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides (**5**) are likewise alkylated with triethyloxonium tetrafluoroborate, but not with methyl iodide, producing the ethylthio derivatives (**35**; $\text{Y} = \text{S}$) $\langle 76CC306, 79JCS(P1)732 \rangle$.

Anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) in which $\text{R}^2 = \text{H}$, alkyl, or aryl are basic and are readily protonated to give salts (**32**; $\text{Y} = \text{NR}^2$) which are more stable than the imines themselves $\langle 94MI 418-01 \rangle$. As for anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**), the anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) offer three sites for protonation. The traditionally assumed protonation at the exocyclic nitrogen corresponding to the derivative (**32**; $\text{Y} = \text{NR}^2$) has never been proved. The salts can be deprotonated with bases like sodium hydrogencarbonate to give the anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) $\langle 72ACS858, 79JCS(P1)736, 92MIP9213847 \rangle$.

Alkylation of anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**36**) (Scheme 10) to give (**37**; $\text{R}^2 = \text{alkyl}$) has not been reported, but acylation, carbamoylation, and sulfonylation produces

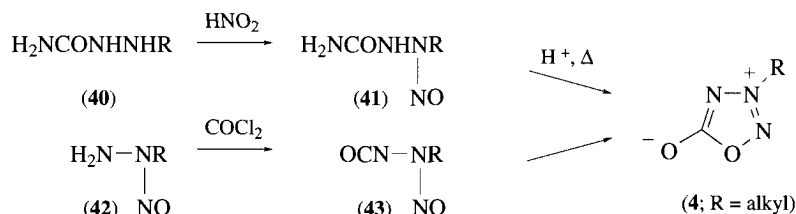
derivatives (**37**; $R^2 = \text{RCO}$, RNHCO , or RSO_2) of enhanced stability <92MIP9213847, 94MI 418-01>. Acylation reduces the basicity, and anhydro-5-benzoylamino-1,2,3,4-oxatriazolium hydroxide (**37**; $R^2 = \text{PhCO}$) gave a hydrochloride upon treatment with HCl in methanol <72ACS858>. Anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**36**) can be deprotonated with strong base. Deprotonation is followed by ring opening to give the carbodiimide (**38**) which recycles upon treatment with acid <72ACS858>. Nitrosation of 3-phenyl anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide (**36**) produces a thermally unstable nitroso derivative (**39**) which decomposes affording 3-phenyl anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**31**) (Scheme 10; $R^1 = \text{Ph}$) <71CPB559>.



Scheme 10

4.18.2.6 Ring Synthesis

3-Alkyl substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**; $R = \text{alkyl}$) are obtained by the action of nitrous acid upon the corresponding semicarbazides (**40**) (Scheme 11) <55JA1280, 65JOC567, 70JMC196, 71JHC89>. At low temperatures the intermediate *N*-nitroso-semicarbazides (**41**) may be isolated but they cyclize on heating in acid solutions <56JA5124>. 3-Methyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**4**; $R = \text{Me}$) has been prepared by another method from *N*-nitroso-*N*-methylhydrazine (**42**; $R = \text{Me}$) and phosgene. The reaction is suggested to proceed through an intermediate isocyanate (**43**) <62BCJ766>.

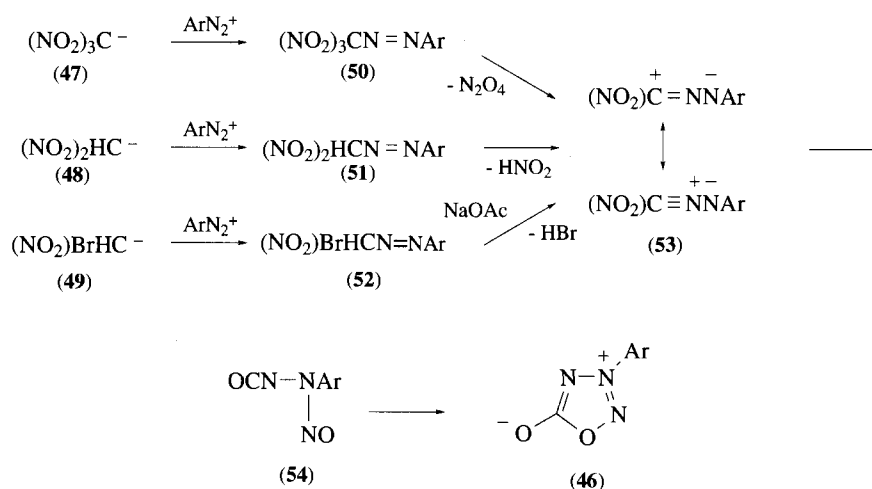


Scheme 11

3-Aryl substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**46**) can be prepared by nitrosation of arylhydrazonomethanedisulfonate salts (**44**) or by coupling of substituted nitromethane ions (**47–49**) with aryldiazonium ions or aryl isocyanides. Thus, treatment of arylhydrazonomethanedisulfonate salts (**44**) with nitrous acid gives rise to the *N*-nitroso compounds (**45**), which upon heating in acidic solution affords the anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide (**46**) (Scheme 12) <1896CB2161, 64JCS906, 79T409, 82JMC1503>. When the trinitromethane

$$\begin{array}{ccccccc} (\text{K}_2\text{S}_2\text{O}_8)_2\text{C}=\text{NNHSO}_3\text{K} & \xrightarrow{\text{ArN}_2^+} & (\text{K}_2\text{S}_2\text{O}_8)_2\text{C}=\text{NNHAr} & \xrightarrow{\text{HNO}_2} & (\text{K}_2\text{S}_2\text{O}_8)_2\text{C}=\text{NNAr} & \xrightarrow{\text{HCl}} & \text{Ar-N=N-O-C(=O)-O-N=N} \\ & & (44) & & (45) \quad \text{NO} & & (46) \end{array}$$

Scheme 12



Scheme 13

$$\begin{array}{c} \text{S} \\ \parallel \\ -\text{S}-\text{C}-\text{NHNHAr} \end{array} \xrightarrow{\text{HNO}_2} \begin{array}{c} \text{S} \\ \parallel \\ -\text{S}-\text{C}-\text{NHNAr} \\ | \\ \text{NO} \end{array} \longrightarrow \begin{array}{c} \text{Ar} \\ | \\ \text{N}^+-\text{N} \\ \diagup \quad \diagdown \\ \text{S} \quad \text{O} \end{array} \quad (56)$$

Scheme 14

$$\text{RNH}-\overset{\text{S}}{\underset{||}{\text{C}}}-\text{NHNHAr} \xrightarrow[\text{RONO}]{\text{HNO}_2} \text{Ar-N}^+-\text{N}=\text{C}(\text{NR})-\text{O}-\text{N}^- \quad (1)$$

4.18.2.7 Important Compounds and Applications

Some 3-substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**), anhydro-5-thio-1,2,3,4-oxatriazolium hydroxides (**5**) and anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) possess pesticidal or herbicidal properties <79BRP2015878>. Anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides (**4**) are moderately active but relatively long-acting hypotensive agents <82JMC1503>.

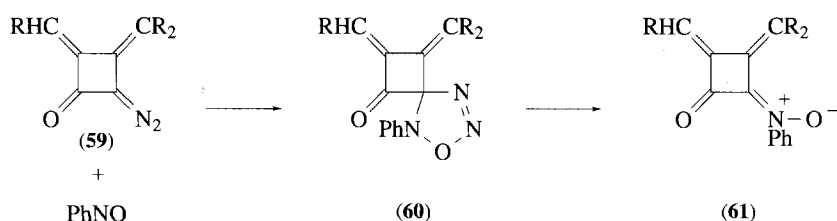
Anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides (**6**) act as NO donors. They stimulate guanylate cyclases selectively and some are potent antiplatelet, fibrinolytic, thrombolytic, or bronchiolytic agents <94MI 418-01, 96BJP401>. Some compounds exhibit antitumor activity <82USP4329355>.

4.18.3 1,2,3,5-OXATRIAZOLES

4.18.3.1 Δ^2 - and Δ^4 -Oxatriazolines

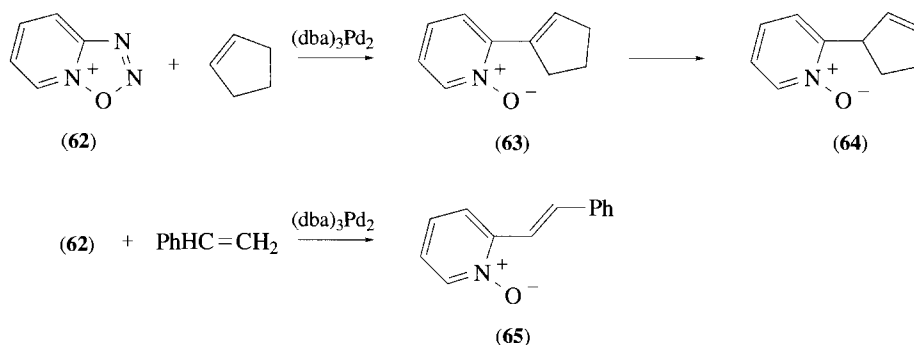
4.18.3.1.1 Reactions

Δ^2 -Oxatriazoline (**60**), formed as shown in Scheme 15, is reported to undergo a facile nitrogen extrusion reaction with formation of a nitrene (**61**) <76BCJ3173>.



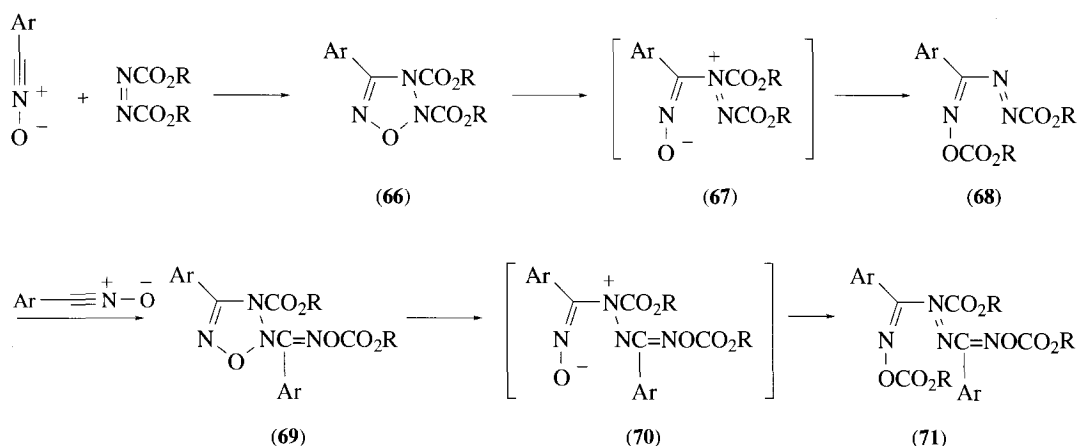
Scheme 15

1,2,3,5-Oxatriazolo[5,4-*a*]pyridinium tetrafluoroborate (**62**) reacts with cyclopentene and styrene in the presence of tris(dibenzylideneacetone)dipalladium with elimination of nitrogen to give 2-alkenyl-pyridine *N*-oxides (**63**) and (**65**) in low yields (Scheme 16) <86CPB7>. Compound (**64**) is formed as a by-product in the reaction with cyclopentene. Most likely the mechanism is related to that operating when diazocompounds are subjected to Pd-catalysis in the presence of alkenes <81T31>.



Scheme 16

Δ^4 -Oxatriazolines (**66**) are thermally unstable, undergoing rapid isomerization in solution with formation of (**68**) <64TL887, 66TL405, 72CB2841>. Betaines (**67**) are considered likely intermediates. The azo compound (**68**) may undergo a further reaction with the nitrile oxides used for oxatriazoline formation, most likely to form a new oxatriazoline (**69**) which isomerizes to (**71**) (Scheme 17) <72CB2841>.



Scheme 17

4.18.3.1.2 Syntheses

The Δ^2 -oxatriazoline (**60**) is obtained from the reaction of nitrosobenzene with diazoketone (**59**), which is thermally labile (Scheme 15) <76BCJ3173>. Δ^4 -Oxatriazolines (**66**) have been prepared by reaction of nitrile oxides or oximes <81USP4268674> with azodicarboxylates. Thus, benzonitrile oxides (Ar = Ph, 4-ClC₆H₄, 4-NO₂C₆H₄) and dimethyl azodicarboxylate react in ether at -15°C to give a precipitate of the colorless crystalline dimethyl 4-phenyl- Δ^4 -1,2,3,5-oxatriazoline-2,3 dicarboxylate (**66**; Ar = Ph, R = Me) (Scheme 17) <72CB2841>. The oxatriazoline (**66**) is unstable in solution and a successful preparation depends on its rapid crystallization from the solution. The diethyl carboxylates are soluble under the experimental conditions and rearrange before isolation. The reaction between 3-nitrobenzonitrile oxide and diethyl azodicarboxylate gives (**68**) <72CB2841> and not 1,2,3,5-oxatriazoline (**66**; Ar = 4-NO₂C₆H₄, R = Et), as originally proposed <64TL887>. Reaction between nitrile oxides and other types of azo compounds has not led to the expected oxatriazolines. Phenyl benzoyl diimide and ethyl benzoylazocarbonate gave rise to some substituted hydrazines by an unknown mechanism. Azobenzene did not react with nitrile oxides and 4-chlorobenzene-diazocyanide reacted at the nitrile group instead of at the N=N bond <72CB2841>.

4.18.3.1.3 Important compounds and applications

No applications of 1,2,3,5-oxatriazolines have been reported.

4.19

1,2,3,4-Thiatriazoles

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*Royal Veterinary and Agricultural University, Copenhagen,
Denmark*

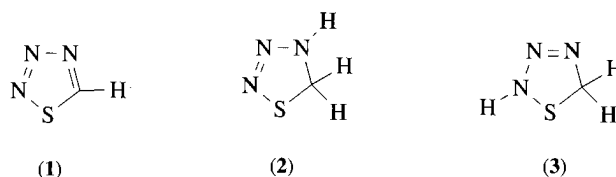
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4.19.1 INTRODUCTION

The chemistry of heteroaromatic 1,2,3,4-thiatriazoles has previously been reviewed by Jensen and Pedersen <64AHC(3)263>, by Holm <76AHC(20)145>, in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(6)579> and by Graubau <94HOU(E8d)630>. Ring-transformation reactions of sulfur-containing heterocycles including 1,2,3,4-thiatriazoles have been reviewed by L'abbé <82T3537>.

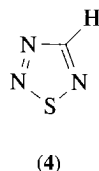
This chapter discusses the chemistry of the fully conjugated 1,2,3,4-thiatriazoles (**1**) and the nonconjugated Δ^2 -(**2**) and Δ^3 -1,2,3,4-thiatriazolines (**3**) (4,5- and 2,5-dihydro-1,2,3,4-thiatriazoles respectively). The chapter mainly concerns new development since 1984, but older literature has been included in several cases in order to give a better general coverage of the topics in question.



4.19.2 THEORETICAL METHODS

4.19.2.1 Aromaticity

As an extension of previous investigations a set of monoheterocycles, including fully conjugated 1,2,3,4- and 1,2,3,5-thiatriazole (**4**), was subjected to AM1 calculations, and the characteristics thus determined, together with available experimental data, treated by PC analysis <90JPR885>.



An index of aromatic character based upon statistical evaluation of the deviations in peripheral bond orders has been devised and applied to five-membered ring heterocycles and their mesoionic derivatives including 1,2,3,4-thiatriazole <85T1409> and 5-phenyl-1,2,3,4-thiatriazol-3-oxide <93T8441>. See also <93QSAR146>.

4.19.2.2 Structure of 1,2,3,4-Thiatriazole-5-thiolate and Acid

5-Thio-1,2,3,4-thiatriazole was originally thought to have an open structure, azidodithiocarbonic acid, but Lieber *et al.* concluded from infrared spectroscopic measurements that it actually possesses the closed 1,2,3,4-thiatriazole structure <57JOC1750>.

The structure of the 1,2,3,4-thiatriazole-5-thiolate anion (CS_2N_3^-) has been examined by Conti *et al.* using the MNDO method <86ICA71>. The closed structure (5) was found to be more stable than the open structure (6) according to the calculated standard heat of formation (ΔH_f) of $-5.4 \text{ kcal mol}^{-1}$ and $31.4 \text{ kcal mol}^{-1}$ respectively (Figure 1). This is in accordance with similar calculations previously carried out for the parent thiatriazole <76AHC(20)145>.

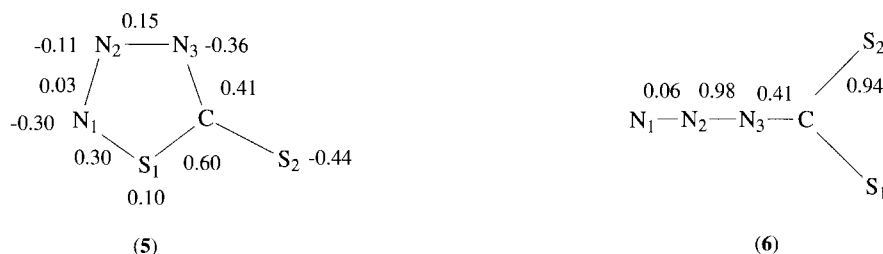


Figure 1 Calculated atom-atom overlap population and atomic net charges <86ICA71>.

The degree of bonding between the atoms is a further criterion for stability and a Mulliken-type population analysis was also carried out for the optimized structure of (5) and (6) with the HFS wave function obtained for these geometries.

Structure (6) is unlikely to be stable because there is almost no bonding between N(1) and N(2). However, the authors refer to the distressing observation that the MNDO optimized form of the structure shows only a residual bond between N(1) and N(2) and a very weak bond between N(2) and N(3). By comparison with a similar HFS calculation for the explosive S_5N_6 molecule the authors suggest that the calculation is in accordance with the observed instability of sodium 1,2,3,4-thiatriazole-5-thiolate solutions which slowly decompose even in the absence of air and light at 4°C <74JINC3851>. The Cd(II), Zn(II) and Pb(II) salts are reported to be explosive even in solution <81JINC2081> and the alkaline salts are shock-sensitive, mainly when dried. The authors point out that according to the interpretation of the calculations the weakness of the NNN bond originates solely from the σ -framework, while the π -electrons provide a substantial bonding to the cycle <86ICA71>. However, thiatriazoles decompose by extrusion of nitrogen from the N(1)-N(2) positions, either directly or via the open form, and the above considerations cannot rationalize this behavior. The calculated electronic density on N(3) and S is of interest in the evaluation of the position of the proton in HCS_2N_3 . Comparison of the ΔH_f values shows that both of these forms of the acid are unstable as compared with the CS_2N_3^- anion by $27.1 \text{ kcal mol}^{-1}$ for the SH (5) and by $29.5 \text{ kcal mol}^{-1}$ for the NH form. Thus the thiol (5) form of the acid should predominate over the thione form by some $2.5 \text{ kcal mol}^{-1}$.

However, for the free acid ^{13}C NMR analysis indicates the presence of a thioketone function instead of a thiol function <77JHC1417> (see Section 4.19.3.2).

The crystal structures of sodium 1,2,3,4-thiatriazole-5-thiolate dihydrate and 5-benzoylthio-1,2,3,4-thiatriazole have been investigated <91AX(C)1018>. The compounds have the expected cyclic structures and benzylation of sodium 1,2,3,4-thiatriazole-5-thiolate is established to occur at the exocyclic sulfur atom rather than at a nitrogen atom of the ring. The MNDO geometry optimization reported by Conti *et al.* for the 1,2,3,4-thiatriazole-5-thiolate anion <86ICA71> is in generally good agreement with the crystal structure reported here. However, there is a large discrepancy for the length of the C—S exocyclic bond which the MNDO calculations predicted to be $1.580 \text{ \AA}$ compared with an experimental value of $1.704 \text{ \AA}$. The authors point out that the calculated bond length is in fact shorter than the bond length given by Pauling for a C—S double-bond ($1.61 \text{ \AA}$) <B-60M1 419-01> and a reported C—S double-bond length of $1.645 \text{ \AA}$ <89AX(C)119>. Clark has pointed out that systematic errors occur in MNDO calculations for specific elements, including calculations for C—S bonds, which are consistently predicted to be too short in thiocyanates <B-M1 419-01>. Another difference is that MNDO calculations indicated strict planarity for the anion, in contrast to slight but definite distortions from planarity as observed in the crystal structure analysis. The 5-benzoylthio-1,2,3,4-thiatriazole molecule is close to planar. See Section 4.19.3.1 for crystal structure data.

4.19.2.3 Electronic Spectrum of 1,2,3,4-Thiatriazole-5-thiolate and Acid

Conti *et al.* calculated the electronic structure and electronic spectrum of 1,2,3,4-thiatriazole-5-thiolate (CS_2N_3^-) and HCS_2N_3 <86ICA71>. According to the ordering of the orbitals as provided by

HFS calculations, the two lowest electronic transitions of $(\text{CS}_2\text{N}_3)^-$ anion are a HOMO–LUMO $n_\sigma\text{-S}(2) \rightarrow \pi^*$ (in-plane lone pair on the exocyclic sulfur atom) and a HOMO–LUMO $\pi \rightarrow \pi^*$ transition. The wavelengths of these transitions as calculated by Slater's transition state method are 350 nm for the $n \rightarrow \pi^*$ transition and 340 nm for the $\pi \rightarrow \pi^*$ transition close to the experimentally observed band $\langle 79\text{TAL}81 \rangle$ with λ_{max} at 310–320 nm, attributed to an overlap of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Neves and Franco found that when increasing the hydrogen ion concentration the 310–320 nm band remained basically unchanged, while a new band appeared at 272 nm $\langle 79\text{TAL}81 \rangle$. Conti *et al.* argued that the $n \rightarrow \pi^*$ transition is likely to be most affected by protonation and calculated this transition by Slater's method for the acid to 287 nm in agreement with the experimental data $\langle 86\text{ICA}71 \rangle$. Similarly, calculations for the acid indicate that $\pi \rightarrow \pi^*$ transitions should give rise to a band at 310 nm.

4.19.3 EXPERIMENTAL STRUCTURAL METHODS

4.19.3.1 Crystal Structure

The crystal and molecular structures of 5-phenyl-1,2,3,4-thiatriazole (7) and its 3-oxide (8) and 3-ethyl (9) derivatives have been determined by x-ray methods $\langle 76\text{ACS(A)}351 \rangle$. Selected values are given in Figure 2.

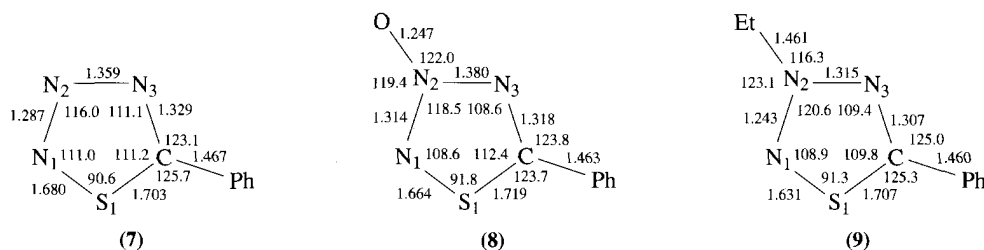


Figure 2 Bond lengths (Å) and bond angles (°) for 5-phenyl-1,2,3,4-thiatriazole (7), its 3-oxide (8) and 3-ethyl-derivatives (9).

The crystal structure of 5-amino-1,2,3,4-thiatriazole (10) has been determined by Zaworotko *et al.* $\langle 79\text{MI} 419-01 \rangle$. They were spurred to initiate crystal structure measurement because previous CNDO $\langle 76\text{AHC}(20)145 \rangle$ and SCF-MO-CNDO calculations $\langle 72\text{JCS(D)}73 \rangle$, based on the unknown, unsubstituted 1,2,3,4-thiatriazole, predicted that the relative ease of alkylation should be $\text{N}(4) \geq \text{N}(2) > \text{N}(3)$ in contrast to the experimentally observed alkylation at the 3-position. However, with a 5-amino substituent, alkylation tends to occur at N(4) which is reasonable if the substituent exerts a mesomeric effect on the π -system of the ring. That this is the case with 5-aminothiatriazole is clear from the following: (1) The sp^2 hybridization of the nitrogen of the amino substituent as evidenced by the angles around it, (2) the closeness to planarity of the entire molecule, and (3) the shortness of the $\text{H}_2\text{N}-\text{C}$ bond (1.331 Å) indicates strong π -bonding (Figure 3).

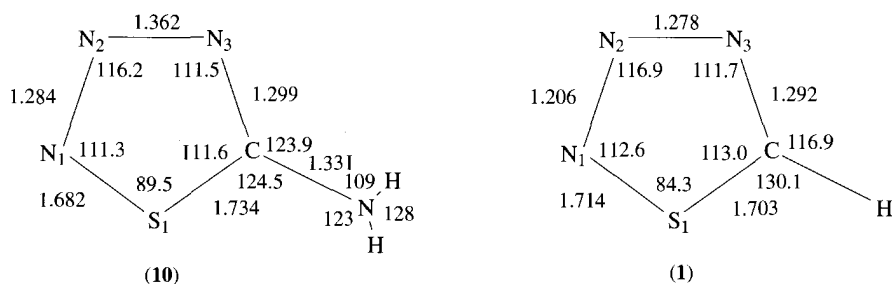


Figure 3 Comparison of observed and calculated structures of 1,2,3,4-thiatriazoles: (a) observed structure of 5-amino-1,2,3,4-thiatriazole (10); (b) calculated CNDO model of 1,2,3,4-thiatriazole.

The crystal structures of sodium 1,2,3,4-thiatriazole-5-thiolate (**5**) dihydrate and 5-benzoylthio-1,2,3,4-thiatriazole have been investigated and atomic parameters, bond lengths and bond angles are reported (Figure 4) <91AX(C)1018>. The compounds have the expected cyclic structures.

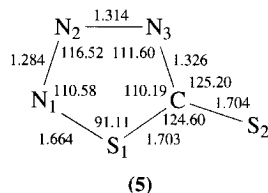


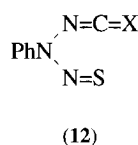
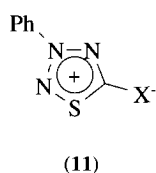
Figure 4 Bond lengths (Å) and bond angles (°) for sodium 1,2,3,4-thiatriazole-5-thiolate dihydrate (sodium and water not shown).

4.19.3.2 NMR Spectroscopy

Proton NMR data are reported for substituted mesoionic 1,2,3,4-thiatriazolium-5-olates and 5-thiolates. Although the spectra are of little diagnostic value they are consistent with the mesoionic structures <79JCS(P1)732>. Representative ^{13}C shifts for C(5) of 5-substituted thiadiazoles are: 5-Ph, 178.46 ppm; 5-PhNH, 173.8 ppm; 5-BzS, 179.8 ppm; 5-PhCOS, 171.5 ppm and for the thiatriazolium salt (**9**) 186.42 ppm <84CHEC-I(6)579>.

Detailed spectroscopic investigations of 1,2,3,4-thiatriazolium-5-olates, the isomeric 1,2,3,4-oxatriazolium-5-thiolates and their ethyl substituted derivatives have been carried out by Jazwinski *et al.* using ^1H , ^{13}C , ^{14}N , ^{15}N , and ^{17}O NMR <88MRC1012, 91BAP265>. The two types of heterocyclic ring systems are in particular characterized by ^{15}N and ^{17}O NMR data. Thus the exchange of ring oxygen for sulfur changes the ^{15}N chemical shifts by -34 ± 4 ppm, -2.5 ± 0.1 ppm, and 57 ± 3 ppm for N(2), N(3), and N(4) atoms, respectively. Similarly, exchange of the exocyclic oxygen for sulfur gives rise to a shift of 18 ± 4 ppm, 7.2 ± 0.1 ppm, and 44 ± 3 ppm respectively. ^{17}O NMR data showed that the signal assigned to the ring atom was observed downfield compared with the exocyclic atom. Although the results are inconsistent with general experience that exocyclic oxygen shows NMR signals at lower field than ring oxygen, the data is in accordance with the ^{17}O chemical shifts observed for sydnone.

Mesoionic 1,2,3,4-thiatriazolium-5-aminides and methylides have also been investigated carefully by Jazwinski and Stefaniak using the same spectroscopic techniques at various temperatures and including NOE experiments <93MRC447>. In particular the ^{15}N NMR data is in agreement with the cyclic structures (**11**) and not the open forms (**12**):

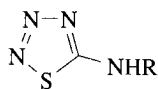


In the case of $\text{X} = \text{C}^-(\text{CN})_2$ two nonequivalent CN groups are observed. Similarly, two nonequivalent ester groups are observed with $\text{X} = \text{C}^-(\text{COOEt})_2$ suggesting that the exocyclic group bond has double bond character <93MRC447> (see <76JCS(P1)744>). With $\text{X} = \text{C}^-(\text{CN})(\text{COOEt})$ only one isomer was observed even at 373 K but it could not be identified <93MRC447>.

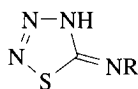
Mesoionic 1,2,3,4-thiatriazolium-5-aminides react with hydrochloric acid or with methyl iodide giving salts. On the basis of coupling constants, the site of protonation or alkylation was assigned to the exocyclic nitrogen atom <93MRC447>. L'abbé *et al.* <77JHC1417> have addressed the question of tautomeric assignment of 5-(monosubstituted)-amino-1,2,3,4-thiatriazoles by means of ^{13}C NMR for which previous evidence favors the amino form over the imino form (see reviews <64AHC(3)263, 76AHC(20)145>).

In order to locate the C_5 absorptions of (**13**) and (**14**) model compounds (**15**) and (**16**) were investigated. C_5 in (**15**) ($\text{R} = \text{Ph}$) absorbed at δ 180.4 ppm comparable with the values found for 5-

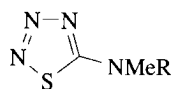
phenyl-1,2,3,4-thiatriazole (7) (δ 178.5 ppm) $\langle$ 75JOC431 $\rangle$ and *S*-alkylated thiatriazolinethiolates (δ 179 ppm) $\langle$ 74JOC3770 $\rangle$. In contrast, (16) ($R = \text{Ph}$) exhibited an upfield chemical shift at δ 156 ppm. Measurements on several 5-(monosubstituted)-amino-1,2,3,4-thiatriazoles gave values from 173.1 to 179.4 ppm demonstrating that they exist in the amino form (at least in solution by NMR) even with strongly electron-withdrawing substituents on the exocyclic nitrogen atom ($R = \text{Ts}$, 173.1 ppm).



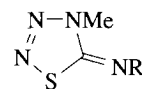
(13)



(14)

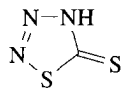


(15)

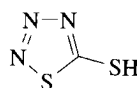


(16)

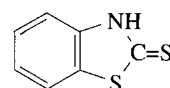
In contrast with (13), the thiatriazolinethione exists in acetone- d_6 solution in the thione form (17), and not in the thiol form (18) as claimed by Jensen and Pedersen $\langle$ 64AHC(3)263 $\rangle$. Thus, at 0°C the ^{13}C NMR spectrum shows a low-field $\text{C}=\text{S}$ absorption at δ 193.1 ppm, comparable with reference compound (19) (δ 190.3 ppm), whereas the C-atom in (18) is expected to resonate in the region δ 175–180 ppm.



(17)



(18)



(19)

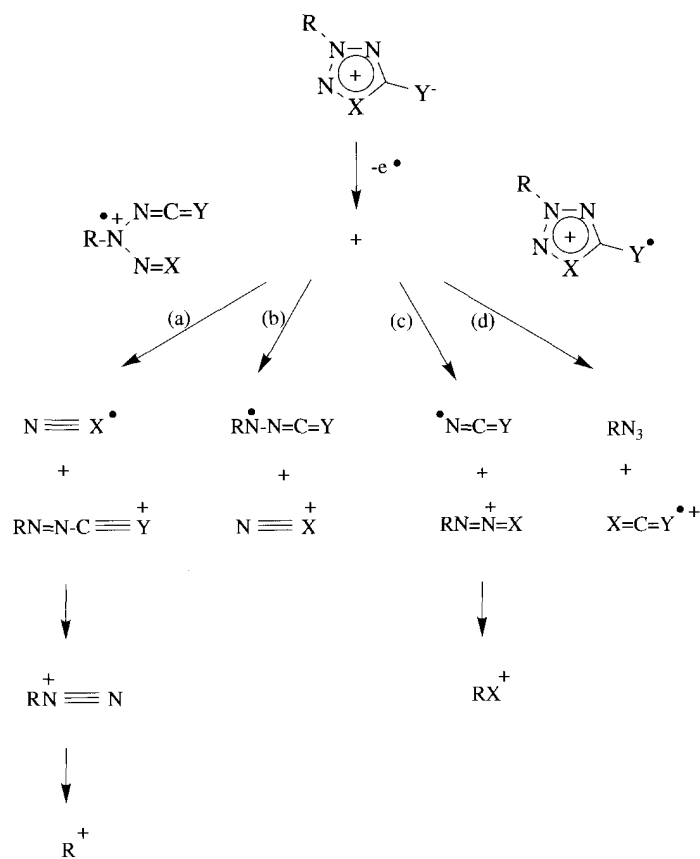
4.19.3.3 Mass Spectrometry

Hanley *et al.* have recorded and analyzed mass spectra of 10 related mesoionic systems of the general structure shown in Scheme 1 $\langle$ 79JCS(P1)747 $\rangle$. The molecular ion can fragment by four different pathways. The major fragmentation pathway is reported to vary with the structural type, but simultaneous fragmentation via all four pathways is not observed. Pathway (c) has only been observed in cases where the hetero atom X is sulfur. Further fragmentation of the ion gives the daughter ion RS^+ together with the corresponding metastable ion. In contrast to mesoionic 1,2,3,4-oxatriazolium-5-thiolates ($X = \text{O}$, $Y = \text{S}$), thiatriazolium-5-thiolates ($X = \text{S}$, $Y = \text{S}$) show an intense molecular ion. They undergo a characteristic fragmentation by pathway (a) losing thionitroxyl, $\text{NS}^\bullet$, to form the daughter ion which undergoes cleavage to give the arenediazonium ion, which finally cleaves to give the aryl cation. The molecular ion also undergoes cleavage via pathway (c), losing the thiocyanate radical. Mesoionic 1,2,3,4-thiatriazolium-5-olates ($X = \text{S}$, $Y = \text{O}$) show a moderately intense molecular ion which fragments by pathway (a) to give the thionitroxyl radical. 1,2,3,4-Thiatriazolium-5-dicyanomethylides ($X = \text{S}$, $Y = \text{C}(\text{CN})_2^-$) show intense molecular ions which decompose via pathway (c). An ion corresponding to RN^+ is observed probably formed by loss of nitrogen from the aryl azide. 1,2,3,4-Thiatriazolium-5-aminides ($X = \text{S}$, $Y = \text{NR}'^-$) show a strong molecular ion and fragment via pathway (c) finally to give $\text{R}'\text{S}^+$ with formation of corresponding metastable ions. The most intense ion in the spectra is the aryl cation. The authors conclude that mass spectrometry is particularly valuable for distinguishing between pairs of isomers of mesoionic systems (X and Y interchanged in the ring and the exocyclic group).

The mass spectra of 5-phenylamino and 5-tolylamino-1,2,3,4-thiatriazoles have been reported $\langle$ 81MI 419-01 $\rangle$.

4.19.3.4 UV Spectroscopy

Absorption spectra for mesoionic 3-phenyl-1,2,3,4-thiatriazolium-5-cyano(ethoxycarbonyl) methylide, 5-di(ethoxycarbonyl) methylide, 5-*p*-toluenesulphonamidate, and 5-(*N*-methylanilino) iodide have been reported $\langle$ 93MRC447 $\rangle$. See also Section 4.19.2.3.



Scheme 1

4.19.3.5 IR Spectroscopy

In-plane vibration frequencies for 5-amino- (**10**) and 5-thiothiatriazole (**18**) have been calculated and compared with observed values (Table 1) <77PIA(A)265>. Structural parameters and force constants were estimated from those of triazoles and other related molecules including thiadiazoles. The results of the normal coordinate analysis are shown below. The stretching force constants for the two compounds (**10**) and (**18**) are respectively: S—N, 3.7, 3.7; S—C, 3.5, 5.0; N—N, 5.6, 5.6; N=N, 5.8, 5.9; C—N, 5.3, 5.3; C—X, 5.5, 3.5 (X = NH₂ and S respectively).

Table 1 Assignments of in-plane vibrations in 5-substituted 1,2,3,4-thiatriazoles.

5-amino (10) ^a		5-thio (18)	
Obs.	Calc.	Obs.	Calc.
1525	1530	1565	1570 $\nu(\text{ring})$
1377	1377	1350	1330 $\nu(\text{ring})$
1315	1300	1230	1227 $\nu(\text{ring})$ ^b
1120	1140	1110	1100 $\nu(\text{ring})$
940	885	900	874 $\nu(\text{NS})$ or (CS)
730	741	710	702 $\nu(\text{CS})$ or (NS)
690	660	690	673 $\delta(\text{ring})$
580	567	498	496 $\delta(\text{ring})$ ^c
480	490	332	330 $\delta(\text{ring})$ ^d

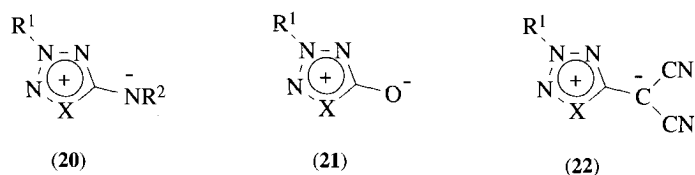
^aNH₂ group vibrations not listed. ^b $\nu(\text{C}=\text{S})$ at 1030 cm⁻¹. ^cMixed with $\nu(\text{C}=\text{S})$. ^d $\delta(\text{NCN} + \text{SCN})$ in 5-aminothiatriazole; $\delta(\text{NCS} + \text{SCS})$ in 5-thiothiatriazole.

4.19.3.6 Raman Spectroscopy

Raman spectra of 1,2,3,4-thiatriazole-5-thiolate (**5**) and its molecular complex with sulfur dioxide have been obtained <88MI 419-01>. Excitation of the spectra with different exciting wavelength (457.9 nm, 514.5 nm and 647.1 nm) shows that in both cases substantial enhancement of several vibrational modes is present. The enhancement is assigned to a $\pi \rightarrow \pi^*$ transition at approximately 320 nm for the thiatriazolthiolate ion (**5**) whereas the enhancement is assigned to a charge-transfer transition at approximately 350 nm for the molecular complex. The presence of several bands with increased intensity in the region of the SO₂ symmetric stretching is interpreted as being due to SO₂ molecules bound to different sites of the ion.

4.19.3.7 Dipole Moments

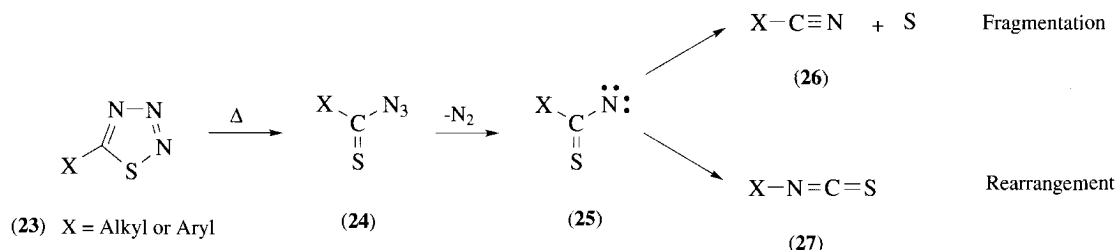
Electric dipole moment studies have provided excellent support for the formulation of certain heterocycles as mesoionic compounds. Hanley *et al.* <78JCS(P1)600> have measured dipole moments for mesoionic 1,2,3,4-thiatriazol-5-imines (**20**), 5-ones (**21**) and 5-ylidenemalononitriles (**22**) using a vector analysis similar to that previously employed for sydnone and other mesoionic compounds assuming that mesoionic rings are regular pentagons. The dipole moment of 3-phenyl-1,2,3,4-thiatriazolium-5-anilide (**20**) was found to be 3.71 D and five derivatives of compounds (**21**) were measured and the ring moment calculated to be 3.8 D. In both cases the dipole moments are rather small but clearly consistent with the mesoionic formulation. 3-Phenyl-1,2,3,4-thiatriazolium-5-dicyanomethanide (**22**) was found to have a dipole moment of 8.84 D.



4.19.4 REACTIVITY OF FULLY CONJUGATED RINGS

4.19.4.1 Thermal Reactions

Thiatriazoles generally decompose upon mild heating into nitrogen, sulfur, and an organic fragment (Scheme 2). Considerable attention has been given to this reaction because of the synthetic possibilities and because of the possible involvement of intermediates such as thioacyl azides (**24**), thioacyl nitrenes (**25**), thiazirines (e.g. **34**) and nitrogen sulfide (**29**).



Scheme 2

Isothiocyanates (**27**) are observed as by-products when the decomposition of 5-alkyl- (**23**; X = alkyl) and 5-aryl-thiatriazoles (**23**; X = aryl) is carried out at elevated (> 100°C) temperature, while nitriles (**26**) only are formed at RT (Scheme 2) <67RTC670, 78JOC4816>.

Jensen and Holm investigated the mechanism for the decomposition of 5-alkoxy-1,2,3,4-thiatriazoles (**23**; X = OR) and found by using 2-¹⁵N-5-isobutoxythiatriazole that the extruded nitrogen originated 98.9% from the N(2) and N(3) positions <69ACS2183>.

The kinetics of the decomposition of 5-alkoxythiatriazoles (**23**; X = OR) in dibutyl phthalate at 15–40°C were studied by manometric measurement of the nitrogen evolved <67ACS2792>. The reaction was shown to be first order with activation energies for different 5-alkoxythiatriazoles (**23**; X = OR) of 101.7–104.2 kJ mol⁻¹ and activation entropies of 13.4–19.7 J mol⁻¹ K⁻¹. Because of only small differences in the activation energies, it was concluded that the thermal decomposition of 5-alkoxythiatriazoles (**23**; X = OR) follows the same mechanism independent of the 5-substituent.

The formation of isothiocyanate (**27**) from 5-alkyl- (**23**; X = alkyl) and 5-aryl-thiatriazoles (**23**; X = aryl) was explained by Jensen *et al.* by a mechanism involving initial ring opening to a thioacyl azide (**24**) followed by extrusion of nitrogen to give a thioacyl nitrene (**25**) which could either lose sulfur forming a nitrile (**26**) or rearrange to an isothiocyanate (**27**) (Scheme 2) <67ACS2792>.

An analogous mechanism was suggested for the 5-alkoxy derivatives (**23**; X = OR), however, in this case rearrangement products (**27**; X = OR) are not observed.

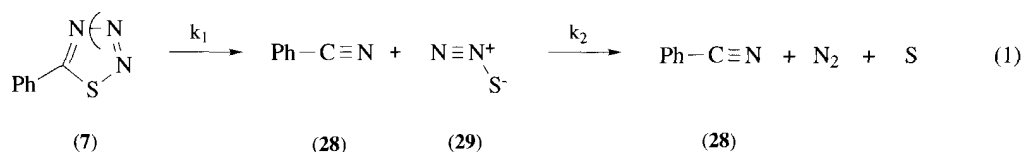
Jensen *et al.* pointed out that if the suggested mechanism is correct the thioacyl azide (**24**; X = OR) must decompose rapidly because the characteristic azide band at approximately 2130 cm⁻¹ was not observed in the infrared spectrum of a decomposing thiatriazole <67ACS2792>.

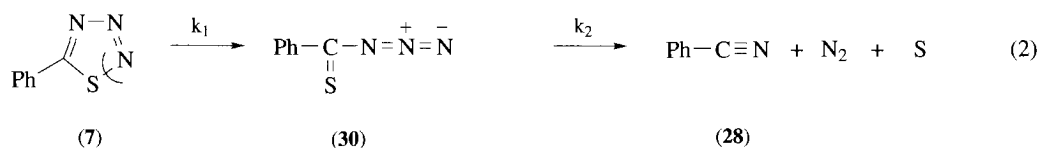
Pilgram *et al.* tried to intercept the proposed thioacyl azide with trivalent phosphorous compounds and they isolated 2,2-dihydro-1,3,4,5,2-thiatriazaphosphorines <71JHC951> but it is not possible to distinguish between a direct attack on the heterocyclic ring and attack on the thioacyl azide formed by ring opening.

Holm *et al.* <78JOC4816> showed that the thermal degradation of 5-aryl-thiatriazoles (**23**; X = Ar) was following first-order kinetics in agreement with the results of Jensen *et al.* <67ACS2792> on 5-alkoxythiatriazoles (**23**; X = Ph). The question of intermediates was approached by trapping experiments involving the presence of 1,3-dipolarophiles such as tetracyanoethylene, dimethyl acetylenedicarboxylate, and other reagents <78JOC4816>. However, these experiments resulted only in isolation of benzonitrile in 90–100% yields from thermal decomposition of 5-phenylthiatriazole (**7**). Since nitrenes normally are extremely reactive species, these results render the participation of thioacyl nitrene (**25**; X = OR) rather unlikely. Furthermore, the results demonstrate that the intermediate nitrile sulfide (**35**) which has been detected in similar trapping experiments during photolysis of 5-phenylthiatriazole (**7**) (see Scheme 4 later in this section) is not involved in the thermal degradation of thiatriazoles.

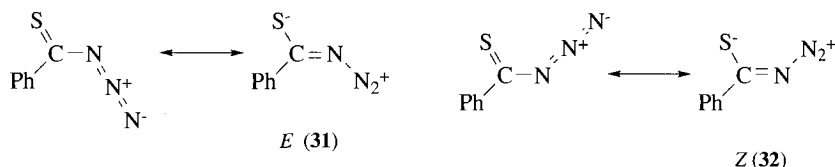
Holm *et al.* discussed the possibility of thioacyl azide (**30**) as an intermediate in the thermal decomposition and stated that if thioacyl azides are intermediates, the first step must be reversible, since thioacyl azides certainly are intermediates in the formation of thiatriazoles from, for example, thioacyl chloride and azide ions <78JOC4816>. Therefore a steady state concentration of thioacyl azide should be present in a decomposing thiatriazole. However, experiments with addition of Na ¹⁵N₃ to decomposing 5-phenyl-thiatriazole (**7**) in ethanol revealed after 50% decomposition, only the natural abundance of ¹⁵N in the remaining thiatriazole. A similar experiment where benzoyl azide was mixed with Na ¹⁵N₃ showed clearly isotopic exchange <78JOC4816>. Finally, thiobenzoyl chloride and tetrabutylammonium azide were mixed at -115°C directly in an UV-cell and heated to approximately -100°C but except for formation of 5-phenylthiatriazole a chromophore due to thiobenzoyl azide could not be observed. Accordingly this probably means that the ring closure to thiatriazole is more rapid than the bimolecular formation of thioacyl azide.

Holm *et al.* studied the isotope effects on the thermal decomposition of [2-¹⁵N]- and [4-¹⁵N]-5-phenyl-1,2,3,4-thiatriazoles by means of mass spectrometry <78JOC4816>. The results showed no significant isotope effect in the decomposition of [2-¹⁵N]-5-phenyl-1,2,3,4-thiatriazole, while a value around 1.04 was estimated for [4-¹⁵N]-5-phenyl-1,2,3,4-thiatriazole, indicating a break of the N(3)—N(4) bond in the rate-determining step. Based on these results Holm *et al.* suggested two different mechanisms for the thermal decomposition of 5-phenyl-1,2,3,4-thiatriazole (**7**) (Equations (1) and (2)) <78JOC4816>. In Equation (1) the primary products are benzonitrile (**28**) and dinitrogen sulfide (**29**), and the isotope effect observed is *a priori* in agreement with retrocycloaddition of dinitrogen sulfide. In Equation (2) the concentration of thiobenzoyl azide (**30**) must be very low because of the apparent very fast equilibrium with the thiatriazole. The rate-determining step (steady-state assumption) is therefore the result of a bond break in thiobenzoyl azide (**30**) for which an isotope effect of 3.7% was calculated in good agreement with the observed isotope effect.





However, all attempts to demonstrate the formation of dinitrogen sulfide (**29**) by mass spectrometry in gas-phase pyrolysis failed and since dinitrogen sulfide (erroneously) had been reported <75CPL(33)393> to be a stable compound at RT Equation (1) was excluded <78JOC4816>. Holm *et al.* stated that the thioacyl azide may exist as two conformers (*E* (**31**) and *Z* (**32**)) (Scheme 3) <78JOC4816> where the rotation around the C—N bond is believed to be restricted because of a partial double-bond character.



Scheme 3

It was suggested that benzonitrile (**28**) is formed from the *E*-conformer (**31**) in a Grob-type fragmentation <69AG543> and the isothiocyanate (**27**) is formed from the *Z*-conformer (**32**) in a Curtius rearrangement.

In the mid-1980s, Wentrup and co-workers, using flash vacuum pyrolysis techniques, were able to obtain direct evidence for N₂S (**29**) as an unstable, primary product in the pyrolysis of 5-phenylthiatriazole <86JOC1908, 88JA3458>.

In the early 1990s, Wentrup and co-workers presented results from the flash vacuum pyrolysis of different 5-aryl-1,2,3,4-thiatriazoles (**23**; X = Ph, Ph(D₅), 2-MeC₆H₄, 4-MeC₆H₄, and PhO), and the isolation of the products in an argon matrix at 12 K <92JPC2065>. N₂S was observed as a major degradation product in all cases. The optimal temperature for N₂S (**29**) production was found to be 650–700 °C (10^{−4} Torr) for (**23**; X = Ph, Ph(D₅) and 2-MeC₆H₄) and 300 °C for (**23**; X = 4-MeC₆H₄ and PhO). Less dinitrogen sulfide (**29**) was observed at higher temperatures, but it was still detectable in a pyrolysis of (**7**) at 1000 °C. Wentrup and co-workers described N₂S (**29**) as a very sensitive molecule and it could only be observed when using very short contact times (≈ 1 ms) and hence a vacuum and a pumping speed as high as possible (typically 10^{−3}–10^{−5} Torr). These findings were given as a reason for the fact that Holm *et al.* did not observe N₂S (**29**) during the gas-phase pyrolysis of 5-phenyl-1,2,3,4-thiatriazole (**7**).

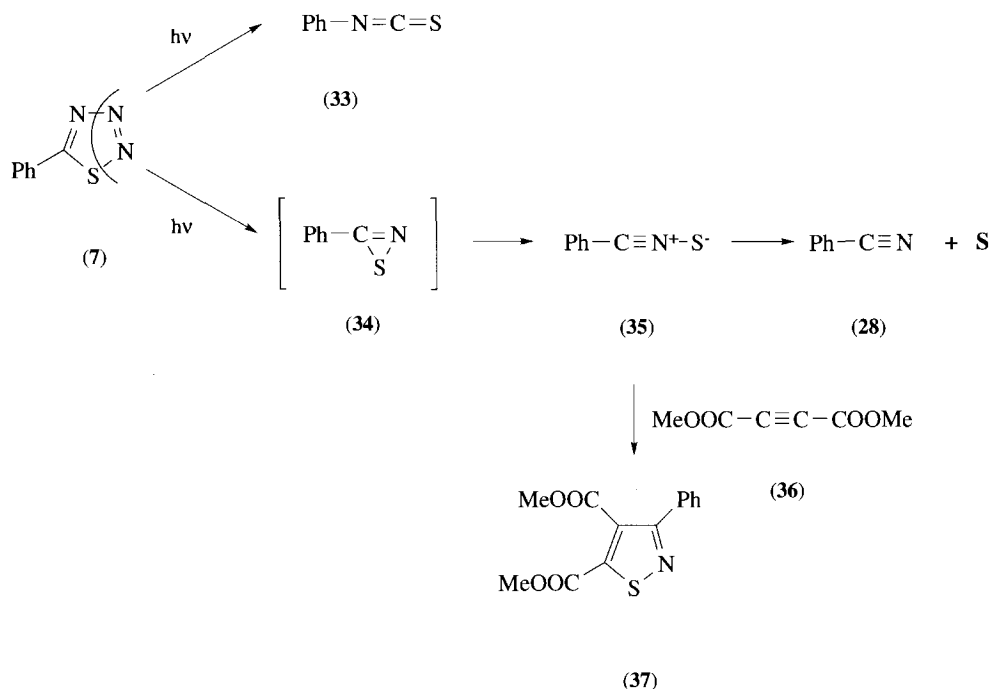
As an overall conclusion two routes seem to operate in the thermal degradation of 1,2,3,4-thiatriazoles: a major route leading to nitrile (**28**) and dinitrogen sulfide (**29**) (Equation (1)), and another leading to isothiocyanate (**27**) most likely via thioacyl azide (**24**) from the *Z*-form (**32**) and presumably accompanied by formation of nitrile (**28**) from the *E*-form (**31**).

4.19.4.2 Photochemical Reactions

4.19.4.2.1 5-Alkyl- and aryl-1,2,3,4-thiatriazoles

The photochemistry of thiatriazoles has previously been reviewed <84CHEC-I(6)579>. Photolysis of 1,2,3,4-thiatriazoles was first studied by Kirmse who found that irradiation of 5-arylthiatriazoles (**23**; X = Ar) and 5-benzylthiatriazole (**23**; X = CH₂Ph) with UV light resulted in the formation of nitriles, sulfur, nitrogen, and a small amount of isothiocyanates (5–10%) (e.g. Scheme 4) <60CB2353>.

Okazaki *et al.* reported formation of sulfur atoms which were identified by trapping experiments with different alkenes resulting in episulfides <71BCJ3167>. Holm *et al.* showed that product formation takes place from the excited singlet state of the 1,2,3,4-thiatriazole <75JA6197>. ¹⁵N-Labeling experiments showed that the extruded nitrogen originates from the N(2) and the N(3) positions and that nitrogen scrambling prior to extrusion does not take place. The yield of photochemically formed isothiocyanate was found to be almost the same (4.8–7.6%) in different solvents and over the temperature range 300 K to 193 K. At 85 K formation of phenyl isothiocyanate (**33**) was observed



Scheme 4

without indication of an intermediate (UV and ESR spectroscopy). On this basis the hypothetical thiobenzoylnitrene was excluded as a precursor for the isothiocyanate (33) <75JA6197>.

Holm *et al.* irradiated 5-phenyl-1,2,3,4-thiatriazole (7) at RT in dimethyl acetylenedicarboxylate (36) and obtained 4,5-dimethoxycarbonyl-5-phenylisothiazole (37) in 9% yield explained by trapping of photochemically formed benzonitrile sulfide (35) <75JA6197>. Irradiation of 3-ethyl-5-phenyl-1,2,3,4-thiatriazolium tetrafluoroborate (9) and 5-phenyl-1,2,3,4-thiatriazole 3-oxide (8) under the same conditions also resulted in formation of (37) in 8% and 21% yield respectively <78JCS(P1)1445>. Active sulfur atoms, formed during photolysis, were disregarded as a source for (37) because addition of *p*-toluonitrile to 5-phenylthiatriazole (7) in dimethyl acetylenedicarboxylate (36) before irradiation did not give rise to a cycloaddition product containing the *p*-tolyl group. Similarly, the presence of sulfur and benzonitrile or 5-(4-chlorophenyl)thiatriazole (source of active sulfur) during photolysis did not give rise to increased amounts of isothiazole <78JCS(P1)1445>. It can be added that investigation of a number of other five-membered C-, N-, and S-containing heterocycles has revealed that facile photofragmentation takes place when extrusion of a small inorganic fragment such as N₂ (thiatriazole), N₂O (thiatriazole-3-oxide), CO, CO₂, etc. is possible. In these cases formation of nitrile sulfide appears to be general, as demonstrated by isolation of (37) in 5–21% yield depending on the starting heterocycle <78JCS(P1)1445>.

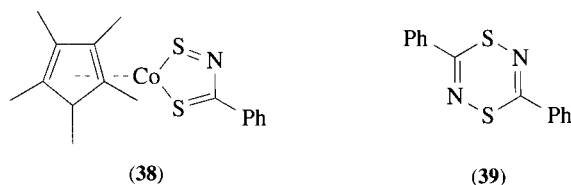
On irradiation of phenylthiatriazole (7) in an EPA (diethylether–isopentane–ethanol (5:5:2)) glass at 85 K a compound was formed which exhibits a UV absorption spectrum (λ_{max} 340 nm and 240 nm) and thermal and photochemical properties identical with those of the compound generated from 4-phenyl-1,3,2-oxathiazolyl-5-oxide and assigned to benzonitrile sulfide (35) <75JA6197>. On irradiation of phenylthiatriazole (7) and phenylthiatriazole 3-oxide at 280 nm in PVC films at 10–15 K an intermediate intervening between the heterocycle and benzonitrile sulfide (35) was detected and considered to be antiaromatic phenylthiazirene (34). On heating to 20 K or higher, increased absorptions at 340 nm and 240 nm (assigned to benzonitrile sulfide (35)) were observed and explained by electrocyclic ring opening of the thiazirene ring (34). At still higher temperatures rapid decomposition of benzonitrile sulfide (35) to benzonitrile (28) took place <78JCS(P1)746>. Irradiation into the bands at 340 nm and 240 nm caused rapid decomposition into benzonitrile (28). The authors concluded that formation of benzonitrile sulfide (35) in significant amounts on heating of irradiated phenylthiatriazole (7) demonstrates the presence of a precursor of the former species, which is stable at 10 K but when heated to around 20 K begins the transformation into benzonitrile sulfide (35).

Phenylthiazirene (**34**) was considered to be the most reasonable nitrile sulfide precursor but no spectral peak could be assigned unambiguously to this otherwise unknown compound <78JCS(P1)746>.

Wentrup *et al.* studied the photolysis of 5-phenyl-1,2,3,4-thiatriazole (**7**) at $\lambda = 310 \pm 11$ nm and at $\lambda = 254$ nm in an argon matrix at 11 K. The photolysis was followed by IR spectroscopy and bands were observed at 2030 cm^{-1} , 2120 cm^{-1} , 2190 cm^{-1} , and 2228 cm^{-1} in intensities depending on the irradiation wave length. The bands at 2120 cm^{-1} and 2190 cm^{-1} were assigned to small amounts of phenylisothiocyanate (**33**) and the band at 2228 cm^{-1} to benzonitrile (**28**). The band at 2030 cm^{-1} was assigned to dinitrogen sulfide (**29**) based on a detailed discussion comparing the results of photolysis with thermolysis of the thiatriazole (see also Section 4.19.4.1). Dinitrogen sulfide (**29**) was reported thermally unstable transforming into nitrogen and sulfur by warming the matrix to 160 K. Bands which could be assigned to benzonitrile sulfide (**35**) (2270 cm^{-1}) were not observed during the photolysis of phenylthiatriazole (**7**) <86JOC1908>.

When compared with the results of Holm *et al.* the lack of benzonitrile sulfide (**35**) bands may be explained by a change in the photochemical pathway due to the microscopic environment (argon matrix at 11 K; Wentrup *et al.* versus PVC/EPA; Holm *et al.*) or to rephotolysis of benzonitrile sulfide (**35**) under the experimental conditions into benzonitrile (**28**) and sulfur. A dependence of the photochemical pathways due to the microscopic environments are known from other cases <76TL873>. For a further discussion of the generation and reaction of nitrile sulfides see the review by Wentrup and Kambouris <91CRV363>.

It has been reported that irradiation of 5-phenyl-1,2,3,4-thiatriazole (**7**) in the presence of [Co (pentamethylcyclopentadienyl)(CO)₂] gives rise to a 1,2,5,3-cobaltadithiazole (**38**) in low yield (2%) <92CL243, 94JOM(473)313>. Several other sulfur, nitrogen containing heterocycles similarly give rise to the same complex (**38**) either photochemically or thermally. Since Kato *et al.* found that the cobaltadithiazole complex (**38**) could not be formed directly from benzonitrile (**28**) and sulfur, it is suggested that the complex (**38**) is formed from 3,5-diphenyl-1,4,2,6-dithiazine (**39**) via benzonitrile sulfide. This proposal is, however, not completely convincing, as the dithiazine (**39**), which is a thermally stable compound, has apparently not been observed either from the thiatriazole or from other precursors (photochemical) of benzonitrile sulfide.



4.19.4.2.2 1,2,3,4-Thiatriazole-5-thiol

Irradiation of thiatriazole-5-thiol (**18**) and its anion (**5**) at 313 nm is reported to give rise to formation of nitrogen, sulfur, and SCN⁻ (HSCN). This scheme is in accordance with the otherwise known photochemical reactions of thiatriazoles but analytical data for product formation is not given. Quantum yields were calculated for the reaction in the pH range 0.0 to 11.8 <86POL2119>.

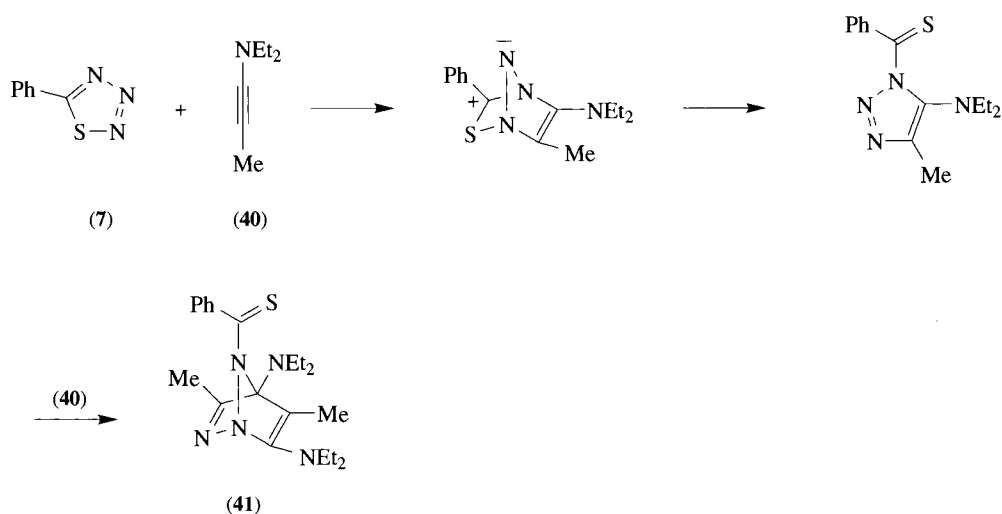
4.19.4.3 Electrophilic and Nucleophilic Attack at Nitrogen

5-Phenylthiatriazole (**7**) is attacked in the 3-position by potent oxidizing (3-ClC₆H₄CO₃H) and alkylating (Et₃O⁺BF₄⁻) agents to give the 3-oxide <75T1783> and the 3,5-disubstituted thiatriazolium salts <75JOC431>, respectively. L'abbé *et al.* have found that alkylation of 5-(4-nitrophenylamino)-1,2,3,4-thiatriazole with Me₃O⁺BF₄⁻ similarly gives rise to methylation at the 3-position with formation of a mesoionic compound <91BSB25>. However, generally methylation of 5-(substituted)amino-1,2,3,4-thiatriazoles with Me₃O⁺BF₄⁻ takes place at the 4-position and methylation with diazomethane gives rise to a mixture of 4- and 5-alkylated products (Section 4.19.7.6). 5-Alkoxythiatriazoles react with trivalent phosphorous compounds to give 2,2-dihydro-1,3,4,5,2-thiatriazaphosphorines. These reactions have been reviewed and discussed in detail <76AHC(20)145>.

84CHEC-I(6)579>. In general the thiatriazole ring is rather inert, being stable towards chlorine, nitric acid, alcoholic alkali and Grignard reagents. 5-Phenylthiatriazole is, however, reduced with LAH <64AHC(3)263>.

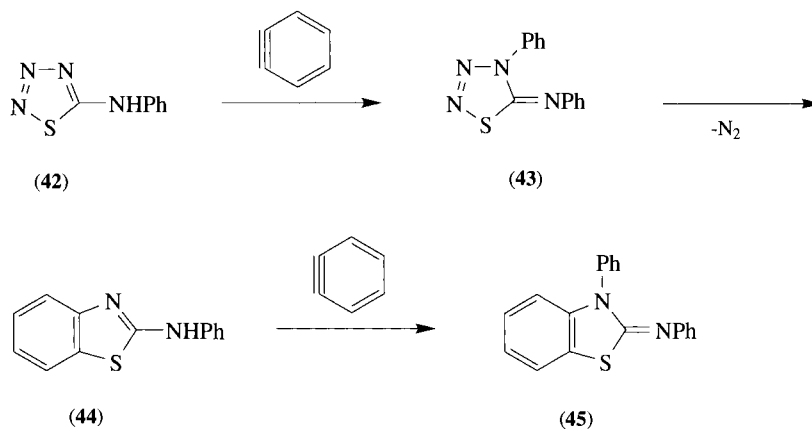
4.19.4.4 Cyclic Reactions

Thiatriazoles are generally not characterized by cycloaddition reactions. Neunhoffer *et al.* were not able to induce a reaction between 5-phenyl-1,2,3,4-thiatriazole (7) and 1,2-diphenylacetylene or dimethyl acetylenedicarboxylate (36) even at 12 kbar <85LA1732>. Similar negative results are reported with other reagents (see Section 4.19.4.1). However, a reaction between *N,N*-diethyl-1-propynylamine (40) and 5-phenyl-1,2,3,4-thiatriazole (7) took place at 12 kbar and a compound assigned structure (41) on the basis of MS and NMR was isolated in 17% yield. The suggested reaction pathway, initiated by a 1,3-dipolar cycloaddition reaction at N(2) and N(4) is shown in Scheme 5. Formation of an alternative triazabicyclo[2.2.1]heptadiene was left open.



Scheme 5

L'abbé *et al.* obtained 3-phenyl-2-phenyliminobenzothiazoline (45) in 50% yield from the reaction of 5-phenylamino-1,2,3,4-thiatriazole (42) with benzyne generated *in situ* from benzenediazonium-2-carboxylate <90JHC923>. However, the reaction does not appear to involve a cycloaddition, and a reaction involving addition of benzyne to give 4-phenyl-5-phenylimino-1,2,3,4-thiatriazoline (43) followed by loss of nitrogen to give 2-(phenylamino)-1,3-benzothiazole (44) and addition of a further molecule of benzyne is suggested (Scheme 6).



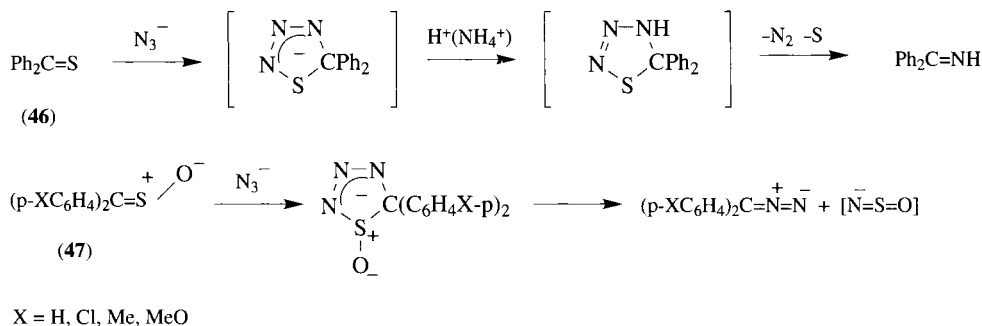
Scheme 6

4.19.5 REACTIVITY OF NONCONJUGATED RINGS

4.19.5.1 Thermal Reactions

4.19.5.1.1 Δ^2 -1,2,3,4-Thiatriazolines

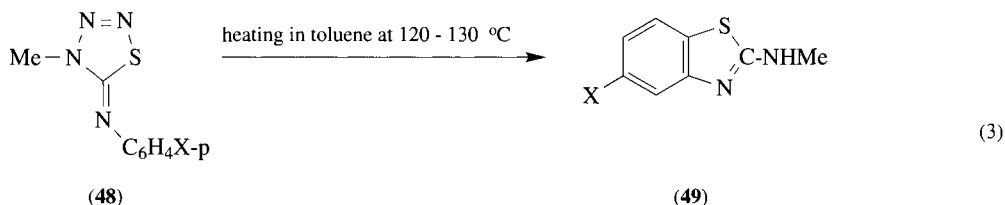
Thermally unstable 1,2,3,4-thiatriazolines are reported as possible transient intermediates in the reaction between azide ion and thiobenzophenone (**46**) or thiobenzophenone *S*-oxides (**47**) (Scheme 7) <76ACS(B)997>.



Scheme 7

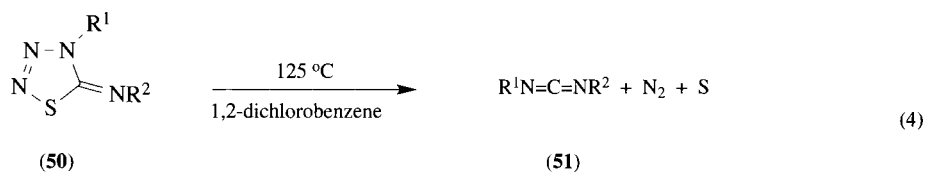
4.19.5.1.2 5-Imino- Δ^2 -1,2,3,4-thiatriazolines and thiaziridinimine intermediates

4-Alkyl-5-aryliminothiatriazolines (**48**) decompose on heating to 120–130°C for several hours to give benzothiazoles (**49**) (Equation (3)) <71AP(304)687, 77JOC1159>. The mechanism of this process is not known but may be the result of electrophilic attack of a 1,3-dipole (see, for example, (**59**)) (thiaziridine open form) formed by loss of nitrogen.



X = H, Me, Cl

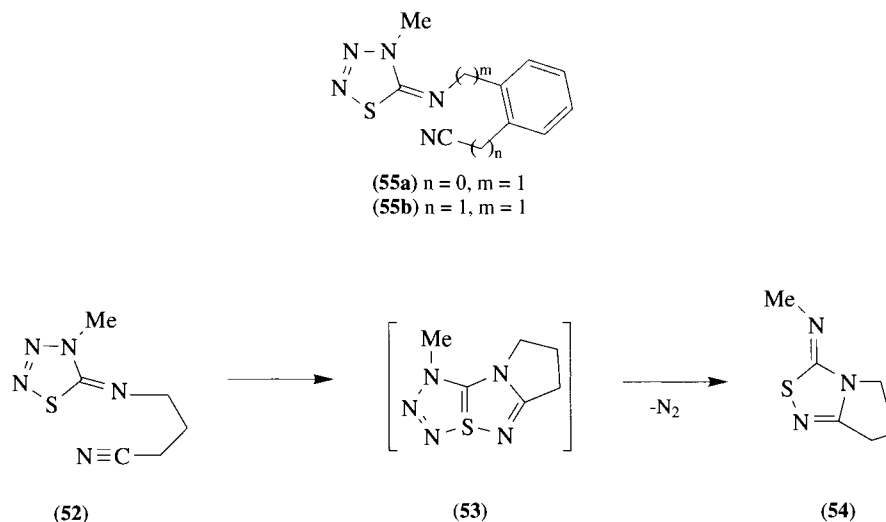
4-Alkyl-5-alkyliminothiatriazolines (**50**) decompose slowly around 40–60°C and rapidly at 125°C with formation of sulfur, nitrogen, and carbodiimide (**51**) (Equation (4)). However, the carbodiimides (**51**) formed react with undecomposed thiatriazoline (**50**), which in part explains the low yields of isolable carbodiimide. It has not been possible by trapping experiments to decide whether the decomposition involves an intermediate as addition of electron-rich alkenes or heterocumulenes induces immediate nitrogen evolution in a bimolecular reaction (see Section 4.19.5.2) <78JCS(P1)1440>.



R¹, R² (yield %): Me, Et (7); Et, Me (16); Et, Et (52)

4-Alkyl-5-picrylimino-1,2,3,4-thiatriazolines are exceptionally thermostable. The 4-benzyl and 4-isopropyl derivative did not thermolyze at 90°C in chlorobenzene or toluene; decomposition started only after prolonged heating at 105°C and was complete after 3–5 days. The resulting mixtures showed no IR spectroscopic evidence of carbodiimide formation (90JHC1059).

4-Methyl-1,2,3,4-thiatriazolin-5-imines bearing a cyanopropyl (**52**), *o*-cyanobenzyl (**55a**) or *o*-(cyanomethyl)benzyl (**55b**) group at the exocyclic imine function have been found to undergo smooth intramolecular cycloaddition–elimination reactions (92JCS(P1)181, 92T7505). The thiatriazolines are synthesized from the corresponding aminothiatriazoles by Meerwein alkylation (Section 4.19.7.6). At 70°C, compound (**52**) gives (**54**) in 91% yield (Scheme 8) but it was found that higher homologues with a longer side chain are thermally stable in benzene at 75°C for one day.

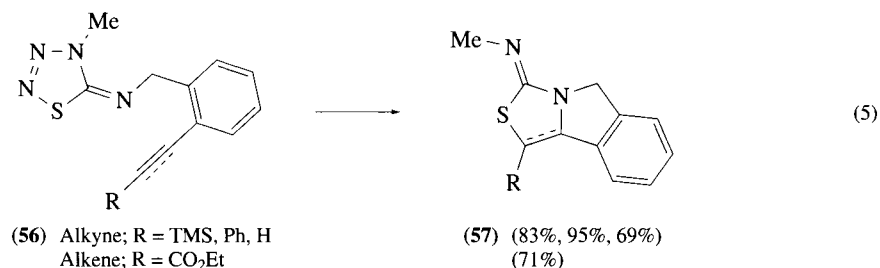


Scheme 8

Introduction of a benzene ring facilitates the intramolecular reaction and when the thiatriazoline (**55a**) is liberated from its tetrafluoroborate salt, a spontaneous elimination of nitrogen takes place at RT. Compound (**55b**) could be isolated but thermolyzes smoothly in ethanol at 75°C to give the expected product.

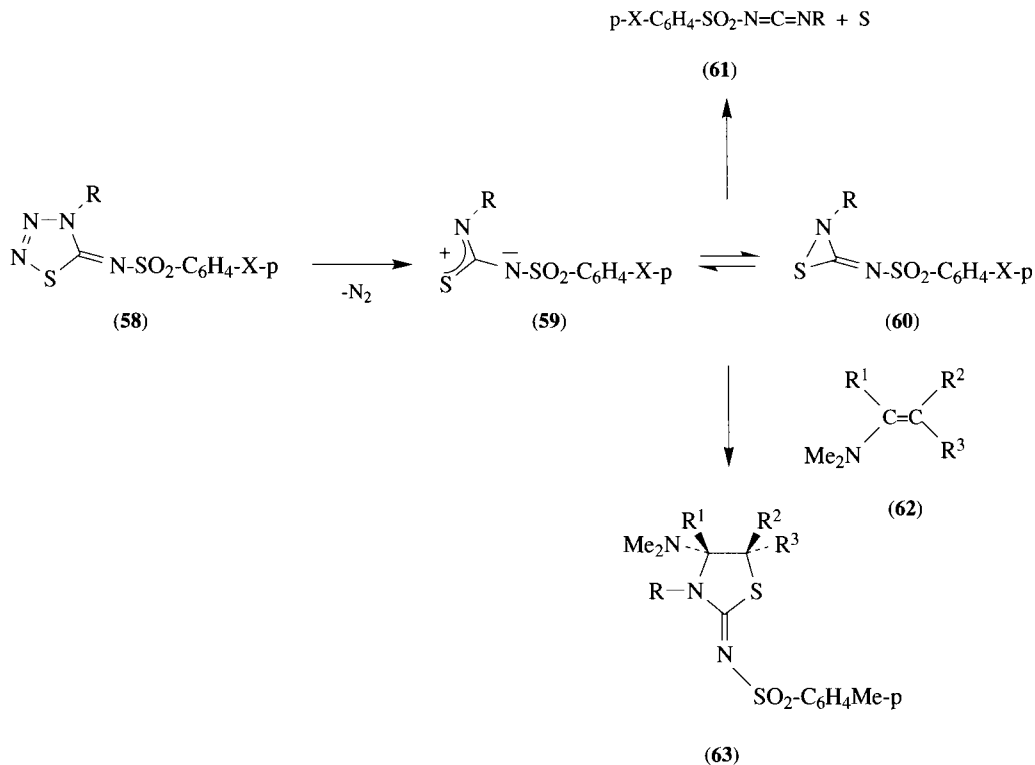
In the case of (**55**) $m=2$ and $n=0$, a 1,2,4-thiadiazolo[3,4-*a*]isoquinoline is obtained in analogy with the mentioned reactions (92T7505). In case of direct attachment of the benzene group to the imine function ($m=0$), a benzothiazole derivative is obtained corresponding to the known decomposition pathway of other aryl substituted 5-iminothiatriazolines (Equation (3)). The facile decomposition of this type of compound is assumed to be caused by intermediate formation of a thiapentalenoid (**53**) intermediate (Scheme 8) having a tetravalent sulfur. The intermediate (**53**) has not been proved directly in the present case but it clearly rationalizes the chain-length dependency of the thermolysis and thiapentalene intermediates may be isolated in other related reactions of iminothiatriazolines (see Section 4.19.5.2).

Similar facile cycloaddition–elimination reactions are observed when the nitrile group is replaced by an alkyne or alkene group. Thus, thermolysis of thiatriazolines (**56**) in refluxing benzene for 3 days provided the intramolecular adducts (**57**) (Equation (5)) (93T4439).



4-Alkyl-5-sulfonylimino- Δ^2 -1,2,3,4-thiatriazolines (**58**) undergo characteristic thermal decomposition with elimination of nitrogen and formation of a 1,3-dipole (**59**) or three-membered ring

intermediate **(60)** (thiaziridinimine) which may lose sulfur with formation of carbodiimides **(61)** or be trapped with a number of different agents as exemplified by enamines **(62)** in Scheme 9 <73JOC2916, 74JA3973>.

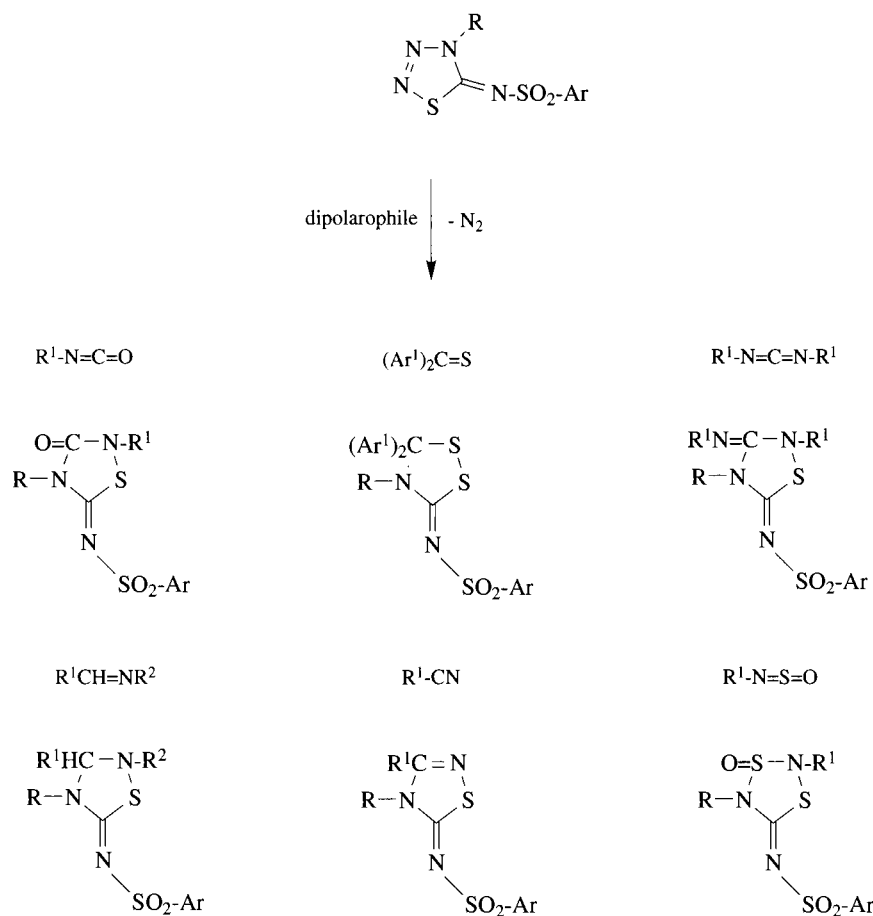


Scheme 9

The indicated stereochemistry of the adduct **(63)** was established by ^1H and ^{13}C NMR spectroscopy and kinetic experiments showed that the rate of thermal decomposition is not influenced by the presence of enamines excluding direct attack on the thiatriazoline. Ynamines react analogously and ketostabilized phosphorous ylides react first to give cyclic adducts which lose Ph_3PO by a Wittig-type elimination. Alkenes such as vinyl ethers, vinyl acetates and the electron-poor alkenes methyl acrylate and dimethyl acetylenedicarboxylate do not give cycloaddition products <73JOC2916, 74JA3973>. Cycloaddition products are also formed with isocyanates, isothiocyanates, and carbodiimides <75S52>.

L'abbé and Yu showed that the presumed intermediate thiaziridinimines (**(59/60)**) could be trapped by thiobenzophenones in a regiospecific manner. Thiocarbonyl compounds such as 3-benzylrhodanine and xanthates react in a similar manner, but reaction with CS_2 could not be accomplished <76JHC883>. Trapping of thiaziridinimines (**(59/60)**) with imines and nitriles has been investigated. Structure elucidation of the cycloaddition products are based on spectral analysis and in the case of cycloaddition products with nitriles a crystal structure analysis has been carried out ($\text{Ar} = \text{MeC}_6\text{H}_4$, $\text{R} = \text{PhCH}_2$, $\text{R}^1 = \text{Ph}$; Scheme 10) <76JOC3403>. Cycloaddition with *N*-sulfonyl amines has been demonstrated and an x-ray diffraction analysis has been carried out on the cycloaddition product ($\text{Ar} = \text{MeC}_6\text{H}_4$, $\text{R} = \text{PhCH}_2$, $\text{R}^1 = p\text{-MeC}_6\text{H}_4\text{SO}_2$; Scheme 10) <78BSB285>. Thiatriazolines thus prove to be versatile compounds for the synthesis of several different heterocyclic systems. Some of the mentioned reactions, which in most cases proceed with moderate to good yields, are summarized in Scheme 10.

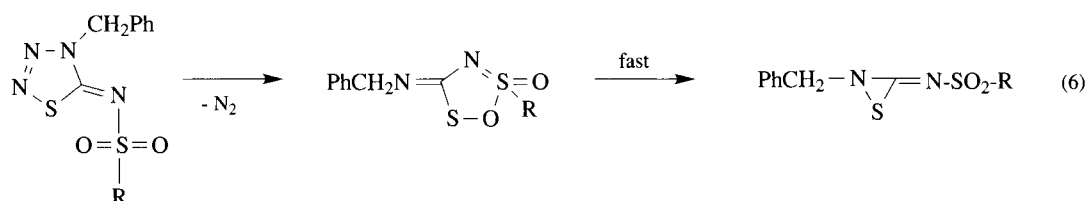
Kinetic investigations using NMR spectroscopy have confirmed thiaziridines as intermediates in these reactions <88BSB83>. Thus thermolysis of 4-alkyl-5-arylsulfonylimino-1,2,3,4-thiatriazolines (**(58)**) was carried out at 60°C in the presence or absence of a coreagent and the rate of decomposition was followed. First-order kinetics were observed in all cases using $\text{PhCOCH}=\text{PPh}_3$, PhCH_2CN , $\text{RN}=\text{C}=\text{NR}$ ($\text{R} = c\text{-C}_6\text{H}_{11}$), $\text{PhN}=\text{C}=\text{O}$ and $\text{PhN}=\text{C}=\text{S}$ as coreagent, excluding a bimolecular



Scheme 10

reaction. Evidence to distinguish between an open (**59**) or closed (**60**) form of the thiaziridine has not been given.

In contrast to 4-alkyl-5-sulfonyliminothiatriazolines which generally undergo first-order reactions via thiaziridinimines (**60**), 4-alkyl-5-aryl or 5-alkyliminothiatriazolines are thermally more stable and undergo bimolecular reactions (see Section 4.19.5.2). There is evidence that anchimeric assistance by the sulfonyl group (Equation (6)) is responsible for this difference in behavior $\langle 90JHC2133 \rangle$. It is of interest to note that the analogous acylaminothiatriazoles are elusive compounds which most likely owe their instability to anchimeric participation by the acyl group in their thermolysis (see Section 4.19.6.1.2).



4.19.5.1.3 Δ^3 -1,2,3,4-Thiatriazolines

Δ^3 -1,2,3,4-Thiatriazolines (see Section 4.19.7.7) decompose to give 2,1-benzisothiazoles $\langle 78JOC2500 \rangle$.

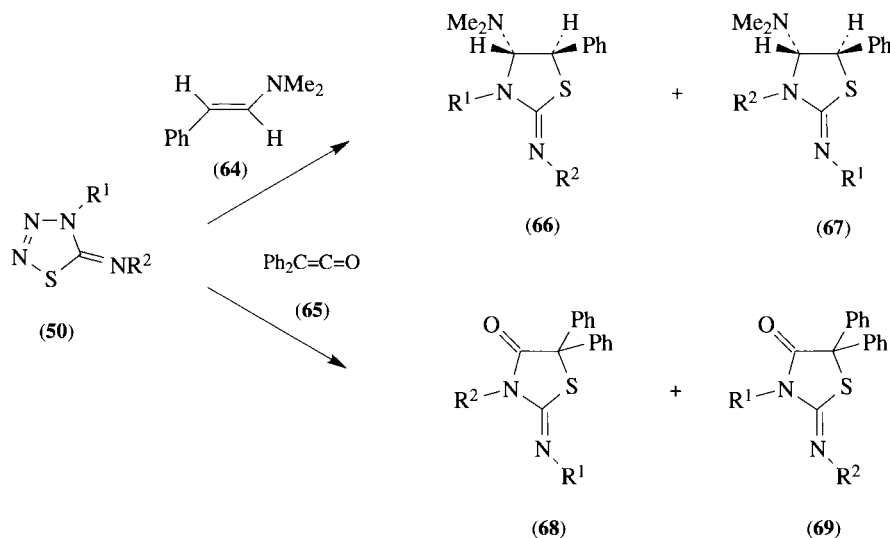
4.19.5.2 Reactions of Δ^2 -1,2,3,4-Thiatriazoles

4.19.5.2.1 Cycloaddition reactions of Δ^2 -1,2,3,4-thiatriazoles

In contrast to 4-alkyl-5-sulfonylimino- Δ^2 -1,2,3,4-thiatriazoles (**58**) (Section 4.19.5.1.2), 4-alkyl-5-alkylimino- Δ^2 -1,2,3,4-thiatriazoles (**50**) react with immediate nitrogen evolution when added to electron-rich alkenes or to heterocumulenes such as enamines, carbodiimides, isocyanates, isothiocyanates, or styrene. Reaction kinetics for certain of this type of system show that they undergo bimolecular processes as described below.

(i) Ketenes and enamines

The results of addition of β -*N,N*-dimethylaminostyrene (**64**) and of diphenylketen (**65**) to 4-alkyl-5-alkyliminothiatriazoles (**50**) are depicted in Scheme 11. In the first case, elemental analysis, mass spectrometry and ^1H NMR spectroscopy are in agreement with structures (**66**) and (**67**) formed in an almost equal amount. In the case of diphenylketen, the structure of the resulting product ($\text{R}^1 = \text{R}^2 = \text{Me}$; 44% yield) has been inferred from independent synthesis from diphenylchloroacetic acid and 1,3-dimethylthiourea. However, the reaction is complex and in the case of $\text{R}^1 = \text{Et}$ and $\text{R}^2 = \text{Me}$, compound (**68**) was formed exclusively in 64% yield under highly dilute conditions, while a mixture of (**68**) and (**69**) is formed under more concentrated conditions ($\approx 10^{-2} \text{ M}$) <78JCS(P1)1440>. L'abbé and Sannen later showed that (**68**) isomerizes to (**69**) in the presence of the ketenes at higher concentrations explaining the observed concentration-dependent product formation. They also reassigned the original incorrectly assigned carbon resonances <78JCS(P1)1440> in the ^{13}C NMR spectra of (**69**) <91BSB29>. Bis(ethoxycarbonyl) ketene reacts similarly with 4-methyl-5-methyliminothiatriazoline to give the expected 5,5-bis(ethoxycarbonyl)-3-methyl-2-methyliminothiazolidin-4-one <91BSB29>.

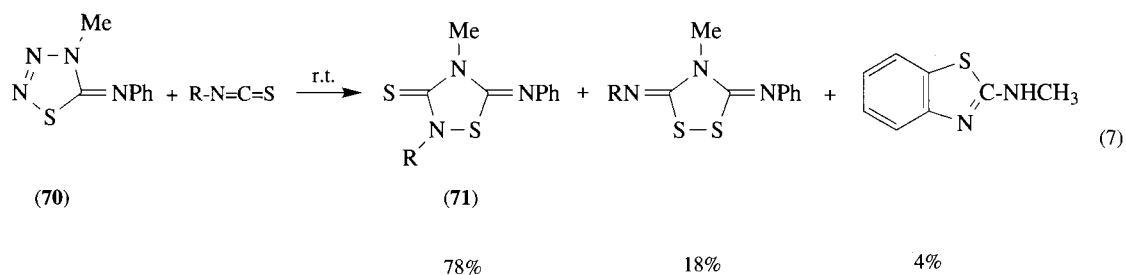


Scheme 11

Addition of electron-poor alkenes such as *trans*-stilbene, diethyl fumarate and maleate, and fumaronitrile to (**50**) do not cause nitrogen evolution. Even on heating cycloaddition products were not isolated, although decomposition was induced. Addition of bases such as benzylamine had no influence on the decomposition rate <78JCS(P1)1440>.

(ii) Isothiocyanates and sulfenes

4-Methyl-5-phenylimino-1,2,3,4-thiatriazoline (**70**) reacts with phenyl isothiocyanate at RT under nitrogen evolution to give compound (**71**) ($\text{R} = \text{Ph}$) as the main product (Equation (7)) <77JOC1159>.



A direct cycloaddition of isothiocyanate to the thiatriazoline ring was considered and three different modes of addition were suggested (Figure 5). Path (a) was considered (C=N addition) to be a major pathway <77JOC1159> but was later rejected in favor of path (b). Thus when 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**70**) reacts with 2-pyridyl isothiocyanate (**72**), dithiazoline (**73**) is formed as the major product (C=S addition, path (b)) at a very early stage of the reaction (12%). As the reaction progresses it then decreases after three hours to reach a steady value of ca. 7% and the isomeric (**75**) reaches a maximum of 35% after six–seven hours where it constitutes the major product. Compound (**75**) then decreases and the other products (**74**) and (**76**) increase continuously during the reaction and are the major end products (30% and 40% respectively after 34 hours). This complicated reaction was followed under a variety of conditions and by analyzing the products by ^{13}C NMR (Scheme 12) <88JHC1459>. Similar observations were made in the reaction of (**70**) with *p*-nitrophenylisothiocyanate <89BSB879>.

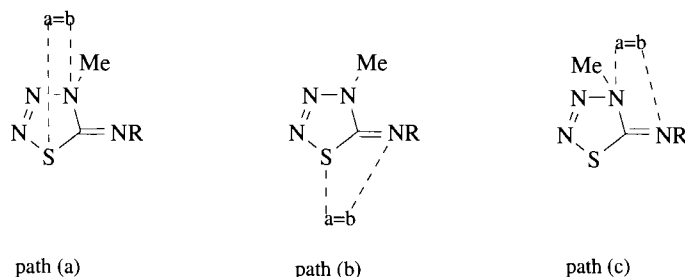
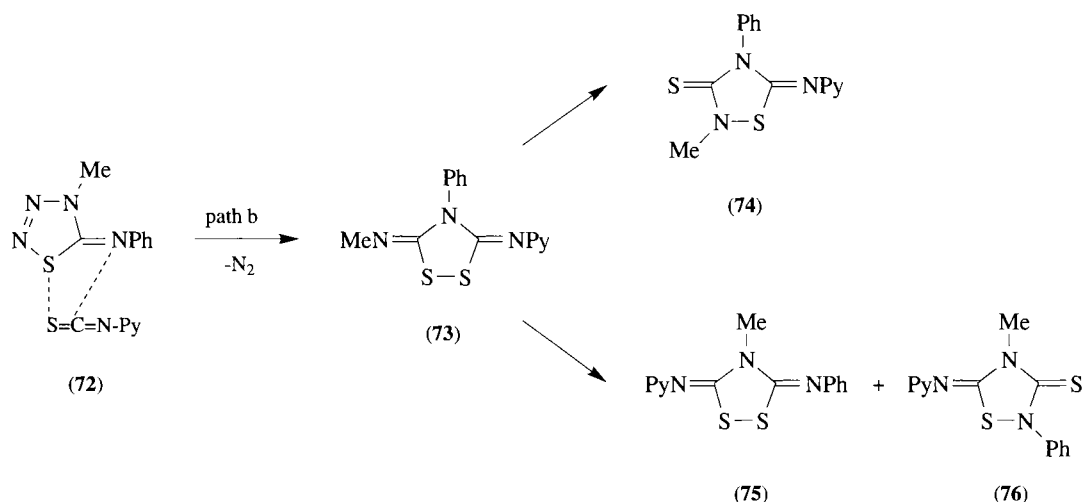


Figure 5 Modes of addition of isothiocyanates to thiatriazoline-5-imines.

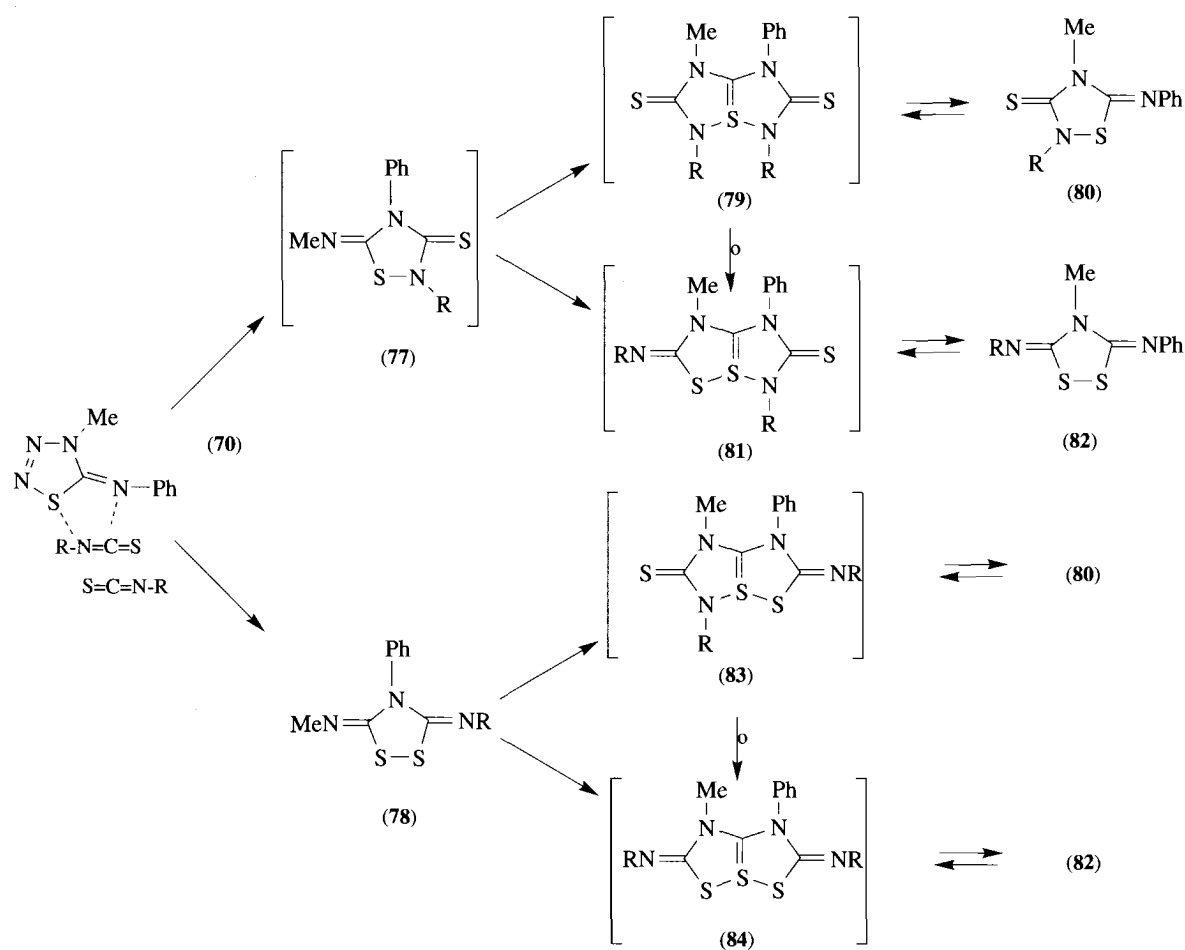


Scheme 12

The results of extensive studies on the reaction of thiatriazolin-5-imines with isothiocyanates are summarized in Scheme 13 <90BSB391, 90JHC199, 90T1281>. Addition takes place with both C=S and C=N bonds of the isothiocyanate to give (**78**) and (**77**) respectively. These compounds combine with a second molecule of isothiocyanate to give (**80**) and (**82**) via thiapentalene-like intermediates

which are known to have weak N—S and S—S bonds allowing for facile isomerization of (79) into (81) and (83) into (84). The final step is the elimination of the first isothiocyanate added, to give the product (82). Compound (77) has not been isolated or characterized but NMR measurements point to its transient existence. Path (c) (Figure 5), which has been suggested only once to account for a product in low concentration, remains questionable. Scheme 13 rationalizes not only the reactions of isothiocyanates with thiatriazolines and explains product formation in the reaction of isothiocyanates with alkyl or aryl azides (Section 4.19.5.2.2) but is in agreement with the other reactions of thiatriazolines described below.

Acyl isothiocyanates ($\text{RCON}=\text{C}=\text{S}$) and sulfenes ($\text{RCH}=\text{SO}_2$) react with thiatriazolines to give $\text{C}=\text{S}$ adducts following path (b) <78JOC4951>.



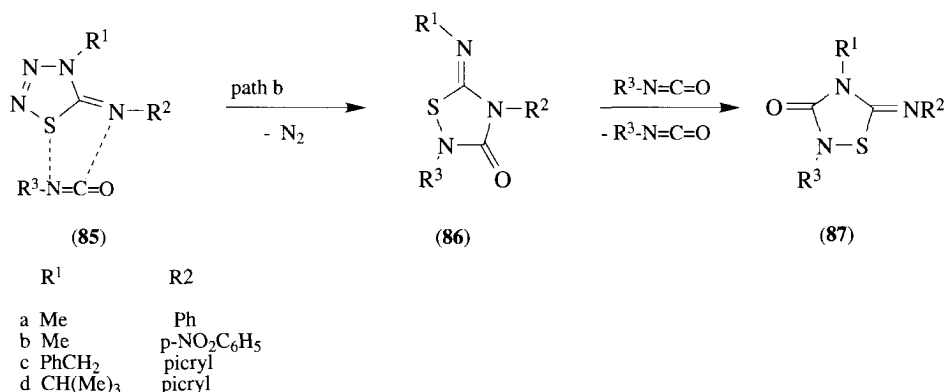
Scheme 13

(iii) Isocyanates

As discussed in Section 4.19.5.2.2 thiatriazolines formed *in situ* may be trapped with isocyanates to give thiazolidines <76AG510>. This reaction has been studied more closely using the stable 4-alkyl-5-arylimino-1,2,3,4-thiatriazolines (85) (Scheme 14) <76AG510, 90JHC1059, 91BSB27>.

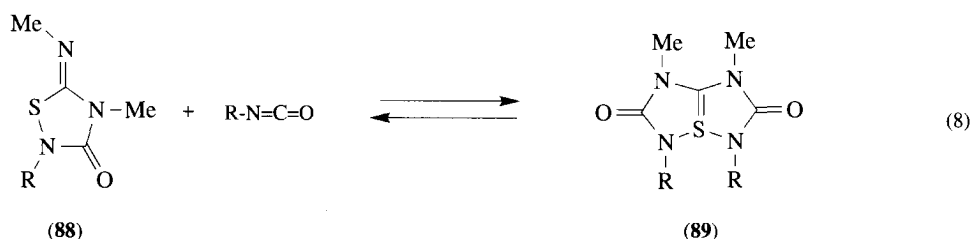
Two pathways were considered: a dipolar cycloaddition across S(1) and N(4) (path (a)) and a dipolar cycloaddition across S(1) and the exocyclic nitrogen N(exo) (path (b)) (Figure 5). The reactions are, however, facilitated by more electrophilic isocyanates ($\text{RSO}_2\text{NCO} > \text{RCONCO} > \text{ArNCO} > \text{Alkyl NCO}$) disfavoring path (a), and the observed reactivity order of the starting heterocycles ((85a) > (85b) >> (85c)) is in better agreement with path (b). The expected intermediate (86) was successfully trapped when the bulky *t*-butyl group was introduced in position

4 (R^1) (**85d**). The isomers (**86**) and (**87**) were obtained in 47% and 32% yields respectively, establishing the consecutive cycloaddition elimination reactions shown in path (b).



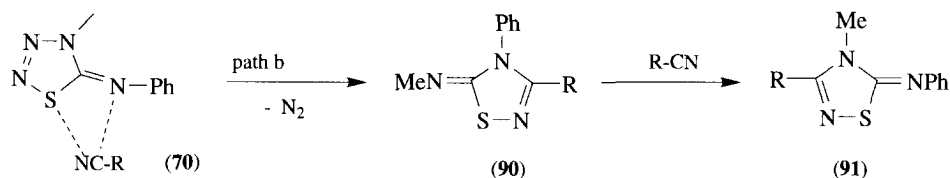
Scheme 14

Further insight into these reactions was obtained when it was discovered that 4-methyl-5-methyl-iminothiatriazolines (**88**) ($R = \text{PhCH}_2$, Ph , $p\text{-MeOC}_6\text{H}_4$, $p\text{-ClC}_6\text{H}_4$, PhSO_2) equilibrate with a thiapentalene (**89**) in the presence of excess isocyanate (Equation (8)). The thiapentalenes (**89**), thus responsible for thiadiazoline isomerization, have been isolated and characterized spectroscopically [91JHC405].



(iv) Nitriles

Pathway (b) (Figure 5) was established for the reaction of 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**70**) with nitriles ($R = \text{CO}_2\text{Et}$, Ts , CCl_3 , PhO) similar to that of isocyanates and isothiocyanates, and the isomeric thiadiazolines (**90**)/(**91**) were isolated under appropriate reaction conditions ($R = \text{CO}_2\text{Et}$) (Scheme 15). The isomerization was shown to be initiated by the presence of nitriles [91JHC333].



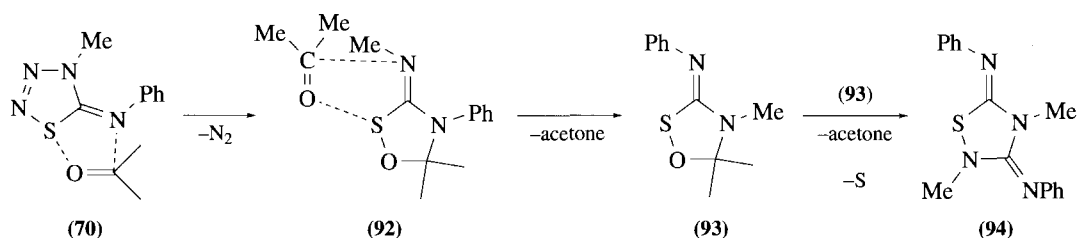
Scheme 15

Martin *et al.* briefly reported on the reaction of 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline with phenyl cyanate to give (**91**) ($R = \text{PhO}$) [85JOC1295]. However, the reaction was carried out in acetone and is now interpreted to proceed via (**92**) (Scheme 16) [91JHC333].

(v) Ketones

4-Methyl-5-phenylimino-1,2,3,4-thiatriazoline (**70**) reacts with acetone to give a thermolabile crystalline compound identified as a 1,2,4-oxathiazole derivative (**93**) (Scheme 16). The reaction is

believed to take place via a primary cycloaddition product (**92**) which undergoes a second fast cycloaddition–elimination reaction with acetone because of its pronounced nucleophilic *N*-methyl-imine function. This reaction sequence is supported by the presence of a ^1H NMR signal at δ 2.85 ppm which first appears and later disappears as the reaction progresses <90JHC1993>.



Scheme 16

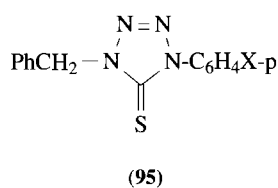
On prolonged standing or heating in acetone compound (**94**) is formed, which probably is a result of fragmentation of (**93**) into acetone, sulfur and carbodiimide ($\text{PhN}=\text{C}=\text{NMe}$) followed by addition of the carbodiimide to (**93**) with elimination of acetone.

1,2,4-Oxathiazolidin-3-imine (**93**) possesses a thioimide moiety similar to 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**70**) and is capable of undergoing cycloaddition–elimination reactions with isothiocyanates to give identical products, however at a much higher rate. Acetone can therefore be used as solvent to catalyze this kind of reaction of thiatriazolines.

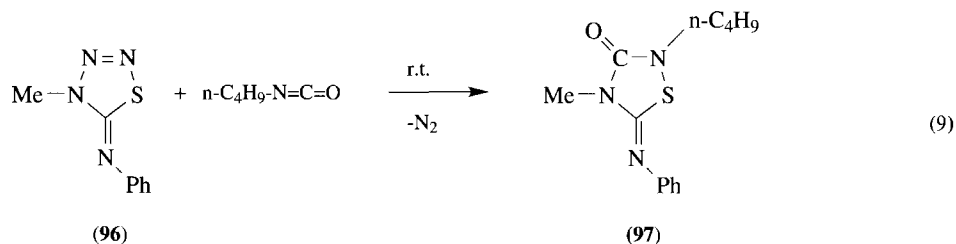
4.19.5.2.2 Cycloaddition reactions of Δ^2 -1,2,3,4-thiatriazolines formed in situ

Aryl isothiocyanates react with alkyl azides to form a mixture of thiatriazolines but the primary products cannot be isolated.

Detailed studies by L'abbé *et al.* support initial formation of 4-alkyl-5-iminothiatriazoles by addition of the azide to the $\text{C}=\text{S}$ of the isothiocyanate. The thiatriazoline then undergoes the type of transformations outlined in Scheme 13. Tetrazoline (**95**) is also formed as a minor product by addition of the azide to the $\text{N}=\text{C}$ of the isothiocyanate <75JHC607, 77JOC1159>, see also <75CC24>.



L'abbé and Verhelst have shown that intermediary thiatriazolines may be trapped with isocyanates to give 5-arylimino-1,2,4-thiadiazolidin-3-ones when isothiocyanate is slowly added (7 days) to a mixture of alkyl azide and isocyanate kept in solution at 80°C <76AG510>. Good to moderate yields were obtained. The suggested intermediacy of thiatriazoline was fully supported by an independent experiment in which authentic 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**96**) was added to butyl isocyanate at RT to give the expected thiazolidine (**97**) in 95% yield (Equation (9)).



4.19.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

4.19.6.1 1,2,3,4-Thiatriazoles

4.19.6.1.1 5-Chloro-1,2,3,4-thiatriazole

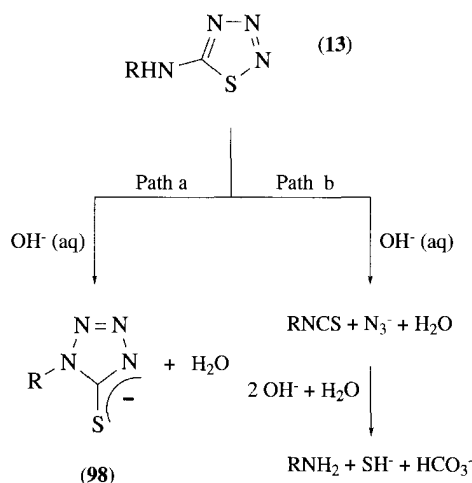
The highly explosive 5-chloro-1,2,3,4-thiatriazole (prepared from thiophosgene and sodium azide) has been used for the preparation of 5-substituted 1,2,3,4-aminothiatriazoles and certain 5-alkoxythiatriazoles (Section 4.19.7). Great care should be exercised in handling any reaction product of thiophosgene and azide ion. In particular the reaction of 5-chloro-1,2,3,4-thiatriazole with azide ion yielded a product assumed to be 5-azido-1,2,3,4-thiatriazole which gave rise to explosion as a suspension in water <61JOC1644>.

4.19.6.1.2 5-Amino-1,2,3,4-thiatriazole

5-Amino-1,2,3,4-thiatriazoles (**13**) have attracted considerable interest as potential precursors for other heterocycles. The reaction of the nucleophilic amino group with different electrophilic centers has been studied by several groups.

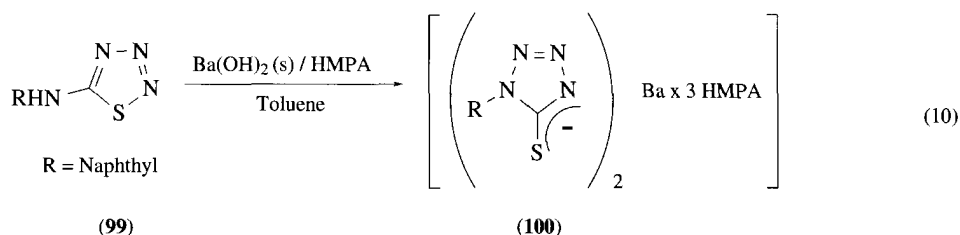
(i) Reaction with base

It has been shown that 5-aminothiatriazoles (**13**) react with sodium hydroxide <1895CB74, 57CJC832, 67JOC3580> to give tetrazole-5-thiolate (**98**). Thus Lieber *et al.* described how treatment with aqueous sodium hydroxide gave rise to a mixture of tetrazole (**98**) (path (a)) and isocyanate and azide (path (b)) (Scheme 17) <57CJC832>.

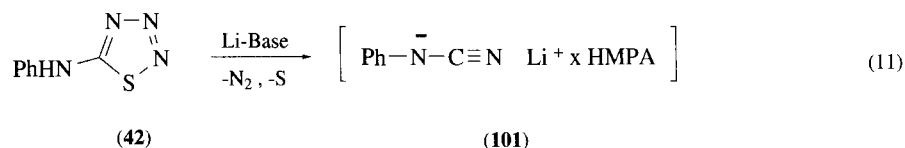


Scheme 17

This base-catalyzed reaction has been discussed in more detail by Snaith and co-workers <92CC1152, 93AG1801>. The reaction between 5-naphthylamino-1,2,3,4-thiatriazole (**99**) and 1 equivalent of solid $\text{Ba}(\text{OH})_2$ in toluene in the presence of 3 equivalents of HMPA gave rise to salt (**100**) in 60% yield (path (a)) for which an x-ray structure has been obtained (Equation (10)) <92CC1152>.

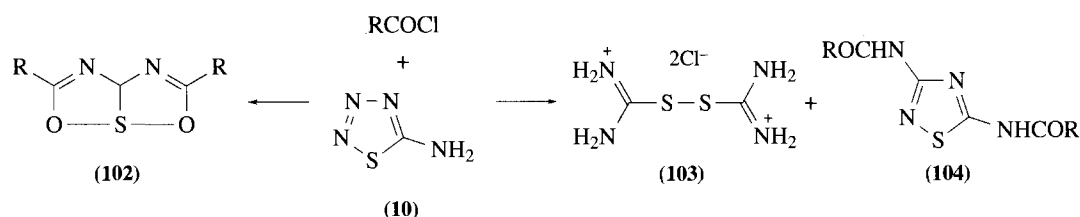


As a contrast to this, when 5-phenylamino-1,2,3,4-thiatriazole (**42**) and an equimolar amount of HMPA in toluene at -78°C is treated with 1 equivalent of solid lithium bases, LiOH, MeOLi, LiNH_2 , $i\text{-Pr}_2\text{NLi}$ or BuLi dissolved in hexane, extrusion of nitrogen and sulfur is observed on heating to room temperature, resulting in formation of PhNCNLi , HMPA complex (**101**) (Equation (11)) <93AG1801>.



(ii) Reaction with carboxylic acid chlorides

Acylation of 5-aminothiatriazole (**10**) with carboxylic acid chlorides were described independently by L'abbé *et al.* <77AG420> and Beer and Hart <77CC143>. The reaction of 5-aminothiatriazole (**10**) with aroyl chlorides in the presence of pyridine or triethyl amine was anticipated to give 5-(aroylamino)thiatriazoles, but resulted in loss of nitrogen and the formation of the hitherto unknown 2,5-diaryl-1,6-dioxo-6a- λ^4 -thia-3,4-diazapentalenes (**102**) (Scheme 18) <77AG420, 77CC143>. A thiapentalene was isolated in low yield under identical conditions using thiobenzoyl chloride <81BSB89>. When the reaction between 5-aminothiatriazole (**10**) and benzoyl chloride is carried out in the absence of base at 50°C , formamidine disulfide (**103**) is formed together with a 1,2,4-thiadiazole (**104**) (Scheme 18). The formamidine disulfide (**103**) is the known decomposition product of 5-aminothiatriazole (**10**) under acidic conditions <64AHC(3)263>.



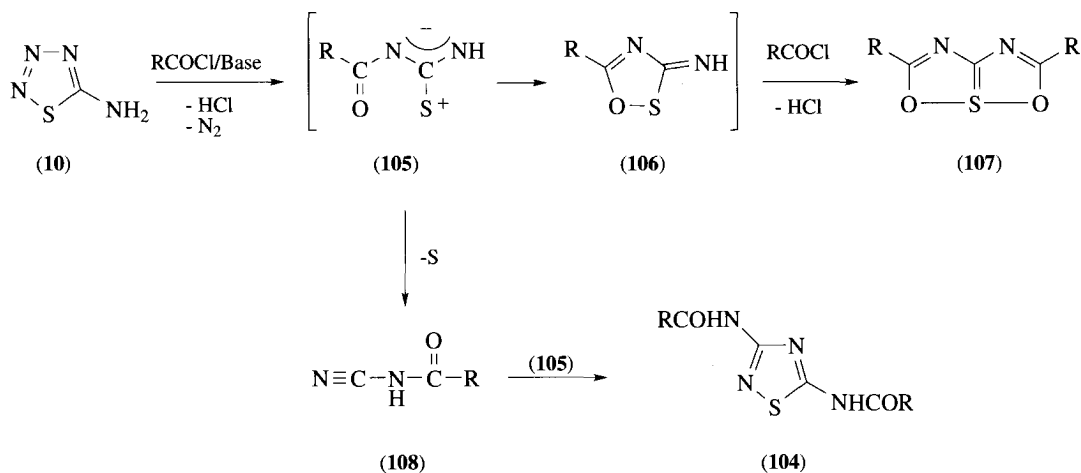
Scheme 18

Formamidine disulfide (**103**) was also formed when 5-aminothiatriazole (**10**) was allowed to react with thiobenzoyl chloride in acetonitrile without addition of base <81BSB89>. Beer and Hart found that 5-aminothiatriazole (**10**) reacted with acetyl chloride or acetic anhydride to give 3,5-diacetamido-1,2,4-thiadiazole (**104**; R = Me) while neither a thiapentalene (**102**) nor 5-acetamido-thiatriazole was observed (Scheme 18) <77CC143>. In contrast, L'abbé and Vermeulen isolated 2,5-dimethyl-1,6-dioxo-6a- λ^4 -thia-3,4-diazapentalene (**102**; R = Me) together with the 1,2,4-thiadiazole (**104**) in approximately equal amounts ($\approx 20\%$) <81BSB89>.

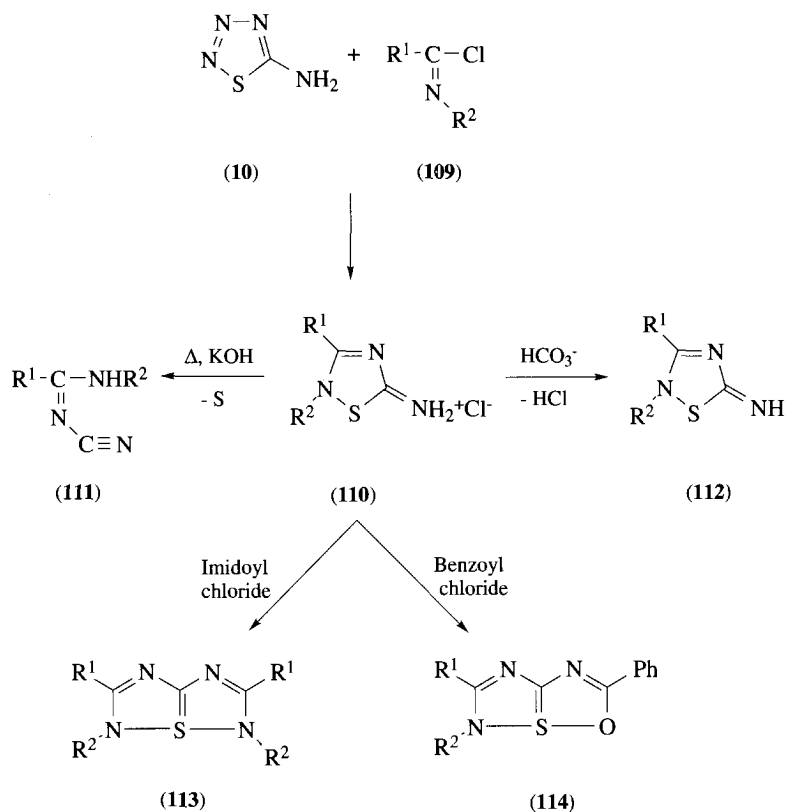
L'abbé and Vermeulen have proposed salts of type (**105**) as key intermediates in the reactions of 5-aminothiatriazole (**10**) with acyl chlorides (Scheme 19) <81BSB89>. The intermediate is expected to undergo cyclization to 3-imino- Δ^4 -1,2,4-oxathiazoline (**106**) followed by reaction with a second molecule of acyl chloride to give the corresponding thiapentalene (**107**). The formation of the 1,2,4-thiadiazole (**104**) was explained as a result of an addition of *N*-acetylcyanamide (**108**), formed by extrusion of nitrogen and loss of sulfur from 5-acetamido-1,2,3,4-thiatriazole, to the key intermediate (**105**).

(iii) Reaction with imidoyl chlorides

5-Amino-1,2,3,4-thiatriazole (**10**) has been described as reacting with equal amounts of *N*-phenyl benzimidoyl chloride (**109**) to give 5-imino- Δ^3 -1,2,4-thiadiazoline hydrochloride (**110**) in 80% yield (Scheme 20). The thiadiazoline is decomposed by strong base into *N*-cyanoamidine (**111**) and sulfur, but the free base (**112**) can be liberated by treatment with bicarbonate. The free base decomposes similarly into *N*-cyanoamidine (**111**) and sulfur when heated in chloroform or water.



Scheme 19



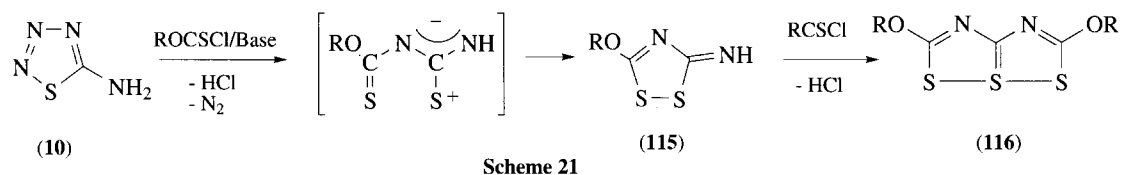
Scheme 20

Further reaction of the 5-iminothiadiazoline hydrochloride (110) with either another equivalent of imidoyl chloride or benzoyl chloride resulted in the formation of the corresponding thiapentalenes (113) and (114) respectively $\langle 81\text{BSB}89 \rangle$. However, it was not possible for the authors to make the tetraazathiapentalene (113) from 5-aminothiadiazole (10) by a direct reaction with 2 equivalents of imidoyl chloride (109) in the presence of triethylamine. This procedure resulted instead in a mixture of *N*-cyanoamidine (111) and 5-imino- Δ^3 -1,2,4-thiadiazoline hydrochloride (110) $\langle 81\text{BSB}89 \rangle$. L'abbé and Vermeulen pointed out that the intermediary thiadiazoline can be used to advantage in preparing unsymmetrical substituted thiapentalenes $\langle 81\text{BSB}89 \rangle$. For further reactions see $\langle 92\text{JHC}1317 \rangle$.

The described reaction between 5-aminothiadiazole and imidoyl chlorides has been used for preparation of certain hitherto unknown oligo-1,2,4-thiadiazolines $\langle 93\text{AP}(326)399 \rangle$.

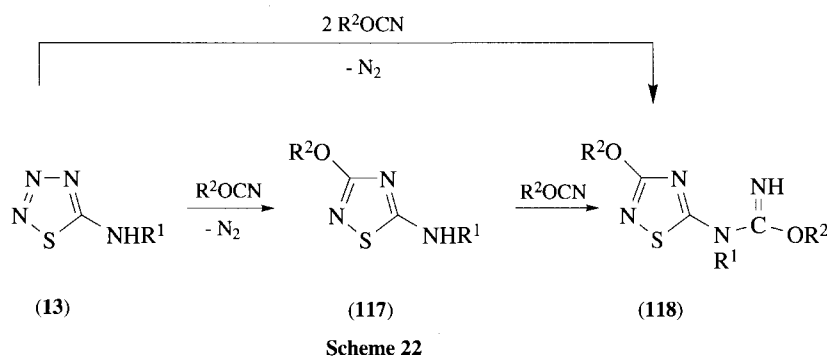
(iv) Reaction with chloroformates and chlorothioformates

Graubaum *et al.* studied the reaction of 5-aminothiatriazole (**10**) with chloroformates in the presence of base and isolated 1,2,4-thiadiazoles (**104**; R = OR) <89M997, 90JPR208>. In the reaction between 5-aminothiatriazole and chlorothioformates in the presence of base the main products were trithiapentalenes (**116**) (Scheme 21). However, in the absence of base the intermediary 5-alkoxy- and 5-aryloxy-3-imino- Δ^4 -1,2,4-dithiazoline (**115**) hydrochlorides are isolated. These reactions are analogous to those of (**10**) and acid chlorides (Section 4.19.6.1.2).



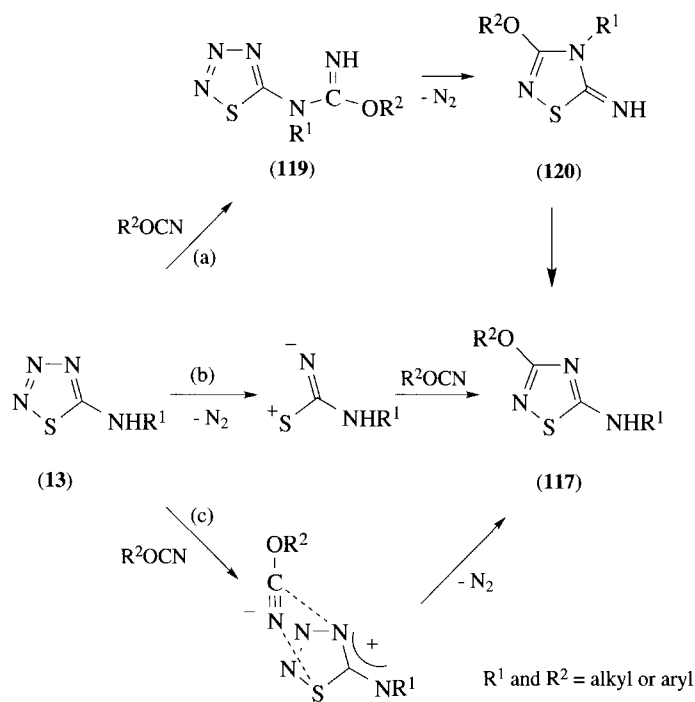
(v) Reaction with cyanates

Martin *et al.* reacted alkyl and aryl cyanates with 5-aminothiatriazoles (**13**) at 0°C in aprotic solvents <85JOC1295>. The reaction led to evolution of nitrogen and the formation of 3-substituted-5-amino-1,2,4-thiadiazoles (**117**) in 40–65% yield. If the reaction was carried out at 30°C or if two equivalents of cyanate was employed a subsequent reaction to the corresponding amidino compound (**118**) took place (Scheme 22).



Trichloroacetonitrile reacts with 5-aminothiatriazole in a similar way to give the 3-substituted-5-amino-1,2,4-thiadiazole <85JOC1295>. Martin *et al.* discussed three different pathways for the formation of the 1,2,4-thiadiazole (**117**) (Scheme 23).

Path (a), which includes a primary attack on the exocyclic amino group giving 5-amidinothiatriazole (**119**) followed by ring closure and extrusion of nitrogen was excluded by the authors because this pathway would lead to 4*N*-substituted thiadiazoles (**120**) but not to 5-amino-substituted-1,2,4-thiadiazoles (**117**) observed experimentally when 5-(alkyl or arylamino)-thiatriazoles were reacted with cyanates. Path (b) involves extrusion of nitrogen in a rate-determining first-order reaction, but can be excluded since the reaction leading to (**117**) is obviously bimolecular. Thus, 5-phenylaminothiatriazole reacts with *p*-tolyl-cyanate in dry DMF within four hours to an extent of 82% while the thiatriazole itself is practically stable in the absence of cyanate. Path (c), which involves a primary attack of the cyanate on the thiatriazole, is thus preferred by Martin *et al.* However, we wish to point out that aryl and alkyl cyanates do not react with thiatriazoles as they are the only products besides sulfur and nitrogen when alkoxythiatriazoles decompose in ethereal solution at 20°C (see refs. 48 and 49 in <76AHC(20)145>). Furthermore, Martin *et al.* report that 5,5-(dimethylamino) and 5,5-(dibenzylamino)thiatriazoles do not react with cyanates even on boiling in acetone for five hours <85JOC1295>. Path (c) seems therefore not likely and we suggest that path (a) involving primary attack on the amino group should be reconsidered.



Scheme 23

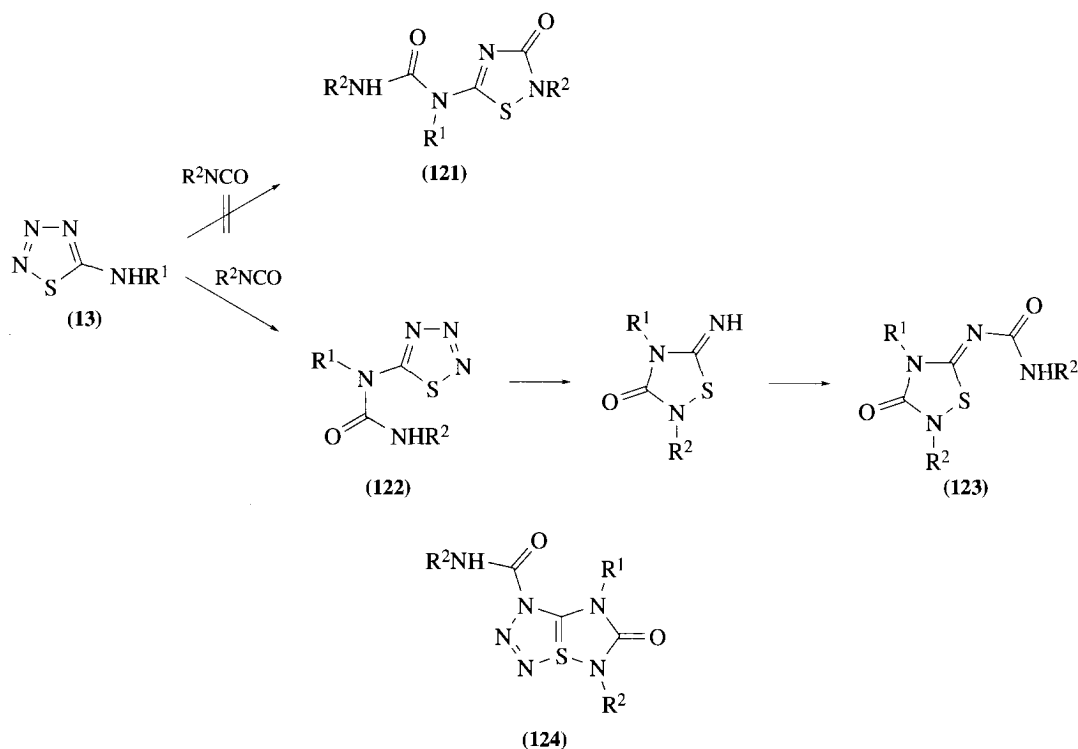
Glatt *et al.* reacted 2-formyl-phenylcyanate with 5-amino- (10) and 5-(phenylamino)thiatriazole (42) <88RRC975>. The products formed may be explained by a mechanism similar to that described in path (a).

(vi) Reaction with isocyanates

Kaugars and Rizzo <79JOC3840> and later Graubaum *et al.* <88ZC327> reported that 5-amino-thiatriazoles (13) react with isocyanates to give (3-oxo- Δ^4 -1,2,4-thiadiazolin-5-yl) ureas (121). The reaction takes place slowly at room temperature but is catalyzed by triethylamine. However, subsequent work by Kaugars *et al.* has shown that the products actually have the structure (123) and can be explained by the sequence shown in Scheme 24 <92JOC1671>. In the absence of base, L'abbé *et al.* were able to isolate an intermediate bicyclic system (124) together with (122) <91JHC1619>.

(vii) Reaction with isothiocyanates

Isothiocyanates were first reported as unreactive towards 5-amino-1,2,3,4-thiatriazoles even at 40°C in the presence of triethylamine <89JPR115>. However, it was later found that they react smoothly in the presence of the stronger base DMAP. The product composition and the reaction pathway was found to resemble the one observed for the oxygen analogue (Scheme 24) <89JPR115, 92JOC1671> except for the formation of trithiapentalenes in the cases where arylisothiocyanates were used <89JPR115>. The formation of trithiapentalenes (127) was explained by Graubaum by the mechanism outlined in Scheme 25 involving initial formation of 5-amino-2-aryl-1,2,4-thiadiazolin-3-thiones (125) <89JPR115>. The thiadiazoline is suggested to undergo a Dimroth rearrangement to 5-amino-3-arylimino- Δ^4 -1,2,4-dithiazoline (126) followed by reaction with a second equivalent of arylisothiocyanate finally leading to the trithiapentalene (127). However, in view of the revised reaction pathway for the corresponding reaction of isocyanates with 5-aminothiatriazole <92JOC1671>, an alternative pathway should be considered involving primary attack of the isothiocyanate on the amino group followed by nitrogen extrusion (Scheme 24).



Scheme 24

5-Alkylamino and 5-arylaminothiatriazoles were reported to be more reactive towards isothiocyanates than 5-aminothiatriazole giving rise to 5-thiourea-1,2,4-thiadiazolin-3-thiones (128) in 50–84% yield. Formation of trithiapentalenes was not observed in these cases <89JPR115>.

(viii) Miscellaneous reactions

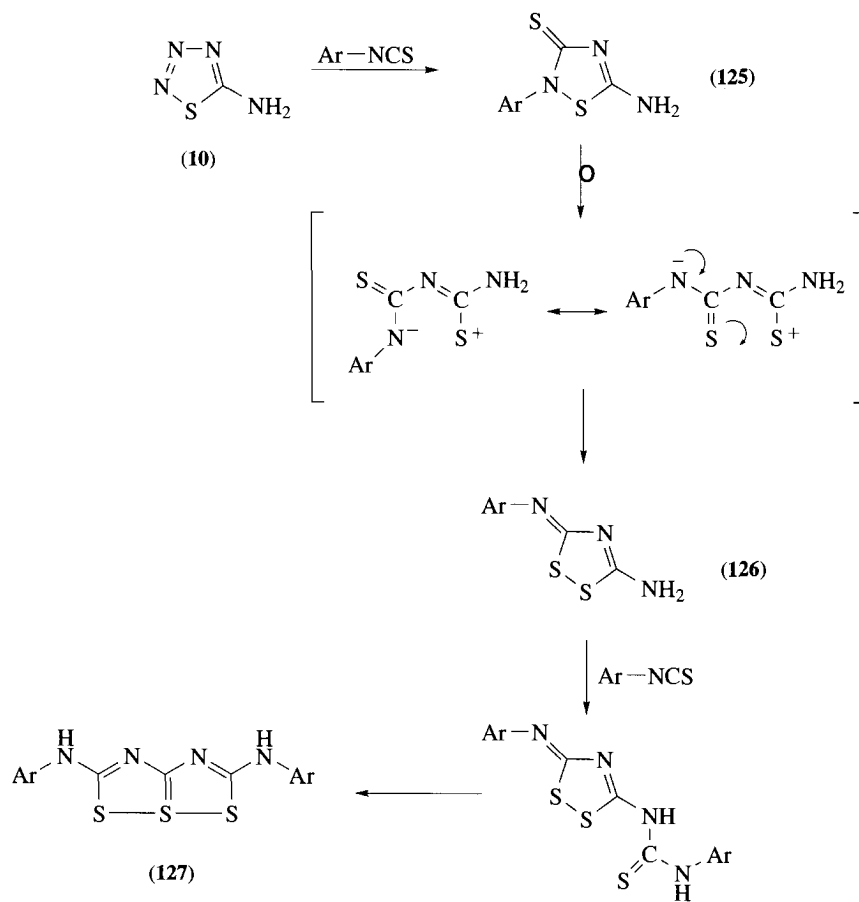
5-Amino-thiatriazole (10) is reported to react with acetylacetone <84KGS269> and other 1,3-diketones <86UKZ82> in the presence of perchloric acid to give pyrimidine derivatives (129) as depicted in Scheme 26. Treatment of 5-amino-thiatriazole (10) with ethoxymethylene malonic acid derivatives in the presence of DMAP gives rise to *N*-(1,2,3,4-thiatriazol-5-yl)aminomethylene malonic acid derivatives (130a–c) as 1 : 1 adducts with DMAP in good yields (60–90%) <93JPR190>. However, in the presence of other bases, e.g. triethylamine, pyridine, or lutidine, the reaction resulted in the formation of nitrogen, sulfur, and unidentified materials. The *N*-(1,2,3,4-thiatriazol-5-yl)aminomethylene malonic acid derivatives (130a–c) are reported as stable compounds at room temperature in the solid form. In solution they decompose into nitrogen, sulfur, and unidentified materials within a couple of hours.

After treatment of (130a) with sulfuric acid in ethanol, bis(4-amino-5-cyanopyridine-2-yl)-disulfide (131) was isolated as the only product in 69% yield. However, if (130b,c) are treated with sulfuric acid in ethanol under otherwise identical conditions the corresponding tetrazolyl-methylene malonic acid derivatives (132) could be isolated in 45% and 48% yields respectively.

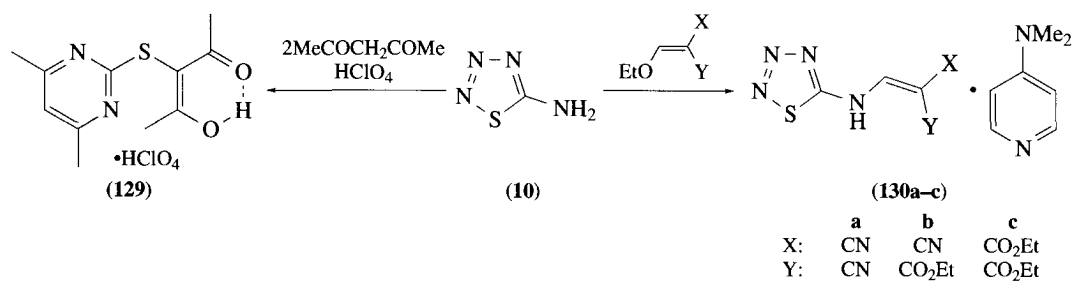
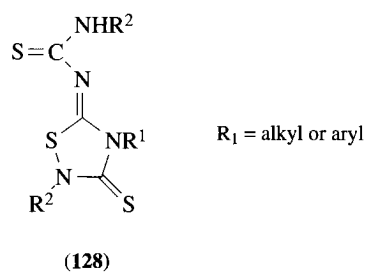
4.19.6.1.3 5-Hydrazino-1,2,3,4-thiatriazole

5-Hydrazinothiatriazole (133) reacts rapidly with ketones and aldehydes to give thermally relatively stable hydrazones (134) in good yields ($\approx 80\%$) <85ZC136, 87JPR409>. Compounds (134) are alkylated with alkyl halides exclusively at the hydrazino functionality (rather than at N(4)) to give (135) (Scheme 27).

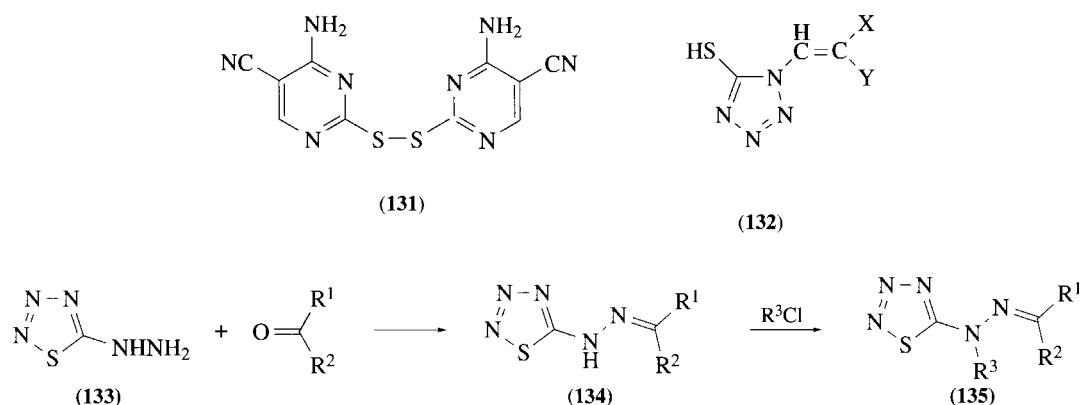
These alkylation products (135) are thermally stable up to about 120°C above which they decompose into nitrogen, sulfur, and polymeric material <87JPR409>.



Scheme 25



Scheme 26



Scheme 27

The hydrazones derived from (133) and oxocarboxylic acids are thermally very sensitive and decompose immediately at 30°C to give sulfur, nitrogen, and polymeric material. Decomposition also occurs on treatment with catalytic amounts of both acid and base.

Some confusion surrounds the structures of the products of reaction of hydrazones (134) with activated nitriles and with isocyanates <87JPR409>. Initially these were assigned structures (136) and (137) respectively but following the work of Kaugars *et al.* <92JOC1671> these structures should be reassigned as (138) and (139). In both cases the reaction is probably initiated by reaction at the hydrazone N as illustrated in Scheme 28. The product obtained from the reaction of the phenyl hydrazone with methyl isocyanate given structure (140) <87JPR409> should again be reassigned as (141). Products analogous to (139) are formed in the reaction with isothiocyanates <89JPR115>.

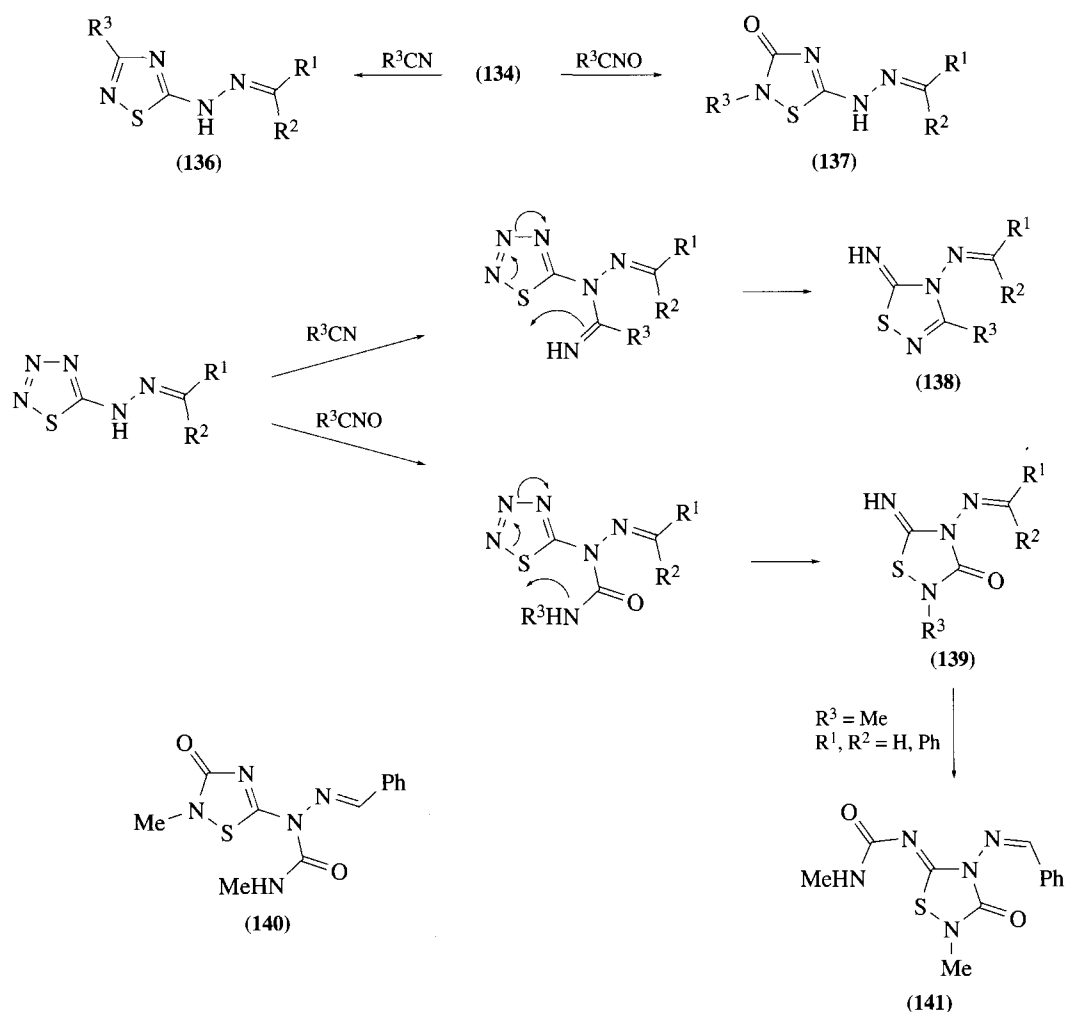
Graubau and Martin isolated the acetylhydrazino thiatriazole (142) in approximately 50% yield from the reaction of 5-hydrazinothiatriazole (133) with acetic anhydride <85ZC136>. On heating to ≈ 40°C, (142) extruded nitrogen and sulfur to give 2-amino-5-methyl-1,3,4-oxadiazole (143) (Scheme 29).

4.19.6.1.4 1,2,3,4-Thiatriazole-5-thiol and its derivatives

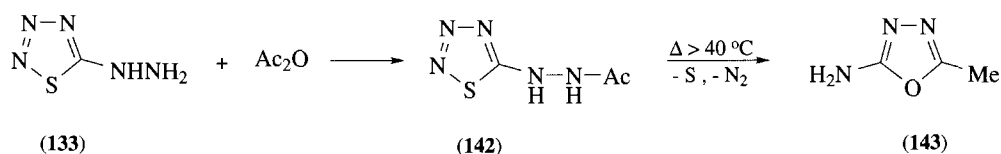
The reaction product between carbon disulfide and water-soluble azides, first investigated by Sommer <15CB1833>, was originally thought to be an azidodithiocarbonate. Lieber *et al.* concluded from infrared spectroscopic measurements that the reaction product was actually the 1,2,3,4-thiatriazole-5-thiolate anion (5) <57JOC1750>. Lieber *et al.* also discussed whether the compound obtained from the sodium salt of 5-thiothiatriazole and methyl iodide is an *N*- or an *S*-derivative <58CI(L)893>. By unequivocal synthesis it was substantiated that it is the *S*-derivative. However, acyl derivatives were formulated as 4-substituted thiatriazoline-5-thiones because isothiocyanates were obtained on thermal decomposition <58CI(L)893>. Jensen and Pedersen challenged this argument, as acyl thiocyanates are very unstable and may easily rearrange to the corresponding acyl isothiocyanates during the thermal degradation experiment <64AHC(3)263>. Christophersen and Holm showed that when so-called thiatriazoline-5-thione was subjected to thermal degradation in solution (CHCl₃), a very sharp band appeared in the infrared spectrum at 2170 cm⁻¹ <71ACS2015>. As the decomposition proceeded, a very strong and complex broad band developed around 1981 cm⁻¹, which could be assigned to benzoyl isothiocyanate, while the band at 2170 cm⁻¹ gradually disappeared. Accordingly the latter band was assigned to labile benzoyl thiocyanate and the acylation product of sodium thiatriazole-5-thiolate with benzoyl chloride hence to an *S*-derivative. From ¹³C NMR measurements L'abbé *et al.* also reached the conclusion that the reaction product is an *S*-derivative <74JOC3770>. The structure of the alkylation product of sodium 5-thiothiatriazole and diphenylmethyl chloride which had also been questioned was shown by unequivocal synthesis to be 5-(diphenylmethylthio)thiatriazole <71ACS2015>.

L'abbé *et al.* have found that 1,2,3,4-thiatriazole-5-thiolate anion (5) reacts in solution at 60°C with desaurins (144) of the type shown in Scheme 30 to produce a trithiolane (145) by the suggested pathway <84BSB405>.

For further reviews of thiatriazole-5-thiol and its alkylation, acylation and oxidation products see <64AHC(3)263, 76AHC(20)145, 84CHEC-I(6)579>.



Scheme 28



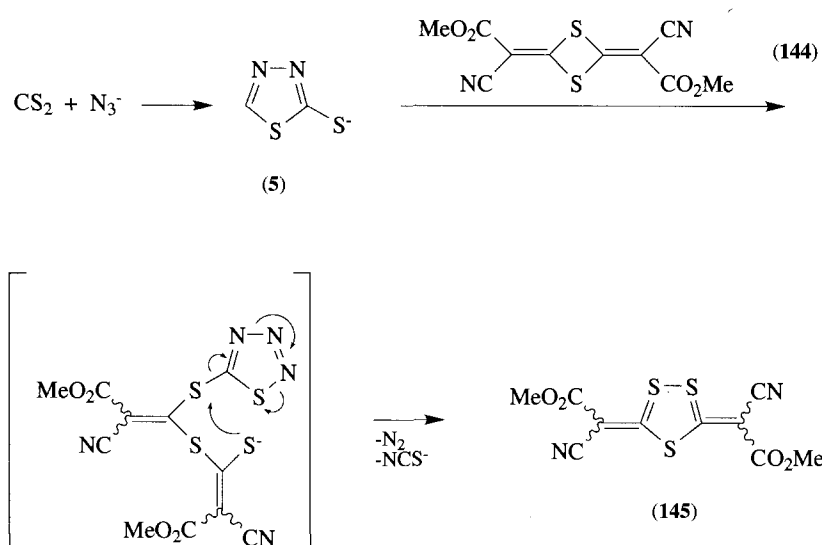
Scheme 29

4.19.6.1.5 5-Alkoxy- and aryloxy-1,2,3,4-thiatriazoles

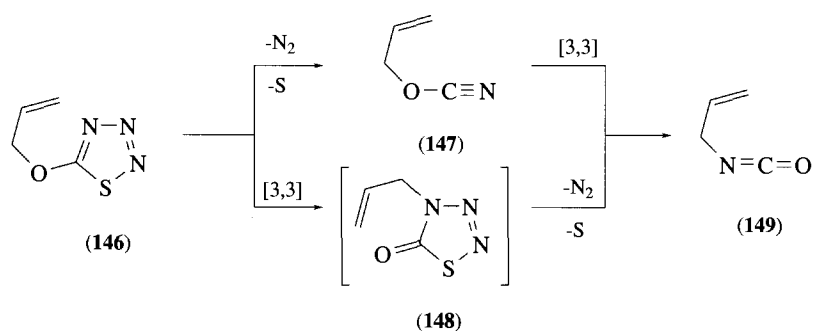
5-Alkoxy- and aryloxythiatriazoles generally decompose with formation of alkyl and aryl cyanates (see Section 4.19.4.1) [76AHC(20)145, 84CHEC-I(6)579]. Christophersen and Holm studied the decomposition of 5-allyloxy-1,2,3,4-thiatriazole (146) to give allyl isocyanate (149) which was believed to proceed by a 3,3 sigmatropic shift of the corresponding cyanate (147) [70ACS1512]. However, the unknown Δ^2 -4-allyl-5-oxo-1,2,3,4-thiatriazoline (148) could not be excluded as a primary product (Scheme 31).

Banert and Groth have isolated such a thiatriazolinone in the decomposition of a substituted allyloxy-1,2,3,4-thiatriazole (150) (see also Section 4.19.7.5) [92AG865]. The thiatriazoline (151), isolated in 46% yield, is a surprisingly stable liquid decomposing only after prolonged heating at 100°C into carbonyl sulfide, alkyl azide (153), nitrogen, sulfur, and isocyanate (152) (Scheme 32).

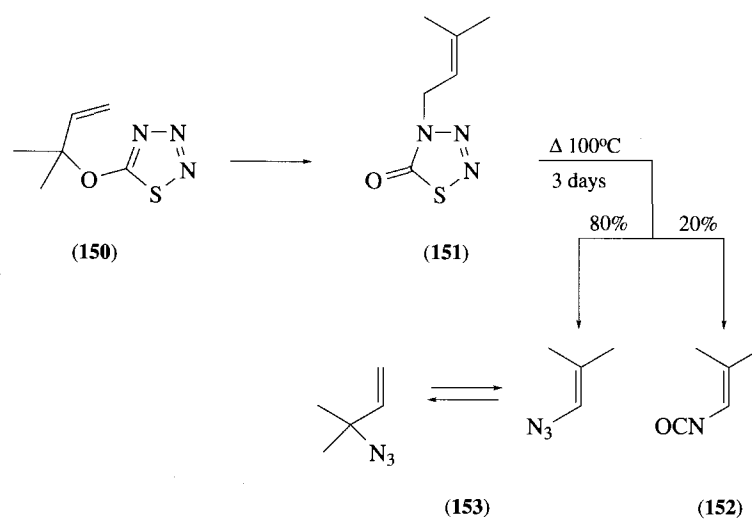
Decomposition of propargyloxy-1,2,3,4-thiatriazole (154) resulted in almost quantitative formation of the allenyl isocyanate (156). If the same reaction was carried out in the presence of hydrogen sulfide compound (157) was obtained, clearly demonstrating propargyl cyanate (155) as



Scheme 30

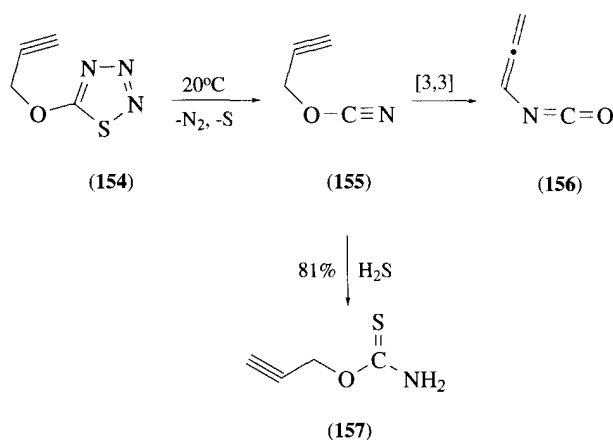


Scheme 31



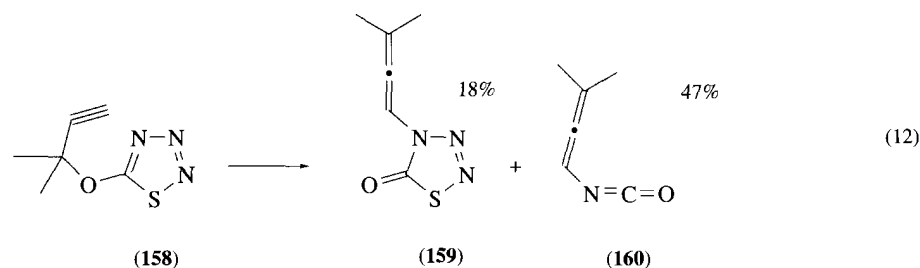
Scheme 32

an intermediate. A detailed NMR study revealed that the cyanate (**155**) was present in a steady-state concentration of approximately 5% during the decomposition (Scheme 33).



Scheme 33

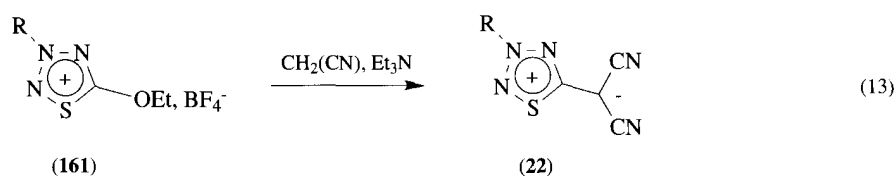
When a substituted propargyloxy-1,2,3,4-thiatriazole (**158**) was decomposed, 5-oxo-thiatriazoline (**159**) was isolated along with the main product, the allenylisocyanate (**160**) (Equation (12)).



4.19.6.2 Mesoionic 1,2,3,4-Thiatriazoles

4.19.6.2.1 Thiatriazoles substituted with C-radicals

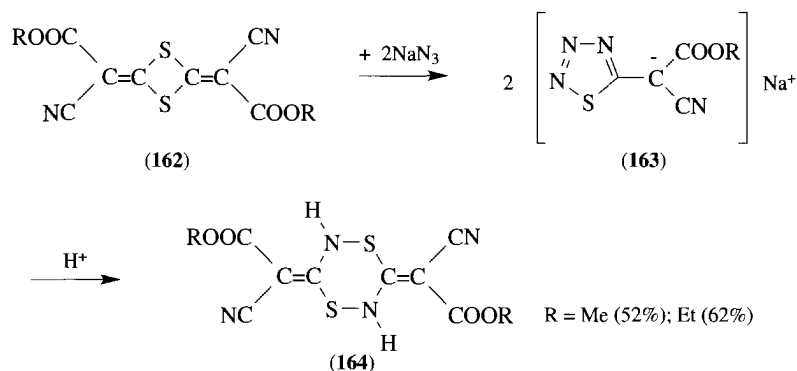
Heating of 5-ethoxy-1,2,3,4-thiatriazolium tetrafluoroborate (**161**) with malononitrile and triethylamine in acetonitrile solution gave crystalline 1,2,3,4-thiatriazolium-5-dicyanomethylide (**22**) (Equation (13)) <79JCS(P1)744>. The structure is supported by spectral properties. The IR spectra show C=C (1500 cm⁻¹) and CN (2200 cm⁻¹) stretching vibrations and the mass spectra shows the correct molecular ions. A dipole moment of 8.8 D (R = Ph) was measured in benzene in good agreement with the proposed structure (**22**).



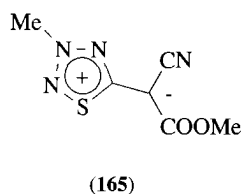
Peseke treated the 1,3-dithietane (desaurin) (**162**) with sodium azide in aqueous ethanol and obtained a product believed to be a thiatriazolinyldenecyanoacetate <81ZC102>. Attempts to isolate the free acid were unsuccessful as upon acidification of the solution of the salt, nitrogen evolution took place and the hitherto unknown 2*H*,5*H*-1,4-dithia-2,5-diazine (**164**) was formed (Scheme 34). According to L'abbé *et al.* the 1,3-dithietane reaction product is best formulated with a negatively

charged methylene carbon atom (**163**) since it exhibits a high field ^{13}C NMR absorption at 57.5 ppm <84BSB405>.

Upon methylation (**163**) yields a thermally stable product, which on the basis of spectral data is assigned the mesoionic structure (**165**) <84BSB405>.

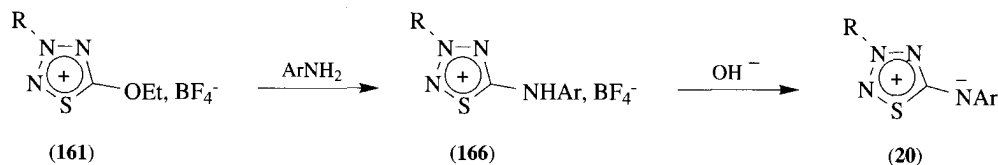


Scheme 34



4.19.6.2.2 5-Amino-1,2,3,4-thiatriazole and its derivatives

Treatment of 5-ethoxy-1,2,3,4-thiatriazolium tetrafluoroborates (**161**) with aromatic amines in boiling benzene affords yellow crystalline 5-arylamino-1,2,3,4-thiatriazolium salts (**166**) in good yields (60–70%) (Scheme 35). These are deprotonated with warm ethanolic aqueous sodium hydroxide to give the red crystalline mesoionic 1,2,3,4-thiatriazolium-5-aminides (**20**). The mesoionic compounds show a strong IR absorption in the region 1580–1590 cm^{-1} , which can be assigned to the exocyclic $\text{C}=\text{N}$ stretching vibration. UV and visible spectra are reported; e.g. (**20a**): λ_{max} 279 (ϵ 29300) nm and 441 (ϵ 1830) nm. The dipole moment of (**20a**) was 3.71 D <76CC307, 79JCS(P1)741>.

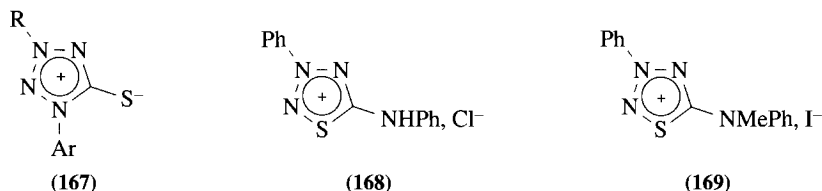


- (a) R = Ar = Ph; (b) R = Ph, Ar = p-MeC₆H₄; (c) R = p-MeC₆H₄, Ar = Ph; (d) R = Ar = p-MeC₆H₄;
 (e) R = Ph, Ar = p-ClC₆H₄; (f) R = p-ClC₆H₄, Ar = Ph

Scheme 35

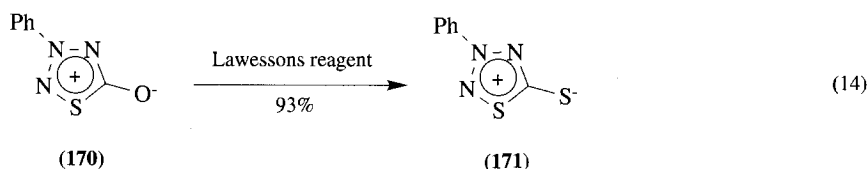
A base-catalyzed rearrangement of (**20**) to (**167**) was attempted but was unsuccessful. A corresponding rearrangement of 1,2,3,4-oxatriazolium-5-aminides is well established (see <76CC307>). The mesoionic 1,2,3,4-thiatriazolium-5-aminides (**20**) react with hydrochloric acid giving the salt (**168**), or with methyl iodide giving the salt (**169**). The proton in (**168**) may in principle either be attached to a ring nitrogen atom or to the exocyclic nitrogen atom. A $^1\text{J}(\text{N},\text{H}) = 82$ Hz coupling

constant for the exocyclic nitrogen atom of (168), and the strong low-frequency shift of the exocyclic nitrogen signal (ca. 100 ppm) suggest that protonation and methylation take place on the exocyclic group <93MRC447>.



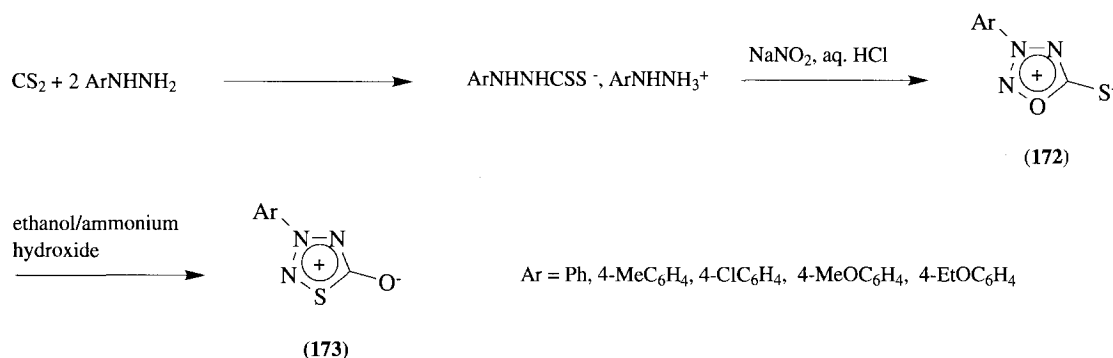
4.19.6.2.3 1,2,3,4-Thiatriazole-5-thiol and its derivatives

Araki *et al.* have found that Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide, provides a convenient one-step conversion of mesoionic olates to mesoionic thiulates <88BCJ2977>. Thus 3-phenyl-1,2,3,4-thiatriazolium-5-olate (170) was converted to (171) in high yield by refluxing for 50 min in benzene (Equation (14)). This compound had previously been prepared from compound (161; R = Ph) by treatment with sodium sulfide in aqueous dimethylformamide at room temperature <79JCS(P1)732>.



4.19.6.2.4 Thiatriazole-5-oxide and its derivatives

Mesoionic 1,2,3,4-oxatriazolium-5-thiolates (172) are convenient starting materials for mesoionic thiatriazole 5-oxides. Thus arylhydrazines and carbon disulfide in ethanol yield arylhydrazinium dithiocarbamate salts, which are nitrosated with sodium nitrite in aqueous hydrochloric acid to give yellow 1,2,3,4-oxatriazolium-5-thiolates (172). These heterocycles are isomerized by warming with ammonium hydroxide in ethanol to give colorless crystalline 1,2,3,4-thiatriazolium-5-olates (173) (Scheme 36) <76CC306>.



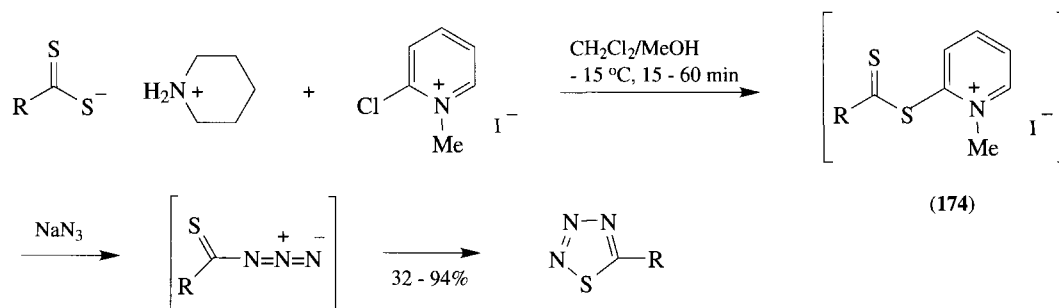
Scheme 36

Corresponding thiatriazolium tetrafluoroborates (161; R = Ar) salts are formed by Meerwein alkylation (triethyloxonium tetrafluoroborate in methylene chloride) of the 5-olates (173) <76CC306>. This type of salt (161) generally serves as starting material for other types of mesoionic compound <76AHC(19)1>. The 1,2,3,4-thiatriazolium-5-olates (173) are reported to be stable towards acid hydrolysis while aryl azide is formed in boiling aqueous sodium hydroxide <76CC306>.

4.19.7 RING SYNTHESIS

4.19.7.1 5-Alkyl- and 5-Aryl-1,2,3,4-thiatriazoles

The syntheses of a number of 5-arylthiatriazoles (**23**; X = Ar) have been reported but only a few 5-alkylthiatriazoles (**23**; X = alkyl) have been prepared by methods which are not generally applicable <64AHC(3)263, 76AHC(20)145>. Ikeda and co-workers have described a convenient method for synthesis of both alkyl and arylthiatriazoles by treating 1-methyl-2-thioacylpyridinium salts (**174**) with azide (Scheme 37) <90S415, 90ZC67>. The synthesis may be carried out as a one-pot reaction or as a two-step reaction where a suspension of sodium azide in acetonitrile is added to a solution of the pyridinium salt (**174**) in acetonitrile. Yields are generally high and the starting materials are readily available. All aliphatic thiatriazoles are isolated as oils. Characteristic MS, IR, and ^1H and ^{13}C NMR data are given.

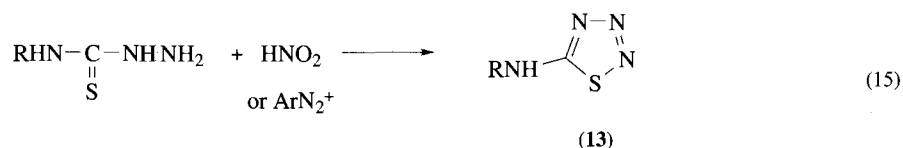


R: Me, Et, Pr, i-Pr, Bu, cyclohexyl, Ph, 2-MeC₆H₄, 4-MeC₆H₄, 2,4,6-Me₃C₆H₂, 4-MeOC₆H₄, 4-ClC₆H₄, 1-naphthyl

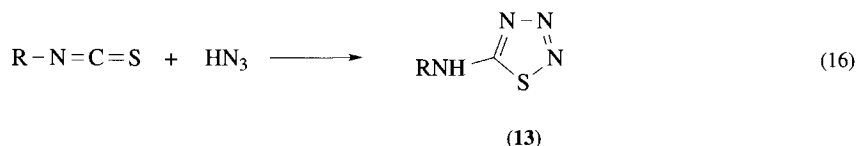
Scheme 37

4.19.7.2 5-Amino-1,2,3,4-thiatriazole

N-Substituted 5-amino-1,2,3,4-thiatriazoles (**13**) were obtained by Freund and Hempel in 1895 by treating thiosemicarbazides with nitrous acid (Equation (15)) <1895CB74>. This method has been used by others to prepare a number of different *N*-substituted 5-aminothiatriazoles (**13**) in good yields ($\approx 80\%$) <81JIC1087>.



5-Aminothiatriazoles (**13**) may alternatively be prepared from isothiocyanates and hydrazoic acid (Equation (16)) <77CCC1557, 80CCC2329, 81BSB63>.



In the case of activated isothiocyanates such as phenylsulfonyl and pyridyl isothiocyanates the enhanced reactivity of the isothiocyanate again only results in reaction at the C=S bond rather than the N=C bond which would have given rise to tetrazoles <77CCC1557>. Floch *et al.* have found that replacement of hydrazoic acid with trimethylsilylazide in 80% aqueous ethanol at 20°C leads to a much faster reaction (2 days vs. 20 days) and good yields (60–80%) <77CCC2945>.

The trimethylsilyl azide used in these reactions may be generated *in situ* from sodium azide

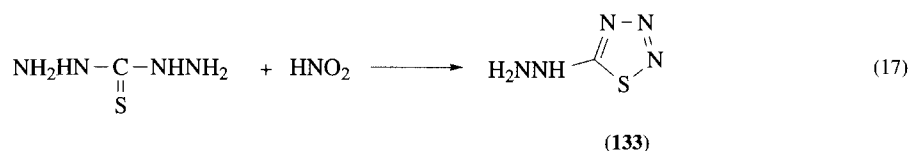
and chlorotrimethylsilane in dry dimethylformamide. After addition of phenyl isothiocyanate the mixture was stirred for 16 hours at room temperature and worked up to give 5-anilino-1,2,3,4-thiatriazole in 83% yield <79S35>. Attempts to use dry benzene as solvent resulted only in very poor yields (1.6–3.4%) <80JOC5130>.

Aza transfer between diazonium salts and 4-substituted thiosemicarbazides is a convenient and very fast method (≈ 15 min) for synthesis of 5-aminothiatriazoles ($\approx 60\%$ yield) introduced by Stanovnik *et al.* <78OPP59>.

For further review on this subject see <84CHEC-I(6)579>.

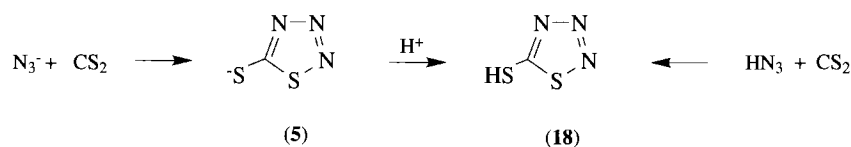
4.19.7.3 5-Hydrazino-1,2,3,4-thiatriazole

5-Hydrazino-1,2,3,4-thiatriazole (**133**) has been little investigated probably because of its pronounced instability. It is formed in the reaction between thiocarbazide and nitrous acid at 0°C in about 50% yield (Equation (17)), but it is recommended not to isolate the hydrazinothiatriazole in the solid state because of possible contamination with the highly unstable 5-azidothiatriazole formed by reaction of 5-hydrazinothiatriazole (**133**) with excess nitrous acid. It decomposes even at room temperature where it is transformed into nitrogen, sulfur and a polymeric material. Detonation has been observed when the hydrazino derivative was heated to around 80 – 90°C <85ZC136, 87JPR409, 89JPR115>.



4.19.7.4 1,2,3,4-Thiatriazole-5-thiol and its Derivatives

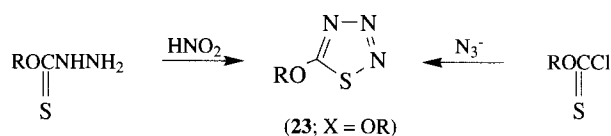
Thiatriazole-5-thiol and its salts are readily obtained from the water-soluble alkali or alkaline earth azides with CS_2 at 40°C <64AHC(3)263>. However, these salts should be handled with extreme care as violent explosions have been reported when the alkali salts are spread on a porous plate or rubbed with a spatula. The slightly soluble heavy-metal salts are very sensitive to shock even under water. An improved method for the preparation and storage of sodium thiatriazole-5-thiolate has been reported. The free acid is obtained by addition of concentrated hydrochloric acid to a chilled solution of the sodium salt but can also be prepared from hydrazoic acid and carbon disulfide (Scheme 38).



Scheme 38

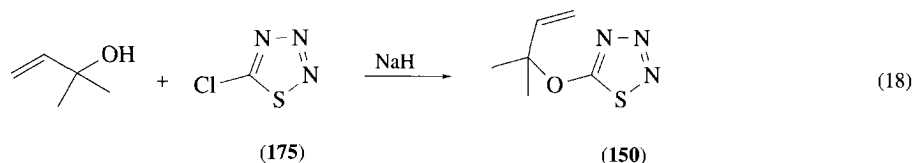
4.19.7.5 5-Alkoxy- and Aryloxy-1,2,3,4-thiatriazoles

This type of compound is prepared from alkoxythiocarbonylhydrazines and nitrous acid or from *O*-alkyl or *O*-aryl chlorothioformates and sodium azide (Scheme 39) (see <84CHEC-I(6)579>).



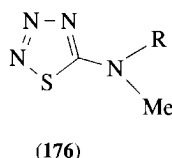
Scheme 39

Allyloxy- (**146**) and propargyloxythiatriazoles (**154**) are obtained in a similar way by treating the corresponding chlorothioformates with sodium azide <92AG865>. However, substituted allyloxy (**150**) and propargyloxy thiatriazoles (**158**) were obtained from 5-chloro-1,2,3,4-thiatriazole (**175**) in the presence of sodium hydride and the corresponding alcohols (35–70% yield) <92AG865>.



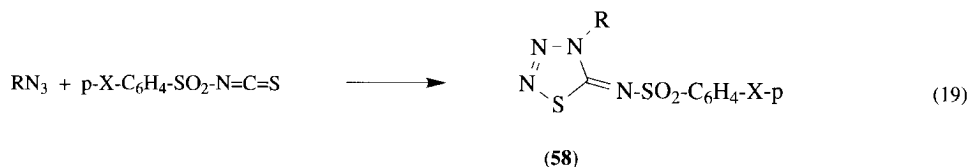
4.19.7.6 Δ^2 -1,2,3,4-Thiatriazolines

Before 1971 certain acylation and alkylation products of 5-thiothiatriazole were formulated as thiatriazolines. Later investigations showed this assignment to be incorrect (see Section 4.19.6.1.4) and true thiatriazolines obtained upon alkylation were first obtained by Neidlein and co-workers <71AP(304)687, 75S52>. They found that 5-(arylamino)thiatriazoles (**13**) can be alkylated to yield 5-(alkylarylamino)thiatriazoles (**176**) and/or 4-alkyl-5-(arylimino)thiatriazolines (**48**) depending on the alkylating agent and the aryl group. With dimethyl sulfate in alkaline solution 5-substituted thiatriazoles were obtained, while alkylation with diazomethane gave either thiatriazolines or a mixture of thiatriazolines and thiatriazoles. Methylation of 5-(sulfonylamino)thiatriazoles with diazomethane similarly give 4-substituted 5-sulfonyliminothiatriazolines, most often in admixture with 5-(*N*-methyl-*N*-sulfonylamino)thiatriazole <75S52>.



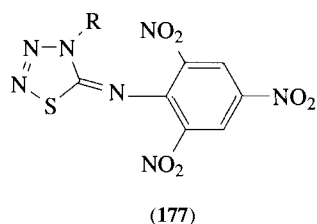
Toubro and Holm have shown that 4-alkyl-5-iminothiatriazolines are obtained exclusively upon alkylation of 5-arylamino-, 5-alkylamino- and 5-sulfonylamino-1,2,3,4-thiatriazoles with trialkyloxonium tetrafluoroborates <78JCS(P1)1440>. These thiatriazoline tetrafluoroborates are crystalline compounds which may be stored at room temperature and serve as convenient sources for the thermally labile free bases, which are liberated with sodium hydrogen carbonate.

L'abbé and co-workers have found that 4-alkyl-5-sulfonylimino- Δ^2 -1,2,3,4-thiatriazolines (**58**) are readily prepared by reaction of the highly reactive sulfonyl isothiocyanates with alkyl azides (Equation (19)) <73JOC2916, 74JA3973>.



Aryl and acyl isothiocyanates were also found to react with alkyl azides, but yield thiatriazoline-5-imines only as elusive intermediates which are transformed *in situ* into a series of bisadducts after loss of nitrogen. Interestingly, L'abbé *et al.* have found that picryl isothiocyanate is an exception to this and reacts smoothly with alkyl azides to yield 4-alkyl-5-picrylimino-1,2,3,4-thiatriazolines (**177**) which are stable below 100°C <90JHC1059>. Kinetic experiments indicate that the reaction between picryl isothiocyanate and alkyl azides most likely is concerted as no significant solvent effect was observed.

See also Section 4.19.5.1 for other thermally unstable Δ^2 -1,2,3,4-thiatriazolines.



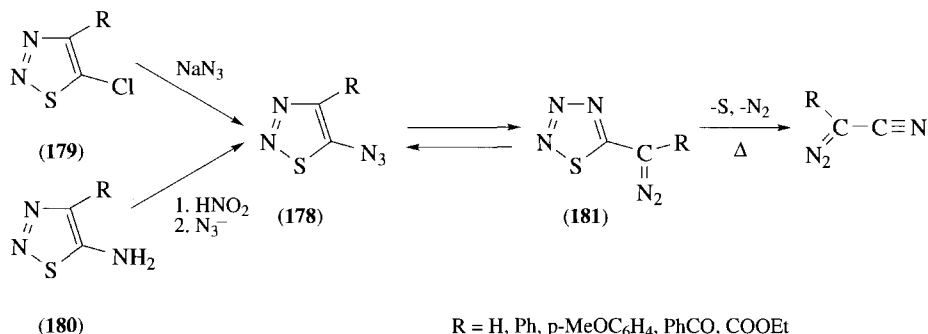
R = PhCH₂; p-MeOC₆H₄CH₂; p-(Me)₃CC₆H₄CH₂; n-C₄H₉; (Me)₂CH; MeOCOCH₂; (Me)₃SiCH₂; ClCH₂CH₂

4.19.7.7 Δ^3 -1,2,3,4-Thiatriazolines

The 1:1 adducts formed from bis(trifluoromethyl)thioketene and aryl azides are believed to be Δ^3 -1,2,3,4-thiatriazolines based on ¹⁹F NMR, IR spectroscopy and on thermolysis which leads to a product believed to be 2,1-benzisothiazole <78JOC2500>.

4.19.8 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

Attempts to make 5-azido-1,2,3-thiadiazole (**178**) by reacting 4-substituted-5-chloro-1,2,3-thiadiazoles (**179**) with sodium azide or by diazotizing 4-substituted-5-amino-1,2,3-thiadiazoles (**180**) followed by treatment with sodium azide, resulted in a partial rearrangement giving a mixture of diazo 1,2,3,4-thiatriazoles (**181**) and azido 1,2,3-thiadiazoles (Scheme 40) <82TL1103, 88BSB163>. The authors suggest that the 5-azido-1,2,3-thiadiazole (**178**) rearranges either via an open intermediate or by a concerted bond-switch mechanism. The ratio of 1,2,3,4-thiatriazole (**181**) to 1,2,3-thiadiazole (**178**) is governed by the electron-withdrawing strength of the 4-substituent.



Scheme 40

4.19.9 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

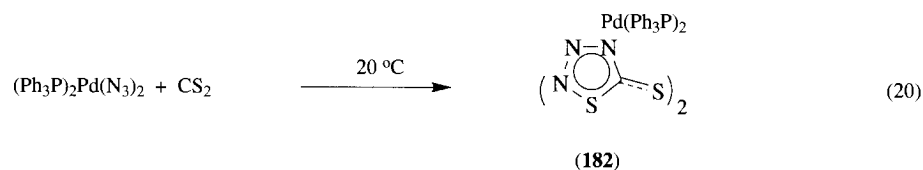
4.19.9.1 Complex Formation of 1,2,3,4-Thiatriazol-5-thiol

Certain palladium complexes of the type PdL(N₃) react with carbon disulfide apparently to give thiatriazolinato complexes. However, they are unstable and decompose at temperatures above 40 °C to produce the corresponding isothiocyanato complexes, PdL(NCS) <90ICA27>.

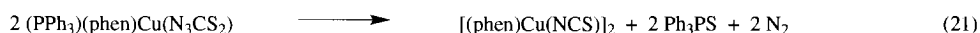
In the same manner as sodium azide and carbon disulfide gives rise to sodium thiatriazole-5-thiolate, carbon disulfide and other types of azide including $[\pi\text{-C}_5\text{H}_5\text{Ni}(\text{PBU}_3)_2]^+ \text{N}_3^-$, tributyltin and organometallic complexes of the type $[(\text{Ph})_3\text{P}]\text{M}(\text{N}_3)_2$ (M = Pt, Pd) have been reported to react, probably with the formation of thiatriazole-5-thiol complexes <76AHC(20)145>. Furthermore, sodium thiatriazole-5-thiolate gives colored precipitates with copper(II) or bismuth salts and the reaction may be used as a test for soluble inorganic azides <76AHC(20)145>. Equilibrium studies of complex formation between thiatriazole-5-thiolate and Ni(II) and Co(II) <80MI 419-01> and of Zn(II)

<81JINC2081> have been reported. Unstable Rh complexes with thiatriazole-5-thiolate appear to be formed in the reactions of pentamethylcyclopentadienyl-rhodium complexes $\text{Rh}_2(\text{C}_5\text{Me}_5)_2(\text{N}_3)_4$ or $\text{Rh}(\text{C}_5\text{Me}_5)(\text{N}_3)_2\text{Ph}_3\text{P}$ with CS_2 . In the first case a dimeric dithiocyanato complex, $\text{Rh}_2(\text{C}_5\text{Me}_5)_2(\text{SCN})_4$ was obtained as the end product, and in the second case a more complex reaction occurred to give the dithiocyanato complex together with sulfur, nitrogen, and PPh_3S . However, an intermediate in the second reaction was isolated on one occasion and the lack of strong IR bands due to $\nu(\text{CN})$ or $\nu(\text{N}_3)$ of this product suggests that it is a 1,2,3,4-thiatriazolato complex of rhodium <79JCS(D)371>. Schenk *et al.* have investigated the reaction of carbon disulfide complexes of tungsten, $\text{W}(\text{CO})_3(\text{R}_2\text{PC}_2\text{H}_4\text{PR}_2)\text{CS}_2$ ($\text{R} = \text{Me}, \text{Ph}$) with ammonium azide <82JOM(232)C41>. The reaction is more than ten times faster than substitution of CS_2 and thiatriazole complexes are formed. Thus an initial dissociation into CS_2 does not take place. The atom in the thiatriazole at which complexation takes place could not be unambiguously determined in this as in other cases of complexes with thiatriazole-5-thiolate referred to above, partly because the tungsten complex undergoes a facile decomposition into an *N*-thiocyanato complex with tungsten <82JOM(232)C41>. The reaction of the complexes $[(\text{Ph})_3\text{P}]\text{M}(\text{N}_3)_2$ ($\text{M} = \text{Pt}, \text{Pd}$) with CS_2 previously reported <67AG(E)169, 68MI 419-01> has been reinvestigated together with the reaction between $[\text{Ph}_4\text{As}]_2[\text{Co}(\text{N}_3)_4]$ and CS_2 <83ZN(B)546>.

The Pd complex (**182**) may be formed as shown in Equation (20) or formed directly from $\text{Pd}(\text{NO}_3)_2$, PPh_3 and $\text{Na}[\text{CS}_2\text{N}_3]$. In the case of this complex an intense IR band at 1223 cm^{-1} may be assigned to a $\nu_{\text{C}=\text{S}}$ vibration, pointing to a Pd—N bonding. The blue solution of $[\text{Ph}_4\text{As}]_2[\text{Co}(\text{N}_3)_4]$ in acetone is changed to deep green within seconds upon addition of CS_2 , but the color is changed back to blue upon standing or heating and the IR spectrum shows that the initial complex decomposes to $[\text{Co}(\text{NCS})_4]^{2-}$ with elimination of sulfur and nitrogen. Ligand field parameters for $[\text{Co}(\text{N}_3)_4]^{2-}$ and $[\text{Co}(\text{N}_3\text{CS}_2)_4]^{2-}$ are practically identical pointing to a Co—N bond in the thiatriazole complex.

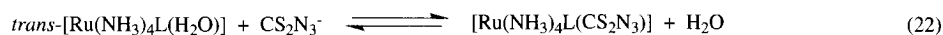


The copper(I) azide derivatives $(\text{PPh}_3)(\text{phen})\text{CuN}_3$ and $(\text{PPh}_3)(\text{TMP})\text{CuN}_3$ ($\text{phen} = 1,10\text{-phenanthroline}$ and $\text{TMP} = 3,4,7,8\text{-tetramethyl-1,10-phenanthroline}$) react with CS_2 to give yellow thiothiatriazolato-copper(I) complexes <84JOM(273)263>. The complexes are formed only if free triphenylphosphine is present in the reaction medium, otherwise isothiocyanate complexes $(\text{PPh}_3)_2(\text{bidentate ligand})\text{Cu}(\text{NCS})$ are formed. Upon refluxing of a methylene chloride solution of $(\text{PPh}_3)(\text{phen})\text{Cu}(\text{N}_3\text{CS}_2)$ decomposition takes place apparently according to Equation (21).



Upon acylation of the copper complex with benzoyl chloride the corresponding 5-benzoylthio-1,2,3,4-thiatriazole is formed. The reaction product is (apparently) incorrectly assigned by the authors to 4-benzoyl-1,2,3,4-thiatriazole-5-thione based upon comparison with the product obtained from direct acylation of thiatriazol-5-thiol and citation of the older incorrect structure assignments. The thiothiatriazolato-copper(I) complexes are formulated as Cu-N(4) complexes. However, this assignment is based upon an IR band at 1200 cm^{-1} attributed to a thiocarbonyl group, again upon comparison with the older literature. Further characterization therefore seems necessary.

Trabuco and Franco have carried out a detailed study on the reaction of Ru(II) tetraamines with CS_2N_3^- <86POL1503>. The kinetics of the reaction were studied spectrophotometrically and formation rate constants for *trans*- $[\text{Ru}(\text{NH}_3)_4\text{L}(\text{CS}_2\text{N}_3)]$ were determined. Thermodynamic parameters were obtained for the exchange reaction in Equation (22). The authors comment on the binding site of the CS_2N_3^- anion suggesting that complexation takes place at the sulfur atom (see also <81JINC2081>). However, quantum mechanical calculations for this molecule (see Section 4.19.2.2) indicate that the electron density at N(4) and at the exocyclic sulfur atom are not very different and the authors do not exclude chelation through nitrogen considering the soft-base character of CS_2N_3^- in the Ru-system.



Formation of thiatriazole-5-thiolate from azide and carbon disulfide has been suggested to be used for quantitative spectrophotometric determination of carbon disulfide <77MI 419-01> and an analytical potentiometric method for determination of thiatriazole-5-thiolate has been developed in which this pseudohalide is oxidized by an excess of permanganate. The mechanism of the complex reaction was investigated and evidence for competitive reactions given <79MI 419-02, 81TAL867>. In the course of these studies it was observed that in the presence of sulfite ions, the determination of CS_2N_3^- , N_3^- or CS_2 is not accurate. In a more detailed study it was found that in the presence of 1,2,3,4-thiatriazole-5-thiolate ions and oxygen, hydrogen sulfite is oxidized to sulfate in the pH range 3–10.5. The rate of oxidation was observed to be faster than that of the direct reaction and a possible reaction is proposed in which CS_2N_3^- acts as a catalyst involving a radical mechanism <91MI 419-01>. Neves and Franco have also investigated other types of agents for the oxidation of CS_2N_3^- <79TAL81>. A method based on the oxidation of hydrogen sulfite to hydrogen sulfate by dissolved oxygen with 1,2,3,4-thiatriazol-5-thiolate as catalyst has been developed for the determination of sulfite. The decrease in absorbance at 313 nm of CS_2N_3^- and the observed rate constant for the reaction were used as a measure of the sulfite concentration. During the reaction the change in absorbance at 313 nm reflects predominantly the oxidation of CS_2N_3^- to $(\text{CS}_2\text{N}_3)_2$. When all dissolved oxygen has been consumed, the formation of $(\text{CS}_2\text{N}_3)_2$ ceases and the latter is reduced by the sulfite <90MI 419-01>. The same series of reactions may also be used for determination of oxygen dissolved in water <89MI 419-01>. The electrochemical reduction of CS_2N_3^- at a mercury and at an amalgamated zinc electrode has been investigated. Major products formed are N_2 , HSCN, and H_2S <86MI 419-01>.

4.19.10 APPLICATIONS

Among other heterocyclic compounds, 5-aryl-2-thiatriazolylamino oxadiazoles have been prepared by diazotization of 4-oxadiazolyl thiosemicarbazides and screened against two fungal species for fungicidal activity <76ABC759>.

4.20

1,2,3,5-Thiatriazoles

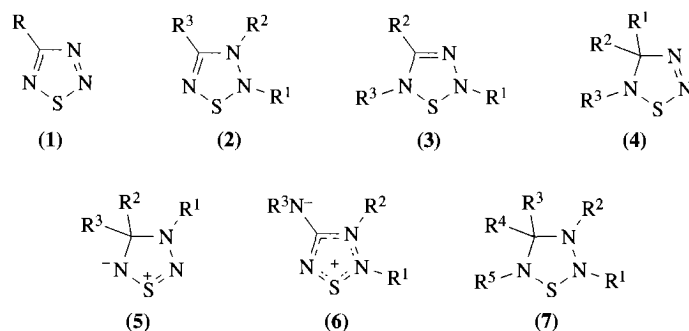
ARNE HOLM and BJARNE D. LARSEN

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Denmark*

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4.20.1 INTRODUCTION

Heteroaromatic 1,2,3,5-thiatriazoles (**1**) have yet to be isolated and characterized but evidence for this apparently thermally unstable type of compound has been presented. 1,2,3,5-Thiatriazolines (**2**), (**3**), and (**4**), 1,2,3,5-thiatriazolidines (**7**), 1,2,3,5-thiatriazole heteropentalenes incorporating the ring system (**5**), and mesoionic 1,2,3,5-thiatriazoles (**6**) are known. Some of these types of heterocycle (**2**), (**3**), (**5**), and (**7**) have been reviewed in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) by Holm <84CHEC-I(6)579>.



4.20.2 EXPERIMENTAL STRUCTURAL METHODS

4.20.2.1 X-ray Crystallography

2,5-Dihydro-2,4-diphenyl-1,2,3,5-thiatriazole 1-oxide (**8**) reacts with phosphorous pentabromide in chloroform to give the yellow 2*H*-1,2,3,5-thiatriazol-1-ium bromide (**9**). Crystal structure determination of the two compounds is reproduced in Figures 1 and 2 <90JCS(P2)1619>. The analysis of (**8**) shows nearly linear intermolecular N—H···O hydrogen bridges leading to a helical arrangement in the crystal. Intermolecular association was also observed in solution. Thus IR spectra of (**8**) do not show frequencies for free NH or OH groups. Furthermore, chemical shifts in the ^1H NMR spectra in deuterio dichloromethane are concentration dependent, particularly that of the exchangeable proton and ^{15}N NMR results are also in agreement with the tautomeric structure (**8**). The effect on the intermolecular association on shifting to DMSO as solvent is also discussed as well as the effect on the electronic spectra <90JCS(P2)1619>.

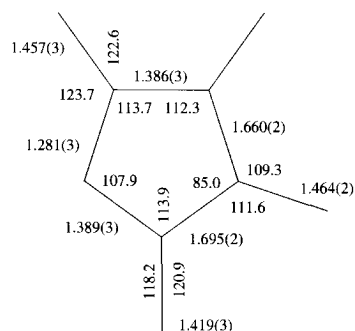
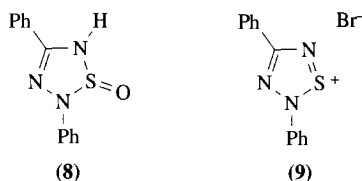


Figure 1 Crystal structure of 2,5-dihydro-2,4-diphenyl-1,2,3,5-thiatriazole 1-oxide (bond lengths in Å and bond angles in °).

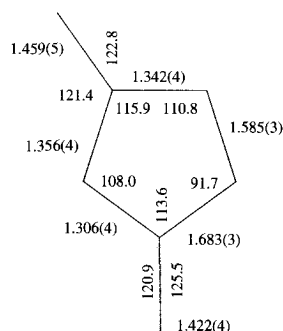


Figure 2 Crystal structure of 2,4-diphenyl-2*H*-1,2,3,5-thiatriazol-1-ium bromide (bond lengths in Å and bond angles in °).

Crystal data is given for a 1,2,3,5-thiatriazolo[1,2-*b*]pyrazoliumolate-5,5-dioxide <83H(20)845>.

4.20.2.2 UV Spectroscopy

UV data has been discussed for diazenes containing condensed thiatriazole and selenatriazole rings (see Section 4.20.7.1) <90JA5373>.

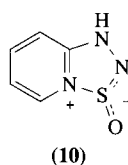
4.20.2.3 ESR, ENDOR, and General Triple Resonance Spectroscopy

Upon treatment of 2,5-dihydro-1,2,3,5-thiatriazole 1-oxides with sodium or potassium (4.20.5.1) in 1,2-dimethoxyethane 2,5-dihydro-1,2,3,5-thiatriazol-5-yl radicals are formed which have been studied by means of ESR, ENDOR, and general triple resonance spectroscopy <90JCS(P2)1619>.

2,5-Dihydro-1,2,3,5-thiatriazole 1-oxide radicals were generated from the thiatriazole oxides upon hydrogen abstraction in the reaction with thermally formed bis(4-methylphenyl)aminyl (4.20.5.1). Only radicals with aryl substituents in positions two and four are persistent, radicals with alkyl groups in these positions could not be detected. The radicals were investigated by ESR, ENDOR, and general triple resonance spectroscopy <92MRC84>.

4.20.2.4 1,2,3,5-Thiatriazolines

Generally, the structures of the 1,2,3,5-thiatriazolines (2) and (3) are inferred from the mode of synthesis. The structure of 1,2,3,5-thiatriazolo[5,4-*a*]pyridine 3-oxide (10) has been studied in detail and the structural data strongly suggests that (10) exists as a pyridinium salt <63CB2519, 70CB1918>.



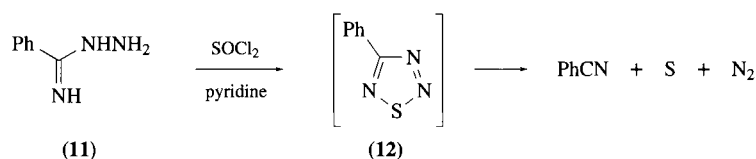
4.20.2.5 1,2,3,5-Thiatriazole Heteropentalenes

The structures of 1,2,3,5-thiatriazole heteropentalenes are deduced from the mode of synthesis and from spectroscopic data <80JOC4065>.

4.20.3 REACTIVITY OF FULLY CONJUGATED RINGS

4.20.3.1 Thermal Reactions

Synthesis of the hitherto unknown, fully conjugated heteroaromatic 1,2,3,5-thiatriazoles has been attempted. Thus benzamidine (11) was treated with 1.07 equivalents of thionyl chloride in the presence of pyridine. At 0°C, evolution of nitrogen took place and benzonitrile was obtained in 37% yield based on (11). The yield of benzonitrile could be raised to 63–65% accompanied by formation of elemental sulfur in ca. 60% yield by using 2.14 equivalents of thionyl chloride. These results suggest formation of 4-phenyl-1,2,3,5-thiatriazole (12) as an intermediate, probably via an S-oxide <88ACS(B)63>. The comparable 5-phenyl-1,2,3,4-thiatriazole decomposes almost quantitatively to nitrogen, benzonitrile, and sulfur, however only on heating to above 100°C (see Section 4.19.4.1). Benzonitrile sulfide appears to be formed in the decomposition of (12) (by elimination of nitrogen) as indicated by isolation of 3,5-diphenyl-1,2,4-thiadiazole (7% yield) when the reaction is carried out in the presence of a large excess (35 equivalents) of benzonitrile <88ACS(B)63>. Benzonitrile is a known scavenger for benzonitrile sulfide although yields are usually low (Scheme 1).



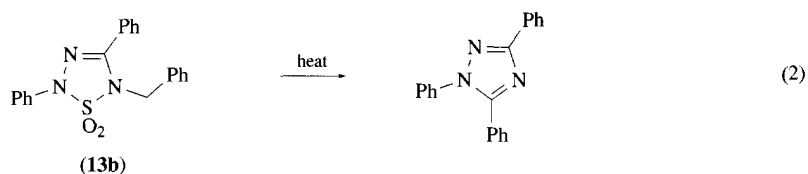
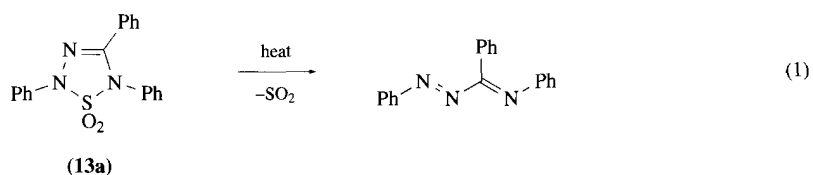
Scheme 1

4.20.4 REACTIVITY OF NONCONJUGATED RINGS

4.20.4.1 Thermal Reactions

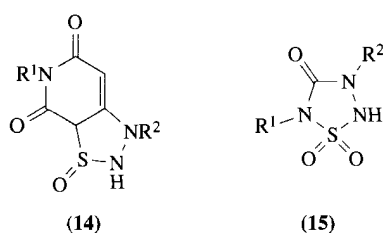
4.20.4.1.1 1,2,3,5-Thiatriazolines

While Δ^3 -1,2,3,5-thiatriazoline *S*-oxides are reported to be thermally stable <70CB1918, 71CB639, 70CB1934, 80LA1376, 81JOC4567>, Δ^3 -1,2,3,5-thiatriazoline *S,S*-dioxides are labile and decompose even at room temperature. Compound (**13a**) decomposes rapidly at 80°C to 1,3,4-triphenyl-1,2,4-triazabutadiene, while (**13b**) is reported to give 1,3,5-triphenyl-1,2,4-triazole. The latter compound is suggested to be formed in a more complex process by two pericyclic reactions followed by dehydrogenation <85M1321> (Equations (1) and (2)).



4.20.4.1.2 1,2,3,5-Thiatriazolidines

Fully substituted thiatriazolidine *S*-oxides are generally reported to be thermally stable. The thermal stability of the 2-unsubstituted thiatriazolidine *S*-oxides (**14**) depends on the substituents R^1 and R^2 <78JOC1677>.



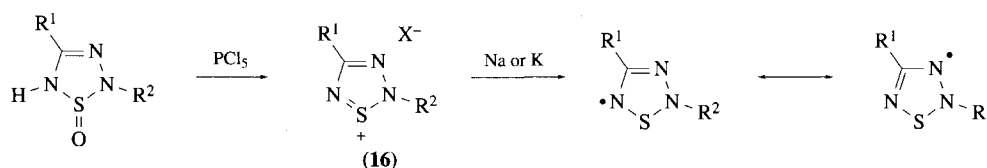
2-Unsubstituted 1,2,3,5-thiatriazolidinone *S,S*-dioxides (**15**) are reported as thermally stable <77JCR(S)239, 77JCR(M)2826> while the corresponding 3-unsubstituted derivatives are thermally unstable, decomposing with SO_2 extrusion <77JCR(S)238, 77JCR(M)2813>.

4.20.5 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

4.20.5.1 Electrophilic Attack at *S*-Oxides

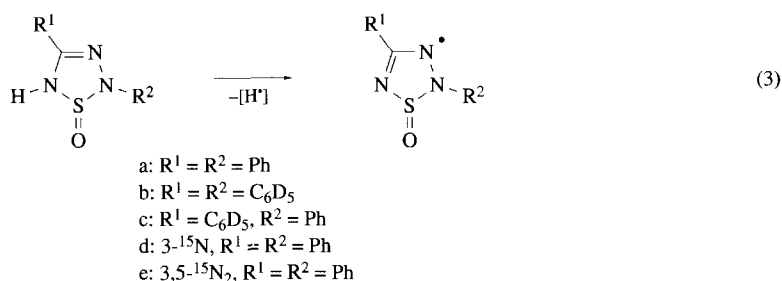
The 2,5-dihydro-1,2,3,5-thiatriazole 1-oxides react with phosphorous pentachloride (or pentabromide) in chloroform to give yellow 2*H*-1,2,3,5-thiatriazol-1-ium salts (**16**). The salts are very sensitive to moisture and hydrolyze back to the starting material. The structure is determined by x-ray crystallography. The yellow color is due to the extended delocalization of the cation which gives rise to a broad band system in the 300 nm to 450 nm range in the absorption spectrum. Upon treatment with sodium or potassium in 1,2-dimethoxyethane a 2,5-dihydro-1,2,3,5-thiatriazol-5-yl

radical is formed which has been studied by means of ESR, ENDOR, and general triple resonance spectroscopy <90JCS(P2)1619> (Scheme 2).



Scheme 2

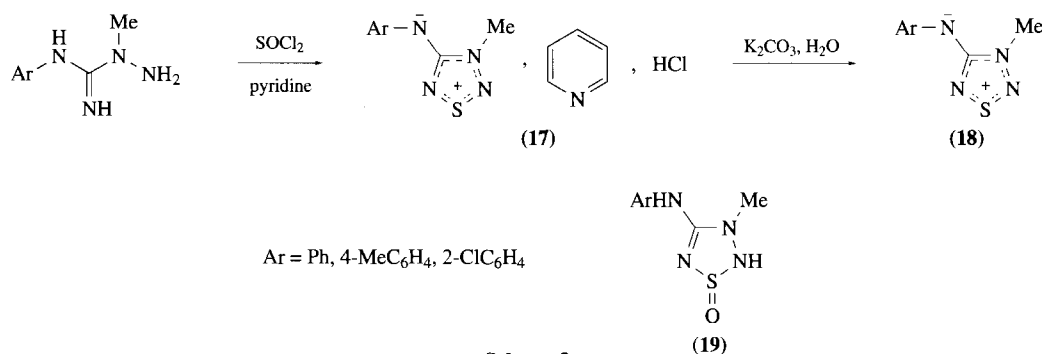
In a continuing study, 2,5-dihydro-1,2,3,5-thiatriazole 1-oxide radicals were generated upon hydrogen abstraction with thermally formed bis(4-methylphenyl)aminyl. Only radicals with aryl substituents in positions two and four are persistent, radicals with alkyl groups in these positions could not be detected (see Section 4.20.2) <92MRC84> (Equation (3)).



4.20.6 RING SYNTHESIS

4.20.6.1 Mesoionic 4-Amino-1,2,3,5-Thiatriazoles

Mesoionic 4-amino-1,2,3,5-thiatriazoles constitute the only class of mesoionic 1,2,3,5-thiatriazoles known. They are prepared by the reaction of 1-amino-1-methyl-3-phenylguanidine with approximately 2 equivalents of thionyl chloride with pyridine as solvent <88ACS(B)63>. They are obtained as the yellow 1:1 pyridine complexes (17). The dark-violet mesoionic 1,2,3,5-thiatriazole (18) was liberated on treatment with aqueous potassium carbonate (Scheme 3). The structure is established on the basis of elemental analysis and spectroscopic data. In particular, the IR spectrum is devoid of NH absorptions. Compound (18) exhibits a long-wavelength absorption at 463 nm in methanol. When mixed with an equivalent amount of pyridinium chloride, complex (17) is formed and the absorption shifts to 350 nm. The mesoionic thiatriazoles are sensitive towards mineral acids and aqueous base and although reaction takes place with 1,3-dipolarophiles such as dimethyl acetylenedicarboxylate, a mixture of products were obtained which were not identified.



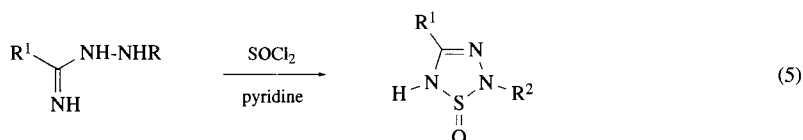
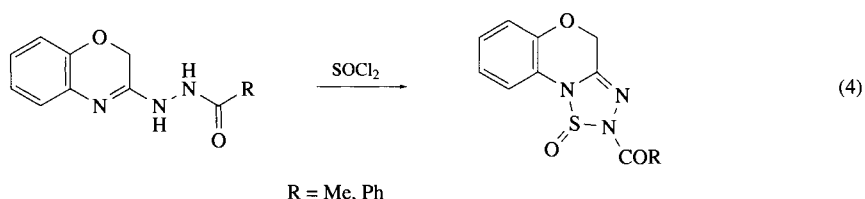
Scheme 3

The formation of (18) most likely proceeds via an S-oxide (19) which rapidly eliminates water. It was observed that 1 equivalent of thionyl chloride gave rise to 18% yield (18), while 2 equivalents

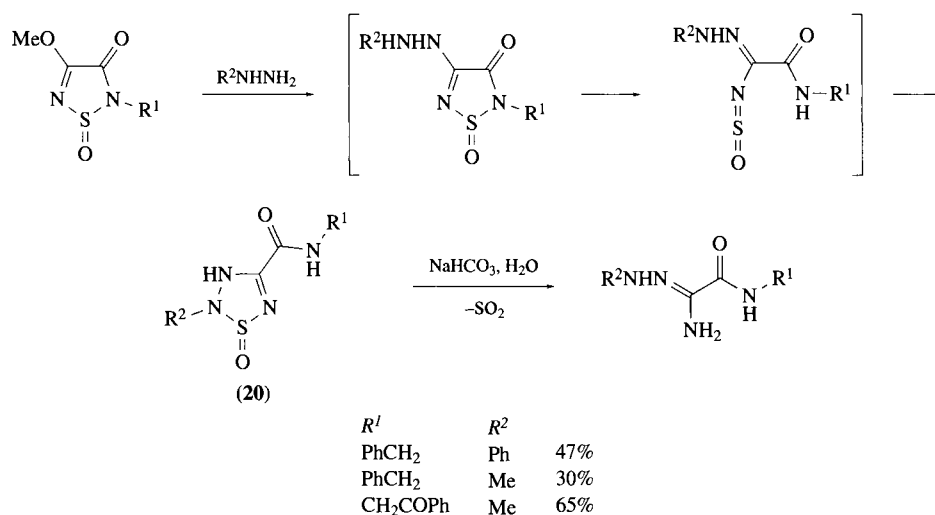
resulted in a 40% yield which could not be raised further even when 7 equivalents were used. These results indicate a complex reaction in which thionyl chloride may be involved in elimination of water from the *S*-oxide <88ACS(B)63>.

4.20.6.2 Δ^3 - and Δ^4 -1,2,3,5-Thiatriazolines

This class of compounds has been prepared only as the *S*-oxides or dioxides. The most common approach to the *S*-oxides involves the cyclization of amidrazones with thionyl chloride but the 1,3-dipolar cycloaddition of a nitrileimine to thionyl aniline has also been utilized <84CHEC-I(6)579>. Examples of the former approach are shown in Equation (4) <89JHC205> and Equation (5) <90JCS(P2)1619>. The structure assignment of the product from Equation (5) is based on x-ray analysis (see Section 4.20.2.1).



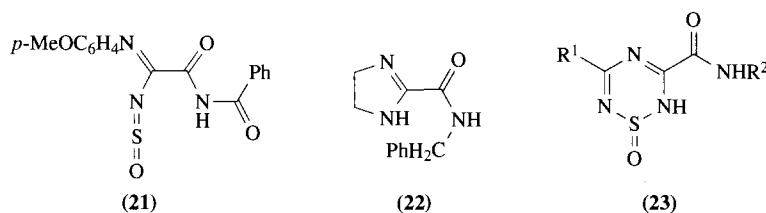
The methoxy group of 4-methoxy-1,2,5-thiadiazole 1-oxide (Scheme 4) undergoes smooth displacement with nitrogen nucleophiles to produce the corresponding amino derivatives. However, when treated with hydrazines ($R^1 = \text{PhCH}_2$; $R^2 = \text{Ph, Me}$) the displacement is followed by rearrangement to give a Δ^4 -1,2,3,5-thiatriazoline *S*-oxide (**20**) <85TL6155>.



Scheme 4

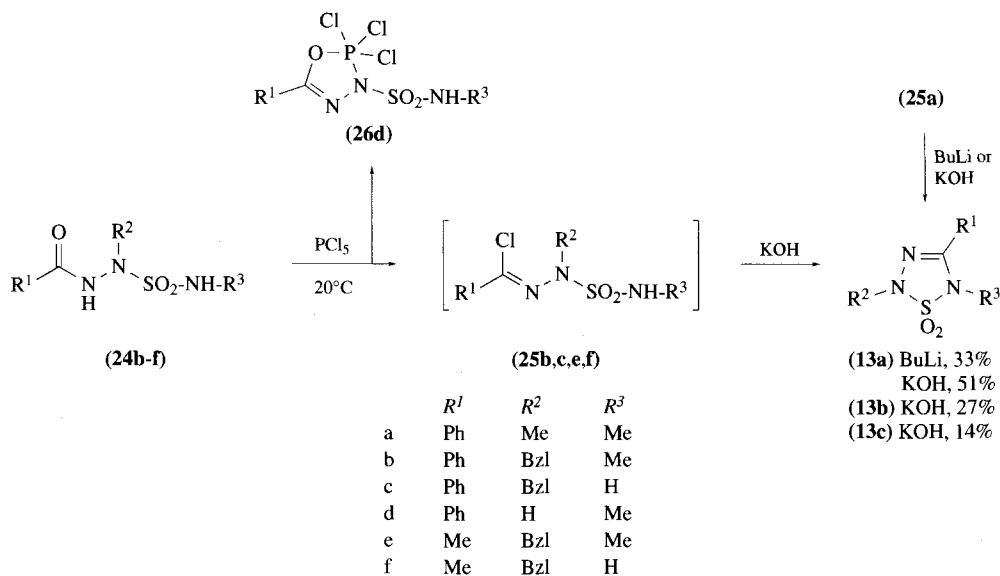
The rearrangement is thought to be initiated by ring opening leading to a sulfinylamine followed by ring closure to the final product. Although the proposed sulfinylamine could not be directly detected, the related (**21**) was found to exist only in the open sulfinylamine form. Obviously, an NH group is necessary for sulfinylamine formation and 1,2-dimethylhydrazine accordingly did not yield

a thiatriazoline *S*-oxide. Benzoylhydrazide behaved similarly, while 1,2-diaminoethane gave an imidazoline (**22**) and amidines ($\text{RC}(=\text{NH})\text{NH}_2$) gave 1,2,4,6-thiatriazene oxides (**23**).



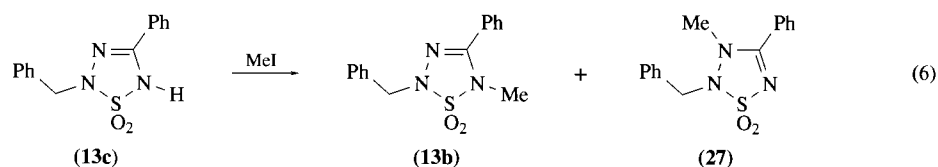
The Δ^4 -1,2,3,5-thiatriazoline *S*-oxides (**20**) are stable at room temperature but are easily hydrolyzed $\langle 85\text{TL}6155 \rangle$. Sulfinylamines are known to react with carbonyl compounds and so with $\text{R}^1 = \text{CH}_2\text{COPh}$, $\text{R}^2 = \text{Me}$, an intramolecular trapping of the carbonyl group leading to a 6-membered pyrazine might have been expected. However, even in this case, the 1,2,3,5-thiatriazole *S*-oxide was formed due to preferential reaction with the highly nucleophilic nitrogen over cycloaddition $\langle 86\text{H}(24)1193 \rangle$.

Knollmueller and Kosma have obtained Δ^3 -1,2,3,5-thiatriazoline *S,S*-dioxides (**13**) by treating *N'*-acyl-sulfamoylhydrazides (**24**) with PCl_5 to form the corresponding *N'*-sulfamoyl-carbohydrazonoyl chlorides (**25**) which were cyclized by addition of KOH or *n*-butyllithium $\langle 85\text{M}1141 \rangle$. The formation of (**25a**) was studied in some detail and it was found that it may be isolated in 59% yield if the reaction is carried out at room temperature, while at higher temperature further conversions take place. The reaction from (**24**) to (**13**) is carried out as a one-pot reaction with KOH in the case of (**24b**), and (**24c**) because the chlorocompounds (**25b**), (**25c**), could not be obtained directly with PCl_5 as other products are obtained under these conditions. When the one-pot reaction was attempted with (**24d**), however, the 1,3,4,2-oxadiazaphospholin derivative (**26d**) was obtained and (**25e**) and (**25f**) did not afford thiatriazolines (Scheme 5).



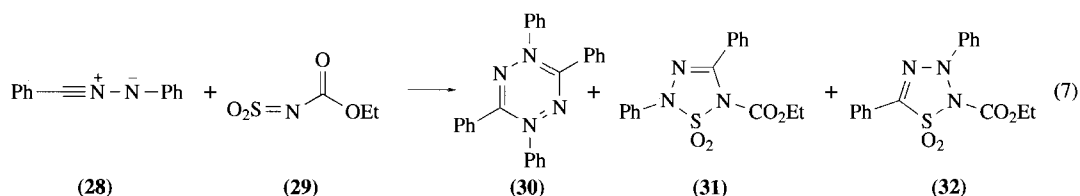
Scheme 5

Compound (**13c**) may exist in two tautomeric forms. Upon alkylation with MeI in DMF (**13b**) and (**27**) are formed (1 : 1) Equation (6).

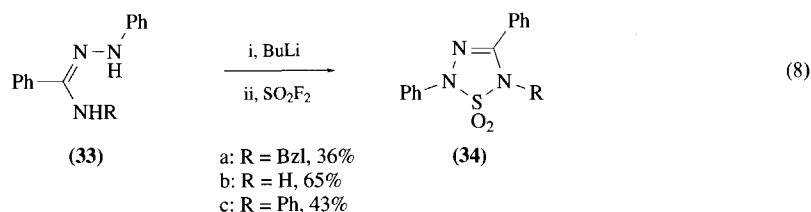


Knollmueller and Kosma $\langle 85\text{M}1141 \rangle$ investigated the possibility of obtaining 1,2,3,5-thiatriazoline

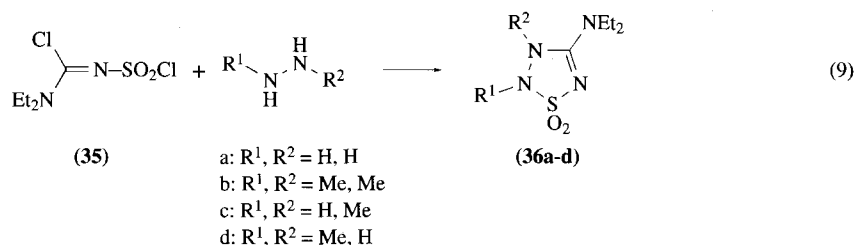
S,S-dioxides by 1,3-dipolar cycloaddition of nitrilimine (28) with *N*-sulfonylamine (29). The reaction led to formation of tetraphenyltetrazine (30) and two isomeric thiatriazolines in 14.5% yield and 12.5% yield respectively. The first thiatriazoline was identified as 2,5-diphenyl-5-ethoxycarbonyl-2,5-dihydro-1,2,3,5-thiatriazol 1,1-dioxide (31) by independent synthesis from 2,4-diphenyl-1,2,3,5-dihydro-thiatriazol 1,1-dioxide and ethyl chloroformate <85M1321>. The second thiatriazoline was, apparently incorrectly, assigned as 3,5-diphenyl-2-ethoxycarbonyl-2,3-dihydro-1,2,3,5-thiatriazol 1,1-dioxide. The regioisomeric 1,3-dipolar cycloadduct structure (32) seems much more likely (Equation (7)).



Knollmueller and Kosma have found that amidrazones (33) do not react with sulfur fluoride in the presence of triethylamine, however, if the corresponding Li-salts are used 1,2,3,5-thiatriazoline *S,S*-dioxides are formed <85M1321> (Equation (8)).

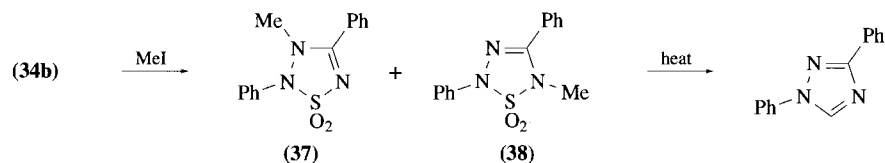


Corresponding 4-diethylamino-substituted derivatives are formed by the reaction of *N,N*-diethyl- (*N'*-chlorosulfonyl) chloroformamidine (35) with hydrazines <85M1321> (Equation (9)).



In the reaction with methylhydrazine (36c) and (36d) are obtained in the ratio 1:15. The two isomers are separated by means of aqueous sodium carbonate in which (36c) is soluble. By methylation of (36d) with methyl iodide, (36b) is formed exclusively (94% yield).

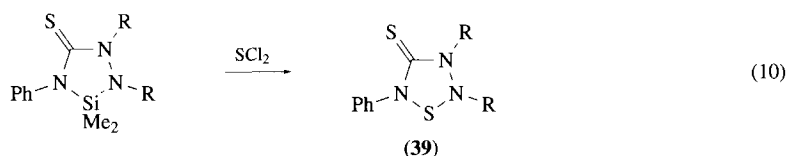
Upon treatment with methyl iodide compound (34b) forms a mixture of (37) and (38) (2:1). The structure assignment is based on the thermal properties. Isomer (37) is stable in boiling benzene while (38) decomposes to 1,3-diphenyl-1,2,4-triazole (Scheme 6).



Scheme 6

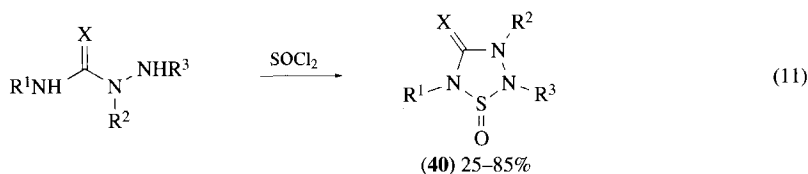
4.20.6.3 1,2,3,5-Thiatriazolidines

3-Sila-1,2,4-triazolidin-5-thiones react with SCl_2 to give 1,2,3,5-thiatriazolidine-4-thiones (39) <78ZC336> (Equation (10)).



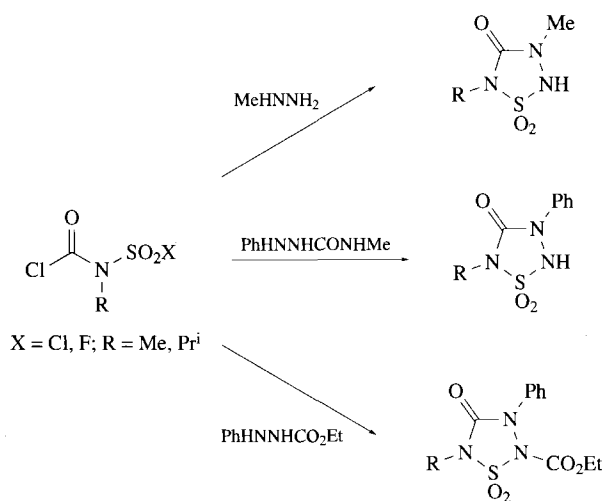
R = Me, 94%, Ph 67%

The same ring system can be prepared from 1,2,4-trisubstituted semicarbazides or thiosemicarbazides and SOCl_2 to give 1,2,3,5-thiatriazolidine *S*-oxide (**40**) <79JHC895> (Equation (11)).



R¹ = Bu^t or Ar; R² = Me; R³ = alkyl; X = O or S

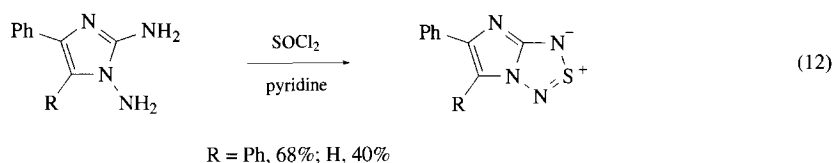
Heterocyclic synthesis using chloro- and fluorosulfonylcarbamoyl chlorides has been studied. 1,2,3,5-Thiatriazolidine *S,S*-dioxides are formed with the reagents shown in Scheme 7 in the presence of sodium hydroxide <77JCR(S)238, 77JCR(M)2813>.



Scheme 7

4.20.6.4 1,2,3,5-Thiatriazole Heteropentalenes

The imidazolo[1,2-*c*]thiatriazoles can be prepared from the corresponding 1,2-diaminoimidazoles as shown in Equation (12). The benzimidazolo[1,2-*c*]thiatriazole can be prepared in an analogous fashion in 47% yield <81JOC4065>.



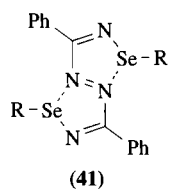
R = Ph, 68%; H, 40%

4.20.7 IMPORTANT COMPOUNDS AND APPLICATIONS

4.20.7.1 Diazenes

An unusual class of selenium-containing, intensely colored diazenes with short intramolecular N-Se contact distances (**41**) have been obtained by the reaction of $\text{PhC}(\text{NSiMe}_3)[\text{N}(\text{SiMe}_3)_2]$ with 1

equivalent RSeCl_3 in acetonitrile ($\text{R} = \text{Me}, \text{Ph}$) or 3 equivalents PhSeCl in dichloromethane ($\text{R} = \text{Ph}$). An x-ray analysis of **(41)** ($\text{R} = \text{Ph}$) confirmed the structure. The corresponding sulfur analogue, *trans*- $\text{PhSN(Ph)CN=NC(Ph)NSPh}$ was obtained in 56% yield as purple-brown microcrystals by the reaction of $\text{PhC(NSiMe}_3)[\text{N(SiMe}_3)_2]$ with 3 equivalents of PhSCl <90JA5373>.



4.21

Three or Four Heteroatoms including at least One Selenium or Tellurium

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4.21.1 INTRODUCTION

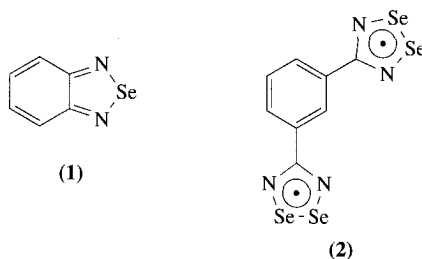
Aspects of the chemistry of compounds belonging to more than 20 systems covered by this chapter have been reported, but the chemistry of only a few of these systems has been studied in detail. Chief among these are the 1,2,3-selenadiazoles, which have generated wide interest owing to their ready conversion into selenium heterocycles, reactive intermediates, and nitrogen- and selenium-free products, and the 1,2,5-selenadiazoles and 1,2,3,5-diselenadiazole systems in which interest stems from their use in the synthesis of potentially useful conducting materials. Compounds belonging to several new systems have been synthesized.

The chemistry of tellurium-containing heterocycles is a growth point in heterocyclic chemistry. The tendency for tellurium to take up the Te(IV) state, especially when bonded to oxygen or the halogens, has resulted in the synthesis of new types of heterocycles containing hypervalent tellurium.

Earlier work on 1,2,3-, 1,2,5-, and 1,3,4-selenadiazoles has been reviewed previously <79AHC(24)109>. Two detailed reviews of five-membered selenium and tellurium heterocycles have covered this area up to 1985 <B-86MI 421-01, B-87MI 421-01>. A short review of condensed 1,2,5-selenadiazoles has been published <83H(20)71> and a review of perfluorinated 2,1,3-benzoselenadiazoles has appeared <92HAC171>. Houben-Weyl's "Methods of Organic Chemistry" provides an excellent comprehensive account of organotellurium chemistry in general and tellurium-containing heterocycles in particular <90HOU(E12b)>. A review of five-membered tellurium-containing heterocycles has been published <86SR(6)15>.

4.21.2 THEORETICAL METHODS

Very little theoretical work has been done on five-membered heterocycles of selenium and tellurium which contain three or four heteroatoms. The multiple-scattering local-density approximation (MS-LDA) method has been applied in two variations to 2,1,3-benzoselenadiazole (**1**) and its O and S analogues. Ionization energies, UV transitions, dipole moments, and nuclear quadrupole coupling constants were calculated and compared with experimental values, and the PE spectrum was assigned. Ionization potentials and principal quadrupole moments calculated using a large partial-wave basis agreed satisfactorily with experimental values but there was poor agreement between calculated and experimental values for UV transitions and dipole moments <92JCS(F1)2641>. Band structure calculations using extended Hückel methods have been performed on the two crystal phases, designated α and β , of the 1,3-phenylene-bridged 1,2,3,5-diselenadiazolyl radical (**2**) (see Section 4.21.3.1). Both α - and β -phases are predicted to have semiconductor properties with band gaps of 0.8 and 1.2 eV, respectively <91JA3559, 92JA1729>.



4.21.3 EXPERIMENTAL STRUCTURAL METHODS

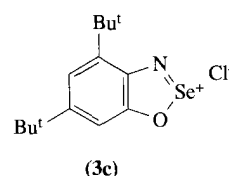
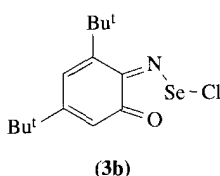
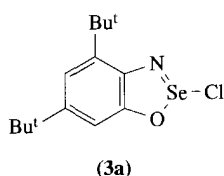
4.21.3.1 X-ray Diffraction

The hypervalent 2-chloro-1,2 λ^4 ,3-benzoxaselenazole structure (**3a**) is a satisfactory alternative to the *o*-quinonoid seleninyl chloride structure (**3b**) for the product from the reaction of 2,4,6-tri-*t*-

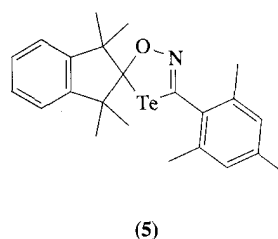
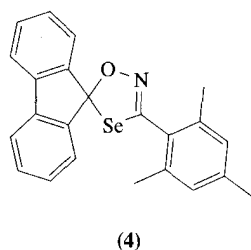
butylaniline with seleninyl chloride. Selected bond lengths and bond angles are listed in Table 1. The Se—N bond shows double-bond character. The elongation of the Se—O and Se—Cl bonds relative to the sum of the respective covalent radii (Se—O, 1.83 Å; Se—Cl, 2.17 Å) and the nearly linear arrangement of the O, Se, Cl sequence are consistent with the three-centre, four-electron O, Se, Cl system in (3a) and exclude the ion-pair structure (3c) <85JCS(D)565>.

Table 1 Bond lengths (Å) and bond angles (°) in 2-chloro-4,6-di-*t*-butyl-1,2,4,3-benzoxaselenazole (3a).

Bond	Å/(°)
Se—N	1.766 (4)
Se—Cl	2.302 (2)
Se—O	2.079 (3)
N—C(3a)	1.310 (5)
O—C(7a)	1.283 (5)
N—Se—Cl	91.1 (1)
N—Se—O	83.7 (1)
O—Se—Cl	174.7 (1)



Crystal structure determinations of the 1,4,2-oxaselenazole (4) <88JA8679> and the 1,4,2-oxatellurazole (5) <94CL1691> have been carried out. Both systems are new. Selected hetero-ring bond lengths (Å) and bond angles (°) in (5) are: Te(4)—C(3), 2.105(7); Te(4)—C(5), 2.175(7); N(2)—C(3), 1.264(8); N(2)—O(1), 1.386(8); C(5)—O(1), 1.471(7); C(3)—Te(4)—C(5), 79.4(3); N(2)—C(3)—Te(4), 116.8(5).



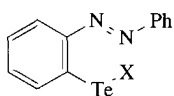
Structure determinations of the formally *o*-tellurated azobenzenes (6a)–(8a) reveal the presence of N to Te bonding and give evidence of electron delocalization in the heteroatom moiety. Selected bond lengths (Å) and bond angles (°) are given in Table 2. The 1-substituted 1,2,3-benzotelluradiazole structures (6b)–(8b) make an important contribution to the molecular structure <79JCR(S)145, 85JOM(293)219>.

The x-ray structure of 2,1,3-benzoselenadiazole (1) has been determined. The double-bond–single-bond arrangement implied by structure (1) is a good approximation to the bonding in the molecule. Bond lengths reveal some electron delocalization in the hetero-ring. Selected bond lengths and bond angles are given in Table 3 <89AX(C)73>. 2,1,3-Benzoselenadiazole (1) reacts with iodine, potassium iodide and hydrogen chloride to give the salt (9), which consists of a sheet structure in which the heterocycle (1) and its protonated form are connected by linear N—H ··· N bonds and secondary selenium–nitrogen interactions (Figure 1) <85ZAAC(523)33>.

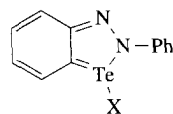
An x-ray structure determination of 1,2,5-telluradiazole (10) shows that the molecule is planar, has C_{2v} symmetry and has the following bond lengths (Å) and bond angles (°): Te—N, 2.023(6); N—C, 1.273(10); C—C, 1.421(11); N—Te—N, 82.5(2); Te—N—C, 109.4(5); N—C—C, 119.4(7). In the solid state, the molecules are held together by weak bonds between tellurium and nitrogen,

Table 2 Bond lengths (Å) and bond angles (°) in the 1 λ^4 ,2,3-benzotelluradiazoles (**6b**)–(**8b**).

Bond	(6b) Å/(°)	(7b) Å/(°)	(8b) Å/(°)
Te—N(2)	2.23	2.26 (4)	2.243 (3)
Te—X	2.55	2.167 (4)	2.672 (1)
Te—C(7a)	2.04	2.074 (4)	2.073 (4)
N(2)—N(3)	1.25	1.270 (5)	1.270 (5)
C(3a)—N(3)	1.43	1.387 (7)	1.379 (6)
C(3a)—C(7a)	1.36	1.404 (6)	1.397 (6)
N—Te—X	167.6	159.0 (1)	166.8 (1)



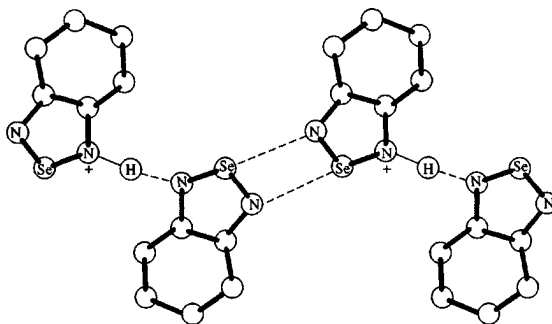
(**6a**) X = Cl
 (**7a**) X = OCOMe
 (**8a**) X = SCN



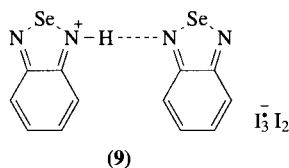
(**6b**) X = Cl
 (**7b**) X = OCOMe
 (**8b**) X = SCN

Table 3 Bond lengths (Å) and bond angles (°) in 2,1,3-benzoselenadiazole (**1**).

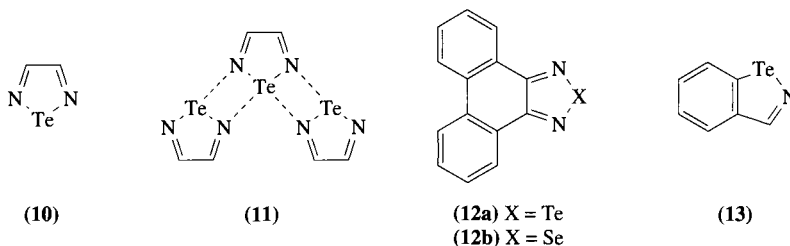
Bond	Å/(°)
Se(2)—N(1)	1.792 (6)
Se(2)—N(3)	1.777 (6)
N(1)—C(7a)	1.321 (9)
N(3)—C(3a)	1.328 (9)
C(3a)—C(7a)	1.438 (9)
C(3a)—C(4)	1.420 (10)
C(4)—C(5)	1.359 (12)
C(5)—C(6)	1.416 (11)
C(6)—C(7)	1.341 (12)
C(7)—C(7a)	1.442 (10)
N(1)—Se(2)—N(3)	94.7 (3)
Se(2)—N(1)—C(7a)	106.8 (4)
Se(2)—N(3)—C(3a)	106.3 (5)
N(1)—C(7a)—C(3a)	116.9 (6)
N(3)—C(3a)—C(7a)	116.3 (6)

**Figure 1** Sheet structure of cation in 2,1,3-benzoselenadiazole-2,1,3-benzoselenadiazolium penta iodide (**9**).

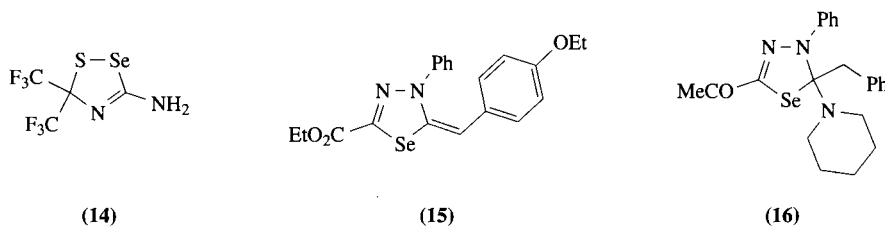
giving rise to a quasi-polymeric ribbon structure (**11**). Each tellurium atom forms two intermolecular Te...N bonds of length 2.764(6) Å which form two sides of a Te, N, Te, N parallelogram $\langle 84\text{AX}(\text{C})653 \rangle$. The crystal structure of phenanthro[9,10-*c*]-1,2,5-telluradiazole (**12a**) shows also the presence of a polymeric ribbon structure $\langle 87\text{ZN}(\text{B})84 \rangle$. Crystals of other heterocycles containing ring



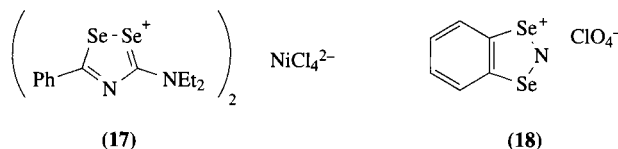
Te—N bonds also consist of quasi-polymeric structures. Thus benzoisotellurazole (**13**) shows short intermolecular Te $\cdots$ N contacts (2.4 Å) <78JHC745>. Intermolecular Se $\cdots$ N bonds are also present in 1,2,5-selenadiazoles but they are weaker and do not give rise to polymeric structures <84AX(C)653>.



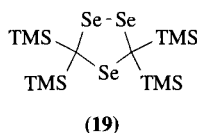
The x-ray structure determination of the 1,2,4-thiaselenazoline (**14**) shows that there is some π -electron delocalization in the $\text{NH}_2\text{—C=N}$ moiety <90CB691>. X-ray crystal structure determinations of the 1,3,4-selenadiazolines (**15**) and (**16**) have been carried out <92MI 421-01, 92MI 421-02>.



The cation in bis-(3-diethylamino-5-phenyl-1 λ^4 ,2,4-diselenazol-1-ylum) tetrachloronickelate (**17**) is a planar delocalized 6 π -electron system. Selected bond lengths (Å) and bond angles (°) are: Se(1)—Se(2), 2.293(1); Se(2)—C(3), 1.911(7); Se(1)—C(5), 1.892(7); C(3)—N(4), 1.347(9); N(4)—C(5), 1.294(8); C(3)—NEt₂, 1.303(9); Se(1)—Se(2)—C(3), 89.7(2); Se(2)—Se(1)—C(5), 89.9(2); Se(1)—C(5)—N(4), 121.6(5); Se(2)—C(3)—N(4), 120.4(5); C(3)—N(4)—C(5), 119.4(6) <92ZAAC(617)89>. An x-ray structure determination of 1 λ^4 ,3,2-benzodiselenazol-1-ylum perchlorate (**18**) shows that the hetero-ring is a delocalized 6 π -electron system. Bond lengths (Å) and bond angles (°) in the hetero-ring are: Se(1)—N(2), 1.724(7); Se(3)—N(2), 1.739(7); Se(3)—C(3a), 1.859(8); Se(1)—C(7a), 1.852(9); C(3a)—C(7a), 1.413(11); Se(1)—N(2)—Se(3), 118.1(4); N(2)—Se(1)—C(7a), 96.3(4); N(2)—Se(3)—C(3a), 96.0(4); Se(1)—C(7a)—C(3a), 115.1(6); Se(3)—C(3a)—C(7a), 114.5(6) <92ZN(B)675>.



The 1,3,4-triselenolane (**19**) has C_{2v} symmetry but is nonplanar and has a C—Se—Se—C torsion angle of 48.4°. The Se—Se bond length is 2.328(1) Å <90CB2325>.



The structure of the radical-cation salt (**20a**) has been established. The salt is dimeric in the solid state. The five-membered ring is nearly planar and is coplanar with the six-membered ring. The dimers are formed by two cations superimposed and almost parallel to one another (Figure 2). This arrangement allows effective spin-pairing between two cations despite coulombic repulsion. Bond lengths (Å) and bond angles (°) differ slightly within and between dimer units. Typical values are: Se(1)—Se(2), 2.298(5); Se(2)—Se(3), 2.293(5); Se(3)—C(2), 1.88(3); Se(1)—C(1), 1.91(4); C(1)—C(2), 1.41(4); Se(1)—Se(2)—Se(3), 97.2(2); C(1)—Se(1)—Se(2), 99(1); C(2)—Se(3)—Se(2), 98(1) $\langle 92\text{AG(E)779} \rangle$.

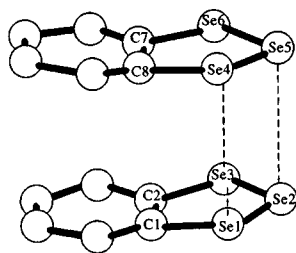
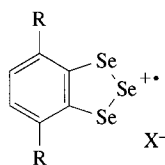


Figure 2 Dimer of the benzo[1,2-*d*][1,2,3]triselenolium radical-cation in the trifluoromethanesulfonate (**20a**).



(**20a**) R = H, X = CF₃SO₃

(**20b**) R = Prⁱ, X = PF₆

(**20c**) R = H, X = Cl

The structures of a series of stable 1,2,3,5-diselenadiazolyl radicals (**2**), (**21a**)–(**21e**) and (**22**) have been determined by x-ray diffraction. The radicals (**21a**)–(**21e**) and the diradical (**22**) form dimer units in the solid state, whose arrangement in the crystal varies with structure. The structure of (**21a**) consists of antiparallel arrays of cofacial dimers with head-to-tail stacking (Figure 3). Lengths of Se—Se bonds within the dimers are 2.329(4) and 2.322(4) Å $\langle 92\text{CC1265} \rangle$. The two hetero-rings in each dimer of (**21b**) are eclipsed, with a dihedral angle between the two rings of 5.5°, and the dimer units are stacked in a herring-bone arrangement (Figure 4; Ph groups are omitted for clarity). Within the dimers the two hetero-rings are connected by two unequal Se ··· Se contacts (3.160(2) and 3.347(2) Å) and the dimer units are connected by secondary Se ··· Se attractions at 3.815 and 4.075 Å $\langle 89\text{JA9276, 91JA582} \rangle$. The radicals (**21c**)–(**21e**) dimerize in a cofacial fashion. Structures (**21c**) and (**21d**) form ribbons of dimers packed in head-to-tail fashion with C≡N ··· Se contacts (3.11 and 3.21 Å, respectively) linking consecutive molecules. Close contacts exist between adjacent ribbons. In (**21e**) the dimers lie in sheets forming extended arrays linked by head-to-tail C≡N ··· Se contacts (3.07 Å) $\langle 92\text{IC1802} \rangle$. The dimeric units of the diradical (**22**) are packed as interleaved columns (Figure 5). The interlocking nature of the dimer units produces close Se ··· Se and Se ··· N contacts between neighboring diradicals $\langle 91\text{JA582} \rangle$. The molecules of the diradical (**2**) do not couple into discrete dimers but form vertical stacks which are linked in a zig-zag arrangement of short Se ··· Se contacts (mean 3.284 Å, solid lines) and long Se ··· Se contacts (mean 4.014 Å, broken lines) (Figure 6) $\langle 91\text{JA3559} \rangle$. The structures of the solvated salts (**23**) $\langle 89\text{JA9276} \rangle$ and (**24**) $\langle 90\text{AX(C)699, 91JA582} \rangle$ have been determined. Reduction of the cations in (**23**) and (**24**) to the corresponding radicals (**21b**) and (**22**) leads to a lengthening of the Se—Se and Se—N bonds $\langle 89\text{JA9276} \rangle$.

In the search for new organic conducting materials, x-ray structure determinations of fused 1,2,5-selenadiazoles and 1,2,5-thiadiazoles have been carried out. Compounds (**25a**) and (**25b**) are planar molecules possessing a two-fold axis and mirror plane. Short C≡N ··· S and C≡N ··· Se contacts connect each molecule in the crystal with four neighbors, forming a virtually planar sheet network (Figure 7). The sheets stack to form infinite layers with face-to-face overlapping between

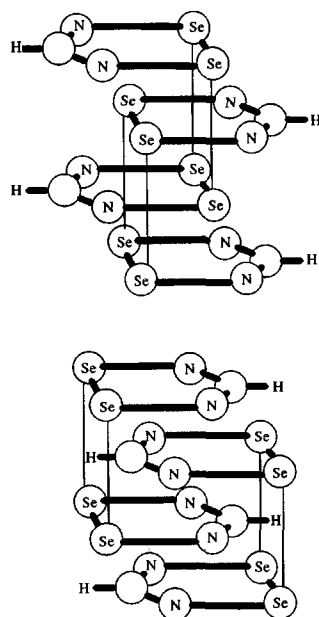


Figure 3 Cofacial dimer of the 1,2,3,5-diselenadiazolyl radical (**21a**) showing head-to-tail stacking.

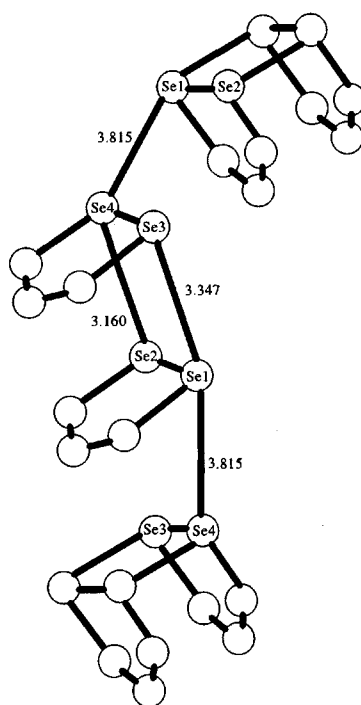


Figure 4 Herring-bone stacking arrangement of the dimer units of the 4-phenyl-1,2,3,5-diselenadiazolyl radical (**21b**).

the heterocycle moieties <87CL2285, 92JA3034>. Molecules of (**26a**) and (**26b**) also form sheet networks involving short S $\cdots$ S contacts <92JOC5517, 92PS(67)327>. Crystals of (**27**) consist of a two-dimensional ribbon network involving strong Se $\cdots$ Se (3.96 Å) contacts <87CL1129>.

4.21.3.2 Proton NMR Spectroscopy

Proton NMR spectra of 1,2,3-selenadiazoles (**28a**)–(**28e**) have been recorded. The chemical shifts of H-4 and H-5 lie in the ranges δ 8.2–8.4 and δ 8.8–9.4, respectively. For (**28a**) $J_{\text{H-4, H-5}} = 3.8$ Hz.

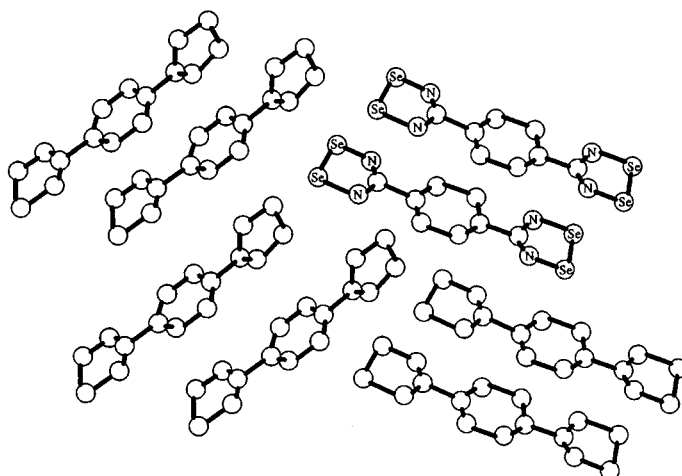


Figure 5 Dimer units of the 1,4-phenylene-bis-1,2,3,5-diselenadiazolyl diradical (**22**) packed in interleaved columns.

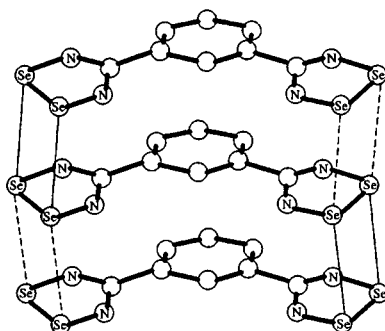
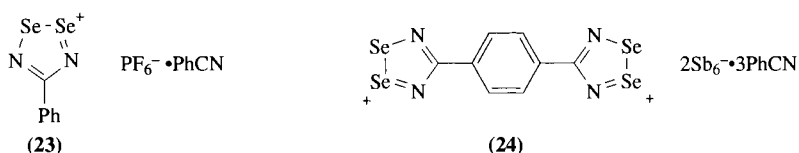
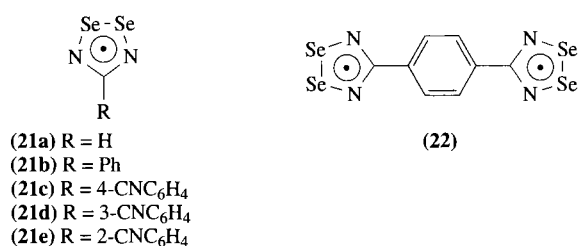


Figure 6 Section of the vertical stack of the 1,3-phenylene-bis-1,2,3,5-diselenadiazolyl diradical (**2**).



The spectra of (**28b**) and (**28c**) show allylic coupling. For (**28b**) $J_{\text{H,Me}} = 0.9$ Hz and for (**28c**) $J_{\text{H,Me}} = 1.2$ Hz. $^1\text{H}-^{13}\text{C}$ and $^1\text{H}-^{77}\text{Se}$ coupling constants (Hz) for (**28a**) are: $^1J_{\text{H-4,C-4}} 191.1$; $^2J_{\text{H-4,C-5}} 13.2$; $^1J_{\text{H-5,C-5}} 191.7$; $^2J_{\text{H-5,C-4}} 9.2$; $^2J_{\text{H-5,Se}} 39.3$; $^3J_{\text{H-4,Se}} \leq 6.0$. Similar values were obtained for the corresponding couplings in (**28b**) and (**28c**) (<81ZN(B)1017>).

Ring protons of 1,2,5-selenadiazoles (**29**) resonate at low field (Table 4). The chemical shifts of ring methyl groups lie at ca. δ 2.6 (<79S979, 87H(26)2153>). The chemical shifts of the ring protons of three 1,2,5-telluradiazoles, (**30a**)–(**30c**), in DMSO-*d*₆ appear between δ 10.7 and 11.5. The 3-methyl

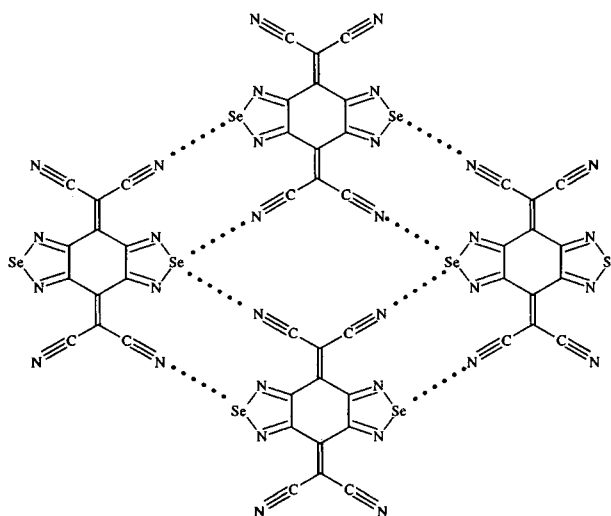
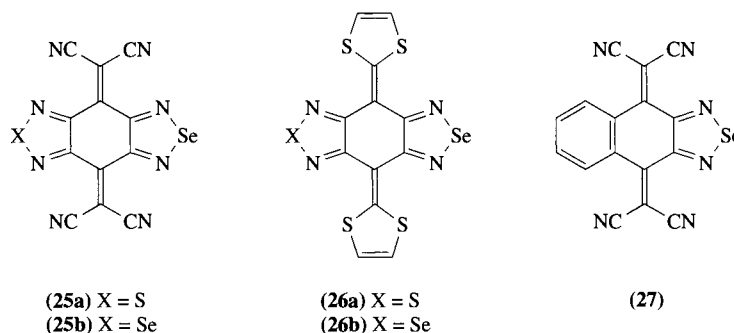
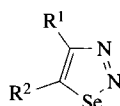


Figure 7 Section of the sheet network of the condensed 1,2,5-selenadiazole (25b) showing C≡N...Se contacts.



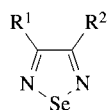
- (28a) R¹ = R² = H
- (28b) R¹ = Me, R² = H
- (28c) R¹ = H, R² = Me
- (28d) R¹ = Prⁱ, R² = H
- (28e) R¹ = Me, R² = Et

signal of (30b) occurred at δ 2.55 (Table 4) <82S681>. These data are consistent with the heteroaromaticity of 1,2,5-selenadiazoles and 1,2,5-telluradiazoles.

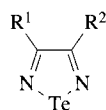
The normal spectrum and the COSY spectrum of 2,1,3-benoselenadiazole (1) oriented in liquid crystals were analyzed in an examination of the AA'BB' system to give detailed information on the symmetry, origin, and connectivity of various transitions <83JMR(55)386>. The benzene ring hydrogens of the salt (18) are strongly deshielded, with δ (CD₃CN) for H-4(7) at 9.25 and H-5(6) at 8.07 <92ZN(B)675>.

4.21.3.3 Carbon-13 NMR Spectroscopy

A comprehensive table of ¹³C NMR data for 37 1,2,3-selenadiazoles has been published earlier <81ZN(B)1017>. Additional data are available for the following groups of 1,2,3-selenadiazoles: 4,5-cycloalkeno-1,2,3-selenadiazoles with double or triple bonds in the carbocyclic ring <88LA221,



- (29a) $R^1 = R^2 = H$
 (29b) $R^1 = H, R^2 = c\text{-C}_6\text{H}_{11}$
 (29c) $R^1 = H, R^2 = 4\text{-MeC}_6\text{H}_4$
 (29d) $R^1 = H, R^2 = 1\text{-naphthyl}$
 (29e) $R^1 = H, R^2 = 2\text{-thienyl}$
 (29f) $R^1 = H, R^2 = \text{vinyl}$
 (29g) $R^1 = \text{Me}, R^2 = c\text{-C}_6\text{H}_{11}$
 (29h) $R^1 = \text{Me}, R^2 = 4\text{-MeC}_6\text{H}_4$
 (29i) $R^1 = \text{Me}, R^2 = \text{PhNHCO}$



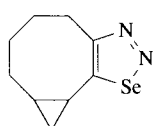
- (30a) $R^1 = R^2 = H$
 (30b) $R^1 = H, R^2 = \text{Me}$
 (30c) $R^1 = H, R^2 = \text{Ph}$
 (30d) $R^1 = R^2 = \text{Me}$
 (30e) $R^1 = R^2 = \text{Ph}$

Table 4 Proton NMR chemical shifts (δ) of ring hydrogens and ring methyl groups in 1,2,5-selenadiazoles (29) and 1,2,5-telluradiazoles (30)^a.

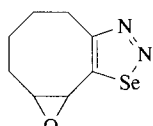
Compound	R^1	R^2	δ	Solvent	Ref.
(29a)	H	H	9.43	(CD ₃) ₂ SO	82S681
(29b)	H	<i>c</i> -C ₆ H ₁₁	9.20	CDCl ₃	87H(26)2153
(29c)	H	4-MeC ₆ H ₄	9.68	CDCl ₃	87H(26)2153
(29d)	H	1-Naphthyl	9.63	CDCl ₃	87H(26)2153
(29e)	H	2-Thienyl	9.64	CDCl ₃	87H(26)2153
(29f)	H	Vinyl	9.80	CCl ₄	79S979
(29g)	Me	<i>c</i> -C ₆ H ₁₁	2.58	CDCl ₃	87H(26)2153
(29h)	Me	4-MeC ₆ H ₄	2.66	CDCl ₃	87H(26)2153
(30a)	H	H	10.81	(CD ₃) ₂ SO	82S681
(30b)	H	Me	10.71, 2.55	(CD ₃) ₂ SO	82S681
(30c)	H	Ph	11.51	(CD ₃) ₂ SO	82S681

^aReference signal TMS.

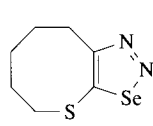
88TL2813, 91JA9258); (31) and isomers <87LA1087>; (32) and isomers <89CB509>; (33) and isomers <92ZN(B)563>; the bis-1,2,3-selenadiazole (34) <88CB735>. The ¹³C signals of C-4 and C-5 in 1,2,3-selenadiazoles are normally near δ 160, with C-4 more deshielded than C-5. Detailed multinuclear NMR studies of (28a), (35a)–(35d) and (36) have been made <90MRC549> (see Section 4.21.3.5).



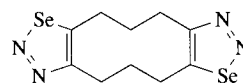
(31)



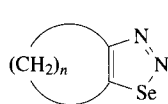
(32)



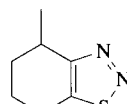
(33)



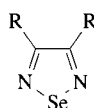
(34)



- (35a) $n = 3$
 (35b) $n = 4$
 (35c) $n = 5$
 (35d) $n = 6$



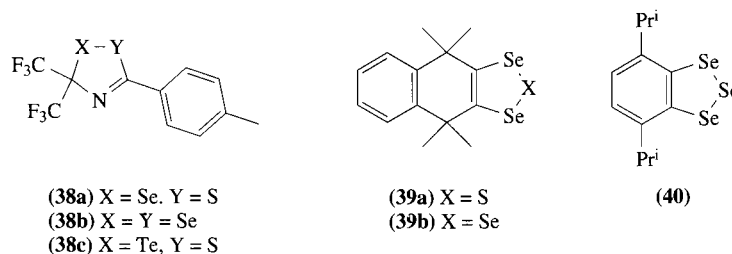
(36)



- (37a) $R = \text{Ph}$
 (37b) $R = \text{OCH}_2\text{CF}_3$
 (37c) $R = \text{CN}$

Carbon-13 NMR spectral data for 1,2,5-selenadiazoles are scarce. The C-3(4) signal is found over a wide range. Examples are: (37a) in $\text{CF}_3\text{CO}_2\text{D}$, δ 167.58 <87HCA1076>; the derivative (37b) in CDCl_3 , δ 150.7 <84ZN(B)1315>; 3,4-dicyano-1,2,5-selenadiazole (37c) in CDCl_3 , δ 139.4 <86CB366>. A series of substituted 2,1,3-benzoselenadiazoles exhibit ^{13}C signals within the narrow range δ 157–162 <87CB1593, 87HCA997>. The spectrum of the fused selenadiazole (12b) in $\text{CF}_3\text{CO}_2\text{D}$ shows a hetero-ring ^{13}C signal at δ 157.42 and the tellurium analogue (12a) in $\text{DMSO}-d_6$ shows the corresponding ^{13}C signal at δ 162.03 <87ZN(B)84>.

The hetero-ring ^{13}C signal from 1,4,3,2-benzodiselenazol-1-ylum perchlorate (18) in CD_3CN is present at δ 174.7 <92ZN(B)675>. The hetero-ring ^{13}C -3 chemical shifts of the thiaselenazoline (38a), the diselenazoline (38b), and the thiatellurazoline (38c) in CCl_4 are δ 175.9, 173.4 and 173.9, respectively, and the corresponding ^{13}C -5 chemical shifts are δ 99.4, 98.7 and 87.2 <79CC80, 80CB2699>. Ring ^{13}C chemical shifts for the thiaselenazoline (14) are: C-3, δ 161.1; C-5 δ 95.3 <90CB691>. The hetero-ring ^{13}C signals of the thiadiselenole (39a) and the triselenole (39b) in CDCl_3 are seen at δ 144.4 and 145.2, respectively <88CL657>, and the hetero-ring ^{13}C signal of the triselenole (40) is present at δ 146.3 <94CC1593>. The ring ^{13}C signal of the 1,2,4-triselenolane (19) in C_6D_6 is present at δ 46.11 <90CB2325>.



4.21.3.4 Nitrogen-14 and Nitrogen-15 NMR Spectroscopy

Remarkably little work has been reported on nitrogen NMR spectroscopy of heterocycles covered by this chapter. Nitrogen-15 NMR data have been compiled for the 1,2,3-selenadiazoles (28a), (35a)–(35d), and (36). The signal from N-2 in compounds (35a)–(35d) showed satellite signals arising from large one-bond coupling with ^{77}Se , enabling signal assignments to be made to N-2 and N-3 (Table 5) <90MRC549>. The ^{14}N NMR spectrum of (37c) in CDCl_3 showed two broad signals at δ 17.7 and -104.1 <86CB366>.

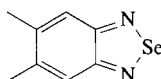
Table 5 Carbon-13, nitrogen-15, and selenium-77 NMR spectral data for the 1,2,3-selenadiazoles (28a)–(28c), (35a)–(35d), and (36)^a.

	(28a)	(28b)	(28c)	(35a)	(35b)	(35c)	(35d)	(36)
$\delta\text{C}(5)^{\text{b,c}}$	143.6			162.1	155.4	160.5	159.2	155.5
$\delta\text{C}(5)^{\text{d,e}}$	143.7	138.0	160.8	162.2	155.6	160.6	159.2	
$\delta\text{C}(4)^{\text{b,c}}$	147.3			170.3	157.3	163.2	160.9	163.3
$\delta\text{C}(4)^{\text{d,e}}$	147.1	157.5	147.6	170.1	157.4	163.4	161.0	
$\delta\text{N}(2)^{\text{b,f}}$	454.6			481.8	457.1	450.9	455.3	459.6
$\delta\text{N}(3)^{\text{b,f}}$	466.8			445.3	461.9	466.3	464.0	463.3
$\delta\text{Se}^{\text{b,g}}$	1498.9			1404.7	1490.2	1532.9	1502.4	1491.3
$^1\text{JC}(5)\text{—Se(Hz)}^{\text{b}}$	135.8			148.8	138.2	136.8	135.3	137.7
$^1\text{JC}(5)\text{—Se(Hz)}^{\text{d}}$	136.8	132.2	137.3					
$^2\text{JC}(4)\text{—Se(Hz)}^{\text{b}}$	29.0			34.4	28.7	29.6	38.7	34.4
$^2\text{JC}(4)\text{—Se(Hz)}^{\text{d}}$	27.9	27.5	33.2					
$^1\text{JN}(2)\text{—Se(Hz)}^{\text{b}}$				83.4	89.8	92.2	89.4	

^aSolvent CDCl_3 . ^b<90MRC(28)549>. ^cReference signal CDCl_3 $\delta_{\text{c}} = 77.0$. ^d<81ZN(B)1017>. ^eReference signal TMS. ^fReference signal $1\text{M } ^{15}\text{NH}_4\text{NO}_3$ in D_2O . ^gReference signal Ph_2Se $\delta_{\text{Se}} = 460.0$.

4.21.3.5 Selenium-77 NMR Spectroscopy

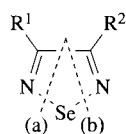
Selenium-77 spectra of several selenium-containing heterocycles have been reported. Unfortunately there has been no uniformity in the use of reference standards. The spectra of fully conjugated heteroaromatic selenium-containing five-membered heterocycles show large downfield ^{77}Se shifts. ^{77}Se , ^{15}N , and ^{13}C chemical shifts, ^{77}Se - ^{13}C one- and two-bond coupling constants, and ^{77}Se - ^{15}N one-bond coupling constants were measured for the 1,2,3-selenadiazoles (**28a**), (**35a**)-(b), and (**36**) (Table 5) <90MRC549>. ^{77}Se - ^{13}C one- and two-bond coupling constants were also reported previously for (**28a**)-(b) <81ZN(B)1017>. ^{77}Se shifts of (**41**) and (**3a**) in CDCl_3 - CH_2Cl_2 were found at δ 1406 and 1326, respectively <85JCS(D)565>. The ^{77}Se spectrum of 1,2,3-benzodiselenazol-1-ylum perchlorate (**18**) in CD_3CN showed a singlet at δ 1621 <92ZN(B)675>. Signals from ^{77}Se in the nonheteroaromatic 1,2,4-thiaselenazoline (**14**), the 1,2,3-triselenole (**40**), and the 1,2,4-triselenolane (**19**) occur at much higher field. The spectrum of (**14**) in CDCl_3 showed a singlet at δ 698.8 <90CB691>. The spectrum of (**40**) showed two singlets at δ 440.9 and 547.0 with $^1J_{\text{Se,Se}}$ 258 Hz <94CC1593>. The spectrum of (**19**) in C_6D_6 showed ^{77}Se signals at δ 686, arising from Se-4, and at δ 704 arising from Se-1 and Se-2 <90CB2325>. Magic angle spinning and static sample ^{77}Se spectra of polycrystalline samples of the diradical dimer (**2**) have been obtained. The spin-lattice relaxation time of ^{77}Se is temperature dependent. The relaxation process is spatially homogeneous <91JA3559>.



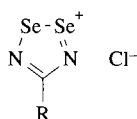
(41)

4.21.3.6 Mass Spectrometry

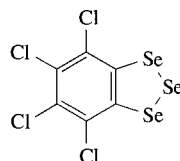
1,2,3-Selenadiazoles break down on being heated to give either a very weak $\text{M}^{+\cdot}$ peak or no $\text{M}^{+\cdot}$ peak. Loss of N_2 occurs followed by extrusion of selenium <84CHEC-I(6)348>. 1,2,5-Selenadiazoles are normally much more stable and many give prominent molecular ion peaks <79S979, 87HCA1076, 87H(26)2153>. An important fragmentation mode, indicated by (**42**), leads initially by route (a) to $\text{R}^2\text{CNSe}^{+\cdot}$ and R^1CN , or by route (b) to $\text{R}^1\text{CNSe}^{+\cdot}$ and R^2CN . Subsequent loss of Se or $\text{Se}^{+\cdot}$ from $\text{R}^1\text{CNSe}^{+\cdot}$ or $\text{R}^2\text{CNSe}^{+\cdot}$ may occur, depending on R^1 and R^2 <84CHEC-I(6)522>. 1,2,5-Telluradiazoles (**30a**)-(b) also give prominent molecular ion peaks <82S681, 87ZN(B)84>. Prominent peaks in the FAB mass spectrum of the salt (**17**) are due to the cation in (**17**) and its principal fragmentation products $\text{PhCN}^{+\cdot}$ and Ph^+ <92ZAAC(617)89>. The mass spectrum of (**3a**) shows a weak $\text{M}^{+\cdot}$ peak (10%) and a very intense peak (97%) at m/e 298 which doubtless arises from the cation in (**3c**) <85JCS(D)565>. The base peak in the spectrum of the 1,2,4-thiaselenazoline (**14**) probably corresponds to $(\text{CF}_3)_2\text{C}=\text{N}-\text{C}\equiv\text{NH}^+$ <90CB691>. The 1,2,3,5-diselenadiazolyl radicals (**21a**) and (**21c**)-(b) give moderately intense (40-62%) $\text{M}^{+\cdot}$ peaks which doubtless arise from the 6π -electron cations present in the corresponding salts (**43a**)-(b). The most intense peaks in the mass spectra of (**21a**), (**21c**)-(b) and (**22**) arise from inorganic fragments NSe_2^+ and Se_2^+ <91JA582, 92CC1265, 92IC1802>. The base peak in the spectrum of the triselenole (**40**) is the $\text{M}^{+\cdot}$ peak coming from the stable radical-cation in the salt (**20b**) <94CC1593>. The triselenole (**44**) was characterized by its mass spectrum <88PS(36)135> as was also the thienotriselenole (**45**) <92POL395>.



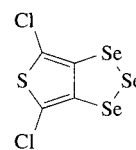
(42)



(43a) $\text{R} = \text{H}$
 (43b) $\text{R} = 4\text{-CNC}_6\text{H}_4$
 (43c) $\text{R} = 3\text{-CNC}_6\text{H}_4$
 (43d) $\text{R} = 2\text{-CNC}_6\text{H}_4$



(44)



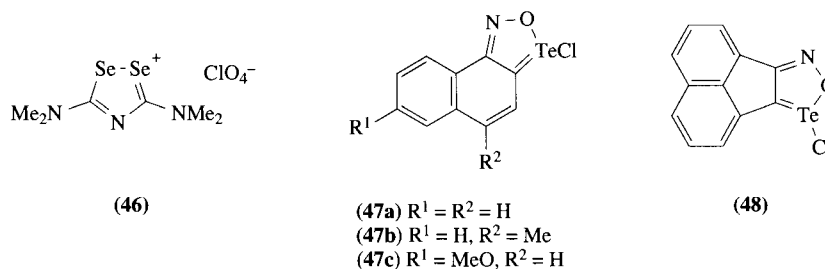
(45)

4.21.3.7 Infrared and Raman Spectroscopy

Very few systematic studies have been carried out. Exceptionally, IR spectra of 1,2,5-telluradiazole (**10**) in solution, in the solid state at room temperature and in the solid state at 10 K have been investigated in the 4000–50 cm^{-1} region and correlated with the spectrum of 1,2,5-selenadiazole (**29a**). The Raman spectrum of (**10**) at room temperature was measured $\langle 84\text{SA}(\text{A})847 \rangle$. IR spectra of 1,2,5-selenadiazoles have been recorded and tentative assignments made $\langle 87\text{H}(26)2153 \rangle$. IR absorption bands have been recorded without assignment for the following heterocycles: 1,2,3-selenadiazoles $\langle 81\text{CB}2382, 87\text{LA}1087, 89\text{CB}509, 92\text{ZN}(\text{B})563 \rangle$; 1,2,4-selenadiazoles $\langle 91\text{BCJ}1037 \rangle$; 1,2,5-selenadiazoles $\langle 84\text{ZN}(\text{B})1315, 86\text{CB}366 \rangle$; 2,1,3-benzoselenadiazoles $\langle 80\text{CB}2699, 85\text{JCS}(\text{D})565, 87\text{HCA}997, 87\text{CB}1593, 90\text{CB}691, 91\text{JA}582, 92\text{ZN}(\text{B})675, 92\text{IC}1802 \rangle$; 1,2,5-telluradiazoles $\langle 82\text{S}681, 87\text{ZN}(\text{B})84 \rangle$.

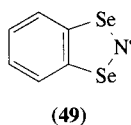
4.21.3.8 UV Spectroscopy

There has been a great decrease in the reporting of UV/visible spectroscopic data. The spectra of 4,5-cycloalkeno-1,2,3-selenadiazoles show two absorption maxima in the vicinity of 295 and 240 nm $\langle 88\text{CB}735, 88\text{TL}2813 \rangle$. A progressive increase in λ_{max} and decrease in absorption intensity occurs along the series 1,2,5-oxadiazole (end absorption), 1,2,5-thiadiazole (253 nm, ϵ 10100), 1,2,5-selenadiazole (285 nm, ϵ 6500), 1,2,5-telluradiazole (336 nm, ϵ 3900) $\langle 82\text{S}681 \rangle$. Substituted 2,1,3-benzoselenadiazoles showed two absorption maxima in the vicinity of 330 and 260 nm $\langle 87\text{CB}1593, 87\text{HCA}1076 \rangle$. The cation in the salt (**46**) has λ_{max} (EtOH) at 275 nm (ϵ 22900) $\langle 87\text{BCJ}2686 \rangle$. UV/visible spectroscopic data were used to characterize several novel hypervalent tellurium heterocycles (**47a**)–(**47c**) and (**48**). Absorption maxima occur in the region 480–510 nm (ϵ 8200–12100) $\langle 86\text{USP}4607000, 87\text{USP}4661438 \rangle$. UV/visible spectroscopic data have been reported for (**25a**) and (**25b**) $\langle 87\text{CL}2285, 92\text{JA}3034 \rangle$ and for (**26a**) and (**26b**) $\langle 92\text{JOC}5517 \rangle$.



4.21.3.9 ESR Spectroscopy

ESR spectra have been obtained for several new types of stable or transient radical species. The spectrum of the radical-cation in (**20a**) showed a low-intensity singlet ($g = 2.0758$ G) with a half-height width of ca. 26.5 G. The signal intensity is solvent dependent owing to a solvent-dependent dissociation of the radical-cation dimer (see Section 4.21.3.1) $\langle 92\text{AG}(\text{E})779 \rangle$. Similar results were reported for the derivative (**20b**) in tetrahydrofuran which gave a signal ($g = 2.0583$ G) whose intensity showed temperature dependence $\langle 94\text{CC}1593 \rangle$. A solution of (**49**) prepared by reduction of (**18**) with Zn dust in dichloromethane at -50°C gave a well-defined spectrum showing a triplet arising from coupling with the ^{14}N nuclei ($g = 2.0168$ G, $a_{\text{N}} = 11.9$ G) $\langle 92\text{ZN}(\text{B})675 \rangle$.



The radical (**21a**) in dichloromethane at 22°C gave a structureless signal ($g = 2.041$ G). In the solid state, (**21a**) is dimeric and diamagnetic with residual spin density 0.01% (see Section 4.21.3.1) $\langle 92\text{CC}1265 \rangle$. The phenyl derivative (**21b**) also gave a broad unresolved signal ($g = 2.0394$ G). Loss

of resolution of hyperfine coupling to nitrogen in **(21a)** and **(21b)** results from anisotropy in the g value (89JA9276, 91JA582). Diamagnetic susceptibilities and spin concentrations as a function of temperature have been measured for the diradical **(2)** in the solid state (91JA3559).

4.21.3.10 Photoelectron Spectroscopy

The photoelectron spectrum of 2,1,3-benzoselenadiazole (**1**), 2,1,3-benzothiadiazole and their tetrafluoro derivatives were measured. Replacement of sulfur by selenium did not appreciably alter the π molecular-orbital ionization energies (91KGS563).

4.21.4 THERMODYNAMIC ASPECTS

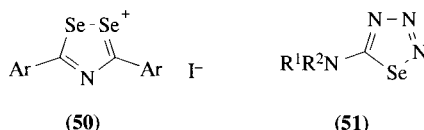
4.21.4.1 Melting Points and Solubilities

1,2,5-Telluradiazole (**10**) has a high melting point (185–188°C) and poor solubility at room temperature in the common organic solvents, whereas 1,2,5-selenadiazole (**29a**) melts at 21°C and is soluble in organic solvents. 1,2,5-Thiadiazole and 1,2,5-oxadiazole are liquids at room temperature and have good solubilities in organic solvents (82S681). The anomalous physical properties of (**10**) have their origin in weak intermolecular Te $\cdots$ N contacts (2.764 Å) present in the crystals of (**10**) (see Section 4.21.3.1) (84AX(C)653).

4.21.4.2 Aromaticity and Stability

A new index of aromaticity has been proposed and applied to neutral and mesoionic five-membered heterocycles. The aromaticity index is based on data from experimentally determined bond lengths which yield statistically evaluated bond orders. A reasonable parallel exists between the aromaticity index and resonance energies (85T1409).

Members of several new classes of stable 6 π -electron cations or 7 π -electron radicals or radical-cations have been synthesized. These include: the cations in the salts (**17**) (92ZAAC(617)89); (**46**) (87BCJ2686); (**50**) (79EGP134093, 86JAP61205269, 87NKK1691); (**20a**) (92AG(E)779); and (**20b**) (94CC1593) (see Section 4.21.3.1). Although formally a 6 π -electron conjugated five-membered heterocycle, 5-amino-1,2,3,4-selenatriazoles (**51**) are thermally unstable and decompose at room temperature to form nitrogen, selenium and cyanamides (83ACS(B)585).



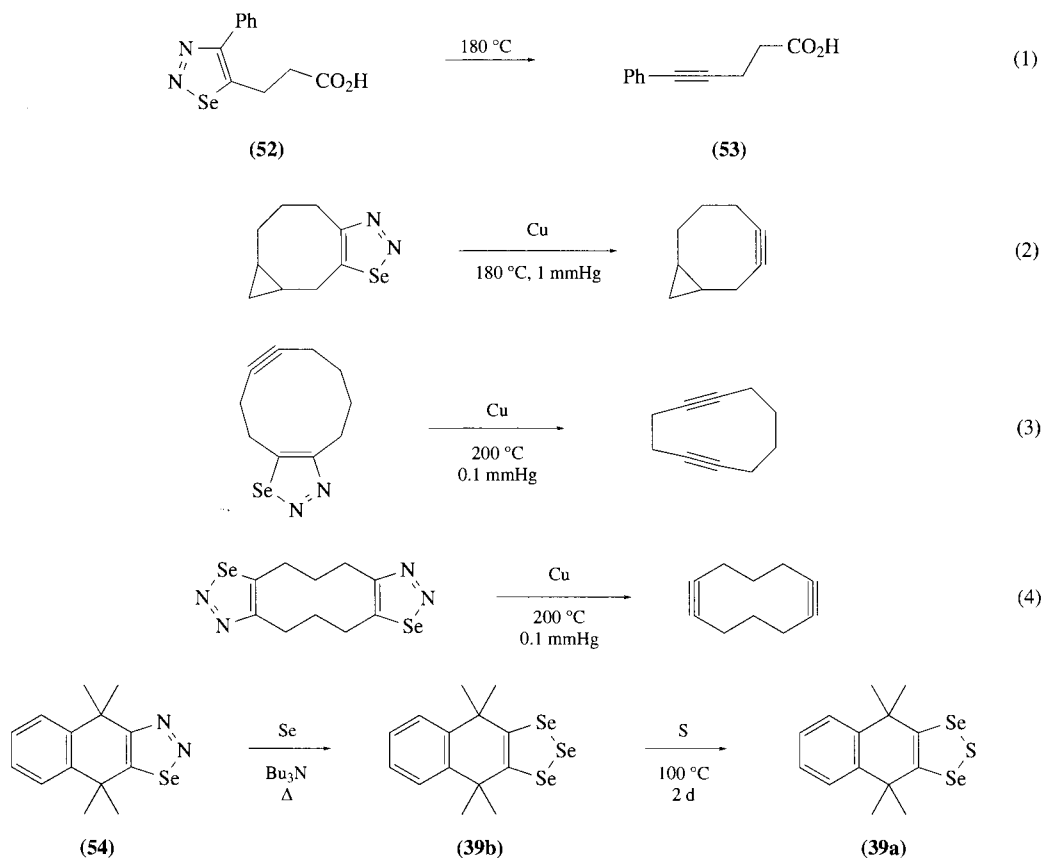
Interest in the design of molecular conductors based on neutral π radicals has led to the synthesis of a series of stable 7 π -electron 1,2,3,5-diselenadiazolyl radicals: (**21a**) (92CC1265); (**21b**) (89JA9276, 91JA582); (**21c**)–(**21e**) (92IC1802); (**2**) (91JA3559); and (**22**) (91JA582). These radicals were prepared by one-electron reduction of the corresponding 6 π electron cation species. The radicals are semi-conductors (see Section 4.21.3.9).

4.21.5 REACTIVITY OF FULLY CONJUGATED RINGS

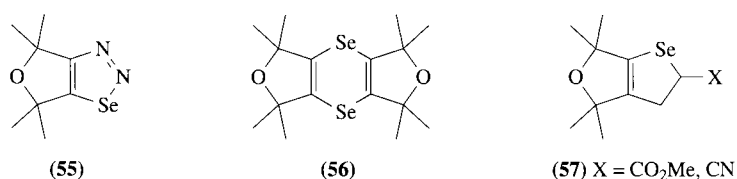
4.21.5.1 Thermal and Photochemical Reactions

The ready thermal and photochemical decomposition reactions of 1,2,3-selenadiazoles resulting in extrusion of nitrogen and selenium or nitrogen only have been exploited widely in synthesis. The scope has been outlined in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (84CHEC-I(6)349). Some new variations are as follows: thermolysis of 1,2,3-selenadiazole carboxylic acids (**52**) affords alkynoic acids (**53**) (Equation (1)) (89JOC2764). Thermolysis of 1,2,3-selenadiazoles fused to carbocyclic rings gives cycloalkynes (Equations (2)–(4)) (86T1711, 87LA1087, 88CB735, 88LA221,

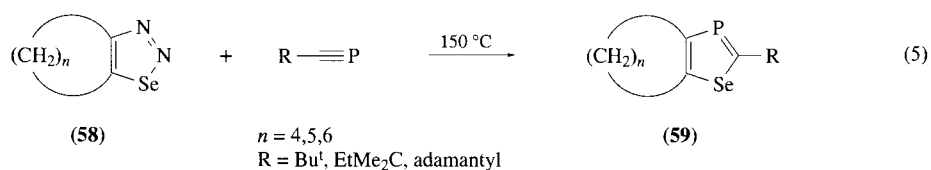
88TL2813, 91JA9258, 92AG(E)791). Prolonged heating of the selenadiazole (**54**) with selenium in butylamine produced the 1,2,3-triselenole (**39b**) which reacted with sulfur to give the thiadiselenole (**39a**) (Scheme 1) <88CL657>. Thermal decomposition of the selenadiazole (**55**) in benzene gives the 1,4-diselenine (**56**). Decomposition of (**55**) in the presence of norbornene or acenaphthylene affords a variety of products including 1,4-diselenines, 2,3-dihydro-1,4-diselenines, 1,2,5-triselenepines and pentaselenepines <87TL5699>. Photolysis of (**55**) in the presence of methyl acrylate or acrylonitrile gives dihydroselenophenes (**57**) in high yield <86TL6107>.

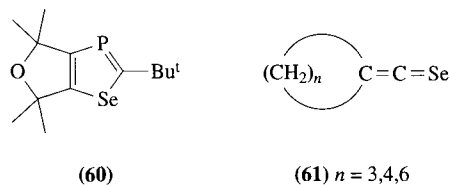


Scheme 1

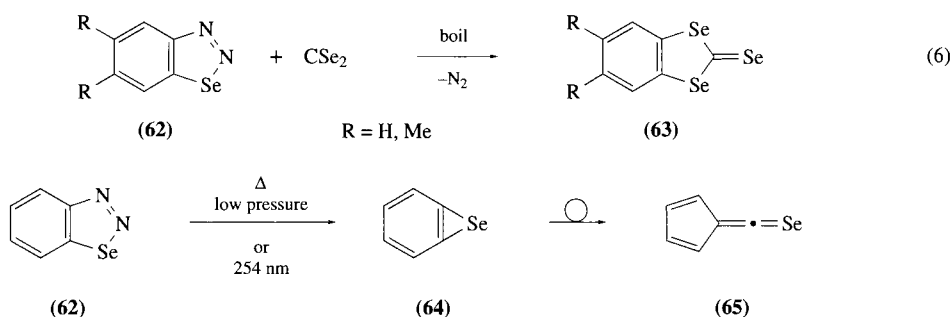


Thermolysis of 4,5-cycloalkeno-1,2,3-selenadiazoles (**58**) in the presence of phosphalkynes produces 4,5-cycloalkeno-1,3-selenaphospholes (**59**) (Equation (5)) and photolysis of (**55**) in the presence of Bu^tC≡P gave (**60**) <91SL356>. Gas-phase thermolysis of (**58**; *n* = 3, 4, 6) gives labile ring-contracted selenoketenes (**61**) <84ZN(B)1536, 85JOC543>. Photolysis (*hν* > 300 nm) of (**58**; *n* = 3) at 12 K in an argon matrix also produces (**61**; *n* = 3) <85JOC543>.



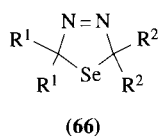


A preparative route to 4,5-benzo-1,3-diselenol-2-selones (**63**) is based on the ready decomposition of benzoselenadiazoles (**62**) in boiling carbon diselenide (Equation (6)) $\langle 83\text{CC}295 \rangle$. Thermal and photochemical decomposition of 1,2,3-benzoselenadiazole gave successively benzoseleniren (**64**) and 6-fulveneselone (**65**) as very reactive products $\langle 80\text{AG(E)}69, 83\text{ZN(B)}611, 84\text{TL}2337 \rangle$ (Scheme 2).

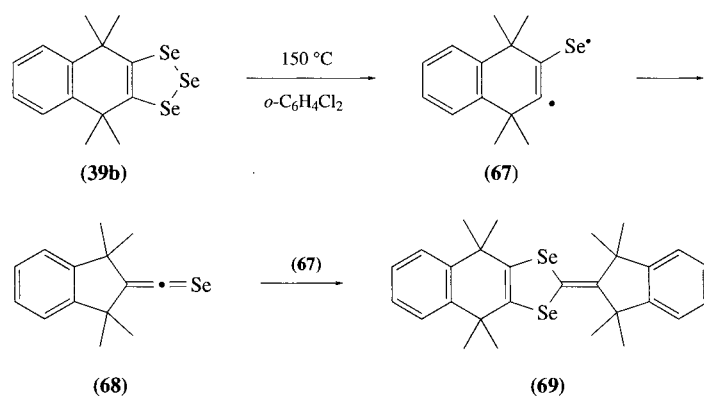


Scheme 2

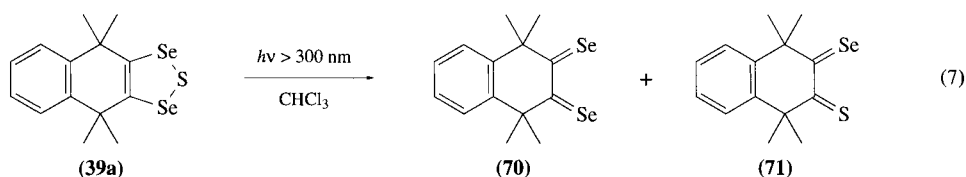
The ready thermal elimination of nitrogen and selenium from 2,5-dihydro-1,3,4-selenadiazoles (**66**) serves as a useful route to sterically crowded alkenes $\langle 84\text{CHEC-I(6)357} \rangle$. Work prior to 1985 has been reviewed $\langle 85\text{T}4843 \rangle$ and subsequent applications have been reported $\langle 85\text{JCS(P1)107} \rangle$.



Thermolysis of the triselenole (**39b**) produces the diselenole (**69**) via intermediates (**67**) and (**68**) (Scheme 3) $\langle 88\text{CL}657 \rangle$. Photolysis of (**39a**) leads to the reactive species (**70**) and (**71**) via a series of reactive intermediates (Equation (7)) $\langle 89\text{TL}2955 \rangle$.



Scheme 3

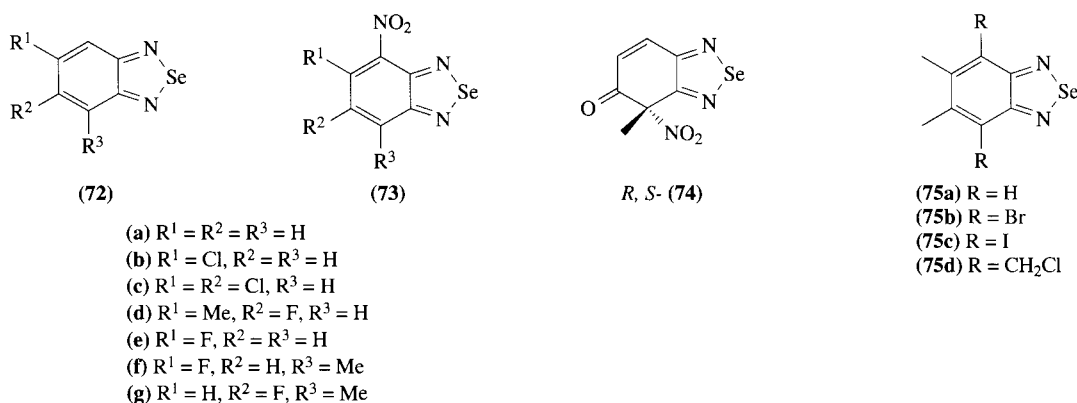


4.21.5.2 Electrophilic Attack at Nitrogen

2,1,3-Benzoselenadiazole (**1**) is alkylated by dialkyl sulfates and dialkyl 2,4-dinitrobenzene sulfonates to give 1-alkyl 2,1,3-benzoselenadiazolium salts <89SC1381>. 2,1,3-Benzoselenadiazole (**1**) reacts with I₂, KI and HCl in CHCl₃ to give the quasi-polymeric structure (**9**) <85ZAAC(523)33> (see Section 4.21.3.1).

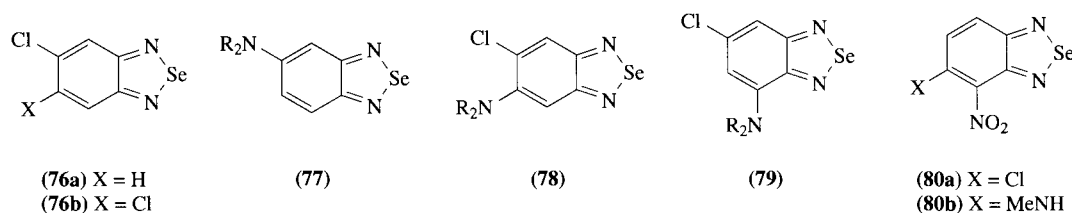
4.21.5.3 Electrophilic Attack at Carbon

2,1,3-Benzoselenadiazoles undergo electrophilic attack at position 4. Nitration of (**72a**)–(**72f**) with HNO₃–H₂SO₄ gave the 4-nitro derivatives (**73a**)–(**73f**) <88JCS(P1)1939, 89ZOR1802, 93JCS(P1)257>. Compounds (**73e**) and (**73f**) were accompanied by phenols resulting from replacement of F by OH, and (**73g**) was accompanied by *R,S*-(**74**) resulting from ipso attack on (**72g**) followed by hydrolysis <93JCS(P1)257>. Halogenation of (**75a**) with Br₂–Ag₂SO₄–H₂SO₄ or I₂–Ag₂SO₄–H₂SO₄ affords the corresponding 4,7-dihalo derivatives (**75b**) and (**75c**), respectively <92JOC6749>, and chloromethylation gives the 4,7-bis(chloromethyl) derivative (**75d**) <86ZOR421>.



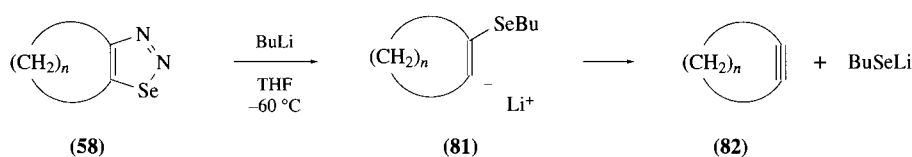
4.21.5.4 Nucleophilic Attack at Carbon

The electron-deficient character of the hetero-ring in 2,1,3-benzoselenadiazole (**1**) promotes nucleophilic substitution in the benzene ring, recalling the nucleophilic substitution of 2,1,3-benzothiadiazoles <84CHEC-I(6)531>. 5-Chloro-2,1,3-benzoselenadiazole (**76a**) failed to react with *O*- and *S*-nucleophiles but underwent substitution with cyclic secondary amines (pyrrolidine, piperidine, morpholine) to give (**77**). 5,6-Dichloro-2,1,3-benzoselenadiazole (**76b**) reacted with pyrrolidine and piperidine to give the monosubstitution products (**78**) and (**79**), the latter product arising by an aryne mechanism. Compound (**76b**) reacted with sodium alkoxides in EtOH–DMF to give 5,6-dialkoxy-2,1,3-benzoselenadiazoles <84JCS(P1)2465>. The chlorine in 5-chloro-4-nitro-2,1,3-benzoselenadiazole (**80a**) is easily substituted by MeNH₂ to give (**80b**) <86ACS(B)404>. Substitution of bromine in various 4-bromo-2,1,3-benzoselenadiazoles by nitrogen nucleophiles has been carried out <90IJC(B)781>. *N*-Methyl-1,3,4-selenadiazolium salts undergo demethylation in boiling pyridine <87UKZ1207>.

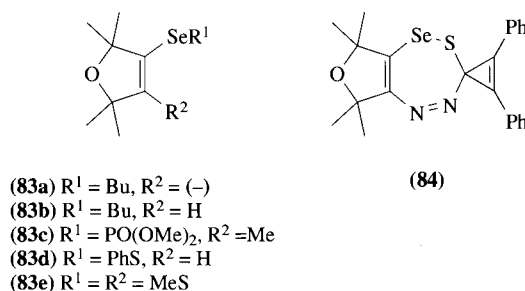


4.21.5.5 Nucleophilic Attack at Selenium and Tellurium

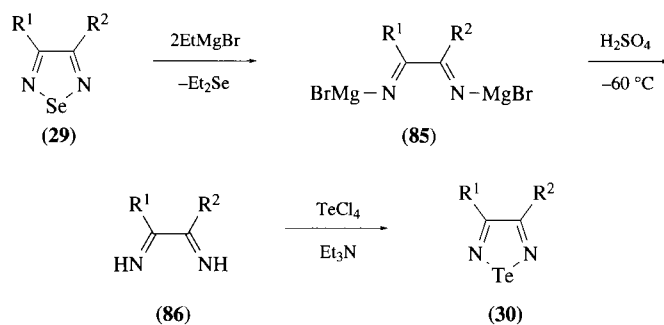
4,5-Cycloalkeno-1,2,3-benzoselenadiazoles (**58**) react with organolithium reagents to form intermediate anions (**81**) (Scheme 4). When the cycloalkeno ring is eight- or higher-membered, spontaneous loss of RSeLi occurs to give cycloalk(en)ynes (**82**). The overall process is an alternative to the thermolysis procedure for the preparation of cycloalkynes (Section 4.21.5.1) <86CB297, 86T1711>. Reaction of (**55**) with butyllithium gave the anion (**83a**) which was quenched with water to give the selenide (**83b**) <87TL4707>. Compound (**55**) underwent nucleophilic attack at Se by P and S nucleophiles. Thus (**55**) reacted with trimethyl phosphite in an Arbusov-type reaction to give (**83c**), with benzenethiol to give (**83d**), and with dimethyl disulfide to give (**83e**) <87TL4707>. Compound (**55**) reacted with diphenylcyclopropenethione with retention of Se and nitrogen to give the thia-selenadiazepine (**84**) <87TL4707>.



Scheme 4

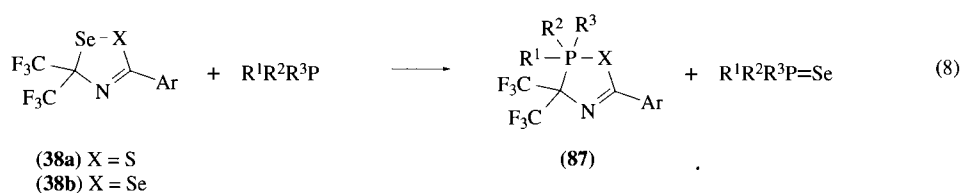


2,1,3-Benzoselenadiazole (**1**) reacts with Grignard reagents RMgX to give symmetrical selenides RSeR <89PJC307>. 1,2,5-Selenadiazoles (**29**) (and 1,2,5-thiadiazoles) are ring-opened by Grignard reagents to give the magnesium salts (**85**) of 1,2-diimines (**86**). Successive treatment of (**85**) with sulfuric acid, tellurium tetrachloride and triethylamine affords 1,2,5-telluradiazoles (**30**) (Scheme 5) <82S681>.



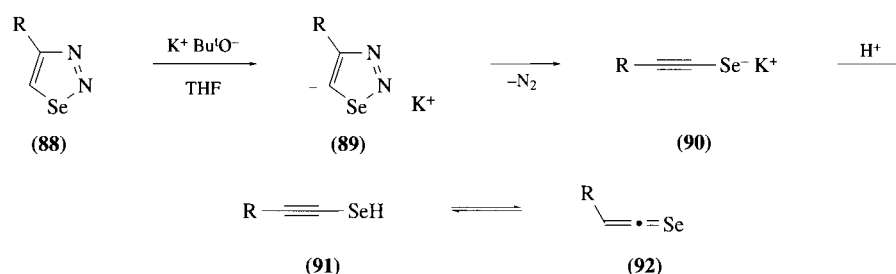
Scheme 5

N-Alkyl-2,1,3-benzoselenadiazolium salts react with sodium hydroxide with elimination of selenium to give *N*-monoalkyl-*o*-phenylenediamines <89SC1381>. The thiaselenazolines (**38a**) and the diselenazolines (**38b**) are attacked by trialkyl phosphites at Se with elimination of selenophosphate and incorporation of phosphorus into the ring (**87**) in place of selenium (Equation (8)) <80CB2699>.

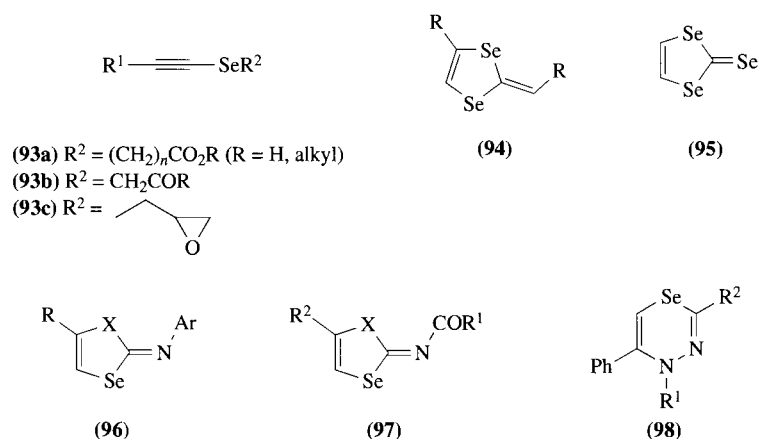


4.21.5.6 Nucleophilic Attack at Hydrogen

1,2,3-Selenadiazole and 4-substituted-1,2,3-selenadiazoles (**88**) are deprotonated at position 5 by strong bases to form carbanions (**89**) which collapse with loss of N_2 to give alkyneselenolate salts (**90**) (Scheme 6). The selenolates (**90**) are versatile synthons whose usefulness has been outlined in CHEC-I <84CHEC-I(6)349> and described in detail elsewhere <B-87MI 421-01>. The selenolates (**90**) undergo Se-alkylation with ω -haloacids and ω -haloesters to give alkyneselenocarboxylic acids and alkyneselenocarboxylic esters (**93a**) <84S660>. Reaction of (**90**) with α -haloketones affords selenoalkyl ketones (**93b**) <86JHC893>. Compound (**90**) reacts with epichlorhydrin to give epoxides (**93c**) <85JHC857>. In the presence of proton sources, the alkyneselenolates (**90**) generate the corresponding selenols (**91**) which equilibrate with the selenoketenes (**92**). [2 + 3]-Cycloaddition of (**92**) to (**90**) affords 1,3-diselenafulvenes (**94**) <84S660, 87TL5635>. Alkyneselenolates (**90**) undergo [2 + 3]-cycloaddition reactions with heterocumulenes. Reaction of (**90**; R = H) with CSe_2 afforded 1,3-diselenol-2-selone (**95**) <86ZC138>. Reaction of (**90**; R = aryl) with aryl isoselenocyanates $ArNCSe$ gives 2-imino-2H-1,3-diselenoles (**96**) <90ZOR179>. Reaction of (**90**; R = aryl) with acyl isothiocyanates and acyl isoselenocyanates affords 1,3-thiaselenol-2-ylidene amides (**97**; X = S) and 1,3-diselenol-2-ylidene amides (**97**; X = Se) <84S512>. Cycloaddition of (**90**; R = Ph) to nitrile imines generated *in situ* is reported to give the 1,3,4-selenadiazines (**98**) <88UKZ538>.



Scheme 6

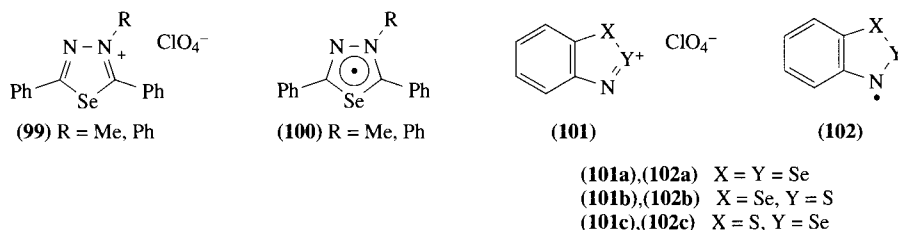


4.21.5.7 Reduction and Electron-Transfer Processes

Selenium is readily removed reductively from 2,1,3-benzoselenadiazoles to give *o*-phenylenediamines. Reducing agents employed include hydriodic acid <87H(26)2069, 88JCS(P1)1939, 92ACS1109, 92JOC6749>, stannous chloride–hydrochloric acid <92JOC6749>, ammonium sulfide or hydrosulfide <86ACS(B)404, 92ACS1109>, and sodium borohydride <92JOC6749>. Application of this process following the introduction of substituents into the benzene ring of 2,1,3-benzoselenadiazoles by electrophilic substitution (see Section 4.21.5.3) provides a method for the preparation of substituted *o*-phenylenediamines that are difficult to obtain by other methods.

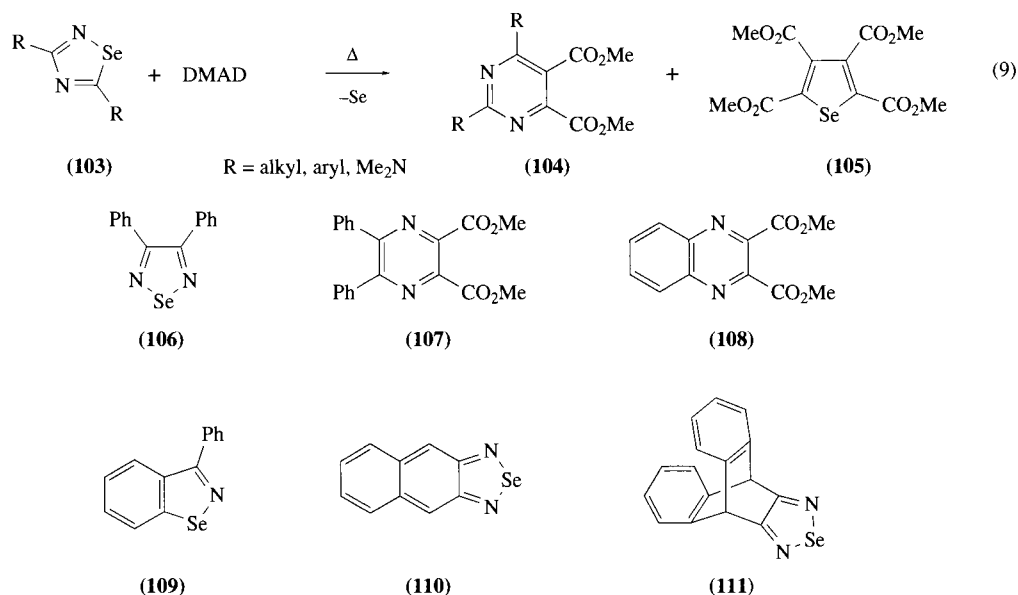
The stable 1,2,3,5-diselenadiazolyl radicals (**21a**)–(**21e**), (**2**) and (**22**) have been prepared by

reduction of the corresponding 1,2,3,5-diselenadiazol-1-ylum chlorides with triphenylantimony $\langle 89JA9276, 91JA582, 91JA3559, 92CC1265, 92IC1802 \rangle$ (see Section 4.21.3.1). The radical **(49)** has been prepared at -50°C by reduction of the salt **(18)** with Zn dust $\langle 92ZN(B)675 \rangle$ (see Section 4.21.3.9). The 1,3,4-selenadiazolium salts **(99)** take up one electron reversibly to form the 7π -electron 1,3,4-selenadiazolyl radicals **(100)** which dimerise, or multi-electron uptake occurs with eventual ring-opening, depending on the solvent system $\langle 84ZOB915, 86ZOB863 \rangle$. The salts **(101a)**–**(101c)** undergo polarographic reduction to form the corresponding radicals **(102a)**–**(102c)** $\langle 85KGS219 \rangle$.



4.21.5.8 Cyclic Transition-State Reactions

1,2,4- and 1,2,5-Selenadiazoles serve as heterodienes in the Diels–Alder reaction. 3,5-Di-substituted-1,2,4-selenadiazoles **(103)** reacted with DMAD with extrusion of selenium to give pyrimidine-5,6-dicarboxylates **(104)** together with methyl selenophenetetracarboxylate **(105)** (Equation (9)). 3-4-Diphenyl-1,2,5-selenadiazole **(106)** reacted with DMAD to give methyl 2,3-diphenylpyrazine-5,6-dicarboxylate **(107)** $\langle 91CL2043 \rangle$. 2,1,3-Benzoselenadiazole **(1)** reacted with DMAD to give the quinoxaline **(108)** $\langle 84MI 421-01 \rangle$. Benzyne, generated from benzenediazonium-2-carboxylate, reacts with **(106)** to give 3-phenyl-1,2-benzisosenazole **(109)** $\langle 88JCS(P1)2141 \rangle$ and not 2-phenylbenzoselenazole as previously supposed $\langle 82CC299 \rangle$. In contrast, naphtho[2,3-*c*]-1,2,5-selenadiazole **(110)** adds benzyne to the central ring to give **(111)** as the primary product which undergoes further reactions $\langle 83T835 \rangle$.



4.21.6 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The hetero-ring in 2,1,3-benzoselenadiazoles activates methyl groups at positions 4 and 5 towards oxidation by selenium dioxide. The corresponding aldehydes are formed $\langle 87HCA997 \rangle$. 4- and 5-Methyl-2,1,3-benzoselenadiazoles are converted into the corresponding bromomethyl derivatives with *N*-bromosuccinimide $\langle 84IJC(B)180, 85MI 421-01, 87CB1593 \rangle$.

4.21.7 SYNTHESSES

4.21.7.1 Introduction

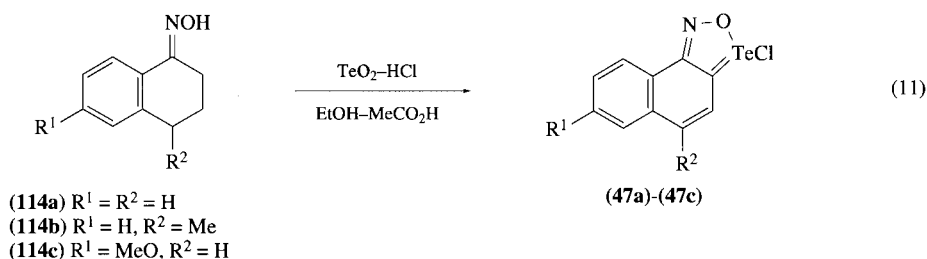
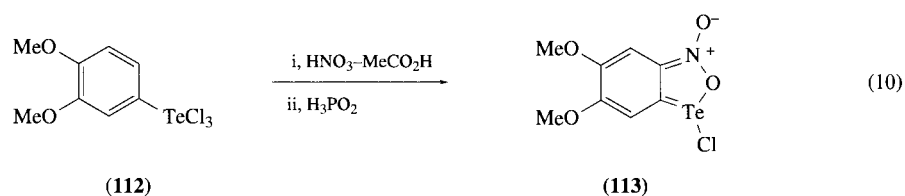
Syntheses of compounds belonging to more than 20 systems covered by this chapter have been published. The majority have been constructed from [4 + 1] or [3 + 2] atom combinations. Very few have been obtained by ring transformations. Several systems have been described for the first time. A large number of publications are concerned with only a few of these systems. These are the 1,2,3-selenadiazoles, whose interest arises from their ready conversion into selenium heterocycles, reactive intermediates, and nitrogen- and selenium-free products, and the 1,2,5-selenadiazoles and 1,2,3,5-diselenadiazole systems whose interest stems from their use in the preparation of potentially useful conducting materials.

4.21.7.2 1,2,3-Benzoxaselenazoles

2-Chloro-4,6-di-*t*-butyl-1,2,3-benzoxaselenazole (**3a**) is formed by reaction of 2,4,6-tri-*t*-butylaniline with seleninyl chloride in boiling toluene. The 1,2,3-benzoxaselenazole system is a new one. The structure of (**3a**) has been established (see Section 4.21.3.1) <85JCS(D)565>.

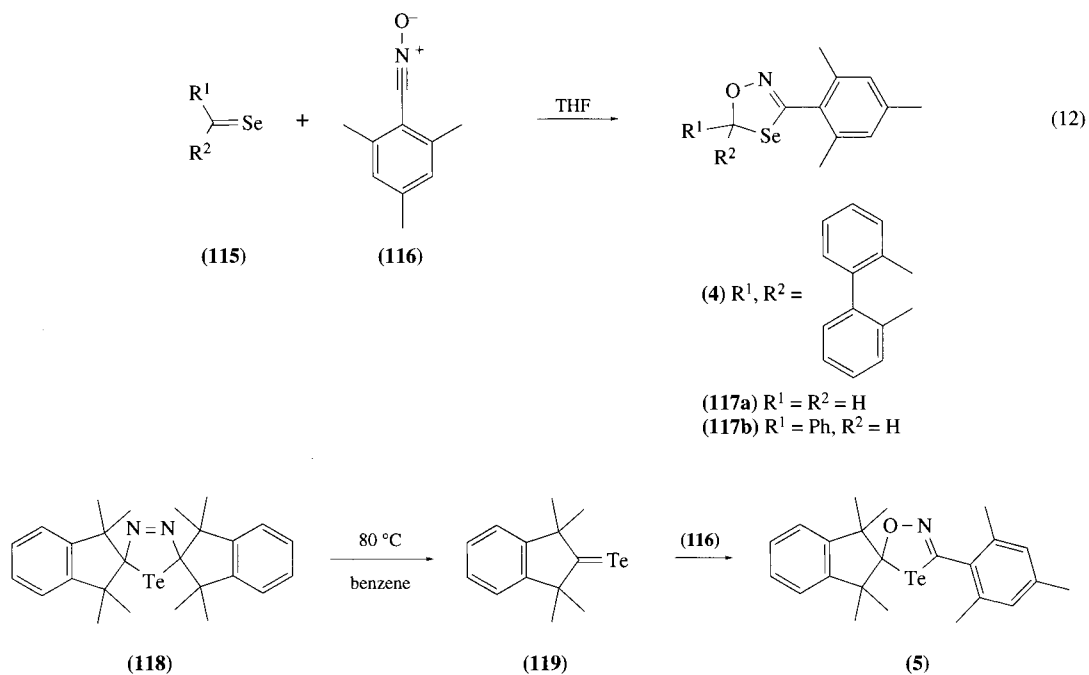
4.21.7.3 1,2,5-Oxatellurazoles

Six derivatives of this system have been reported. Compound (**113**) was obtained by successive nitration of 3,4-dimethoxyphenyl tellurium trichloride (**112**) and partial reduction of the resulting 6-nitro derivative of (**112**) (Equation (10)). Compounds (**47a**)–(**47c**) were obtained by reaction of the oximes (**114a**)–(**114c**) with tellurium dioxide (Equation (11)) <86USP4607000, 87USP4661438>.



4.21.7.4 1,4,2-Oxaselenazoles and 1,4,2-Oxatellurazoles

Selenoaldehydes and selenoketones (**115**) react regiospecifically in [2 + 3]-cycloaddition reactions with 2,4,6-trimethylbenzonitrile-*N*-oxide (**116**) to give the 1,4,2-oxaselenazolines (**4**), (**117a**), and (**117b**) (Equation (12)) <87TL5121, 88JA8671>. The telluroketone (**119**), prepared by thermolysis of the 1,3,4-telluradiazoline (**118**), reacted with (**116**) to give the 1,4,2-oxatellurazoline (**5**) (Scheme 7) <93JA7019>. 1,4,2-Oxaselenazolines and 1,4,2-oxatellurazolines are new heterocyclic systems. The structures of (**4**) and (**5**) have been established by x-ray crystallography (see Section 4.21.3.1).

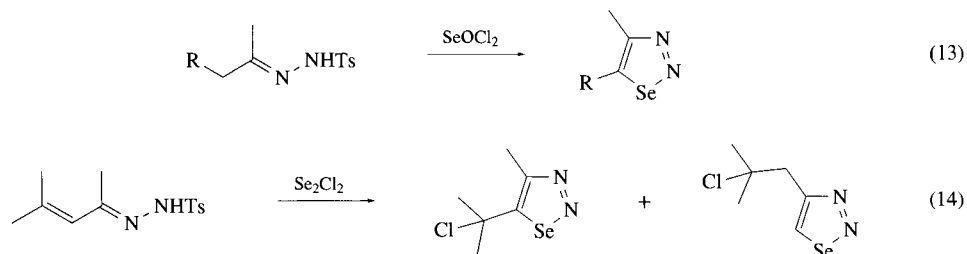


Scheme 7

4.21.7.5 1,2,3-Selenadiazoles

The Lalezari synthesis of 1,2,3-selenadiazoles, which involves the oxidation of semicarbazones by selenium dioxide, is the most general and useful synthesis of 1,2,3-selenadiazoles, and has been applied extensively. The scope and mechanism are summarised in CHEC-I <84CHEC-I(6)352> and also in another review <79AHC(24)109>. Many 1,2,3-selenadiazoles have been prepared as intermediates for the ultimate preparation of other organic compounds (see Sections 4.21.5.1 and 4.21.5.5). Other 1,2,3-selenadiazoles have been prepared for biological activity evaluation <85IJC(B)618, 86MI 421-02, 86MI 421-03, 86MI 421-04, 87MI 421-02, 87MI 421-03, 88MI 421-01, 90ACH433, 90JIC757, 90MI 421-01, 90MI 421-02, 90MI 421-03, 90PHA791, 91MI 421-01, 92IJC(B)396>.

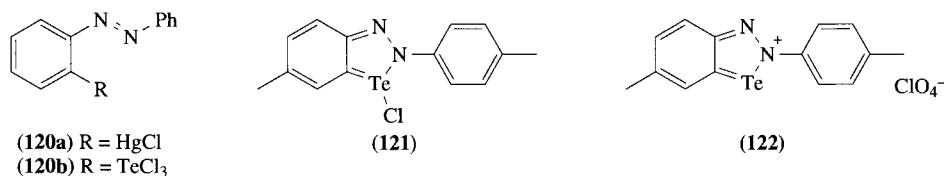
p-Tosylhydrazones of aldehydes RCH_2CHO and ketones $R^1CH_2COR^2$ react with seleninyl chloride or diselenium dichloride to give 1,2,3-selenadiazoles. The tosylhydrazones of ketones RCH_2COMe ring-close regiospecifically at the CH_2 group (Equation (13)), unlike the reactions of the semicarbazones of the ketones RCH_2COMe with selenium dioxide (Lalezari method) which gives mixtures of regioisomers. The tosylhydrazones of $\alpha\beta$ -unsaturated aldehydes and ketones give side-chain chlorinated 1,2,3-selenadiazoles (Equation (14)) <89JCR(S)186>.



4.21.7.6 1 λ^4 ,2,3-Benzotelluradiazoles and 1,2,3-Benzotelluradiazolium Salts

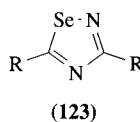
Azobenzene reacts with mercury(II) chloride to give (120a) which undergoes transmetallation with $TeCl_4$ to give (120b). Partial reduction of (120b) with hydrazine affords 1-chloro-1 λ^4 ,2,3-

benzotelluradiazole (**6b**) from which (**7b**) and (**8b**) are obtained by reaction with sodium acetate or sodium thiocyanate, respectively <79JCR(S)145, 85JOM(293)219>. The crystal structures of (**6b**), (**7b**) and (**8b**) have been determined (Section 4.21.3.1). Compound (**121**), prepared in a similar manner to (**6**), reacted with silver perchlorate in acetone to give the first 1,2,3-benzotelluradiazolium salt (**122**) <90JOM(391)179>.



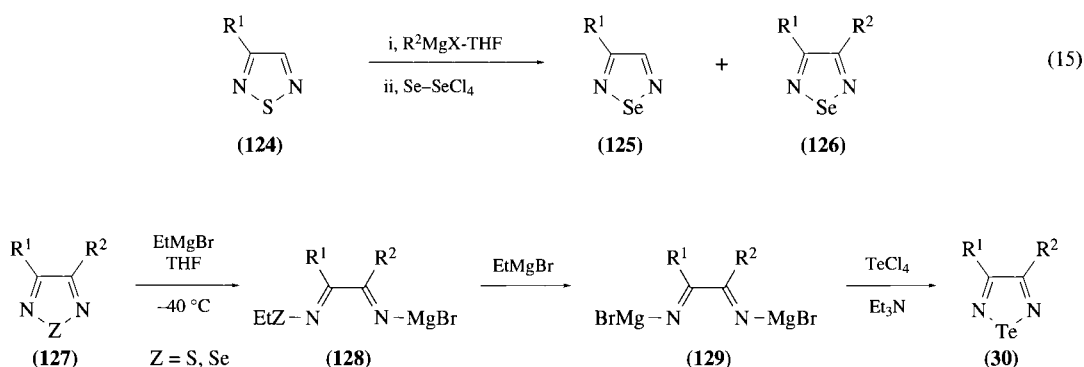
4.21.7.7 1,2,4-Selenadiazoles

Symmetrically substituted 1,2,4-selenadiazoles (**123**) are obtained by oxidation of primary selenoamides with *N*-bromosuccinimide <91BCJ1037>.



4.21.7.8 1,2,5-Selenadiazoles and 1,2,5-Telluradiazoles

Mixtures of mono- (**125**) and disubstituted 1,2,5-selenadiazoles (**126**) are formed by the thiophilic reactions of Grignard reagents with 1,2,5-thiadiazoles (**124**) and treatment of the resulting ring-opened intermediates with a 1 : 1 mixture of selenium and selenium tetrachloride (Equation (15)). In most cases, the disubstituted product (**126**) is obtained in greater yield <79S979, 87H(26)2153>. In a related one-pot procedure 1,2,5-telluradiazoles (**30**) are obtained by ring-opening of 1,2,5-thiadiazoles or 1,2,5-selenadiazoles (**127**) with Grignard reagents with successive formation of (**128**) and (**129**) and ring closure of the resulting intermediate diimine salts (**129**) with tellurium tetrachloride (Scheme 8) <82S681>. Phenanthro[9,10-*c*]-1,2,5-telluradiazole (**12a**) was obtained from (**12b**) by the same method <87ZN(B)84>.

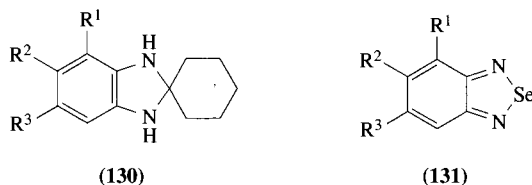


Scheme 8

4.21.7.9 2,1,3-Benzoselenadiazoles

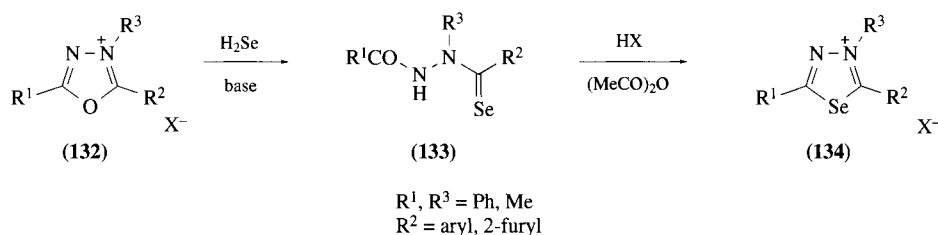
Reaction of *o*-phenylenediamines with Se(IV) reagents continues to be the method of choice for the synthesis of 2,1,3-benzoselenadiazoles. Selenium dioxide is commonly used <84HCA574,

88JCS(P1)1939, 89PJC307, 89ZOR1802, 90JCB(B)781, 92ACS1109, 92JOC6749, 93JCS(P1)257). Seleninyl chloride has also been employed (84ZN(B)1315, 85JCS(D)565, 86CB366, 92PS(67)327) as has selenium tetrachloride (90JFC(50)359, 90KGS1124). Spiro imidazolines (130) are readily transformed by selenium dioxide into 2,1,3-benzoselenadiazoles (131) (88S871, 92JCS(P1)685). Condensed systems consisting of a 1,4-benzoquinone ring fused to one or two 1,2,5-selenadiazole rings have been synthesized by reaction of 2,3-diamino- or 2,3,5,6-tetramino-1,4-benzoquinone with $\text{SeOCl}_2\text{-Et}_3\text{N}$ (82CB2898, 87CL2285, 92JA3034, 92PS(67)327).



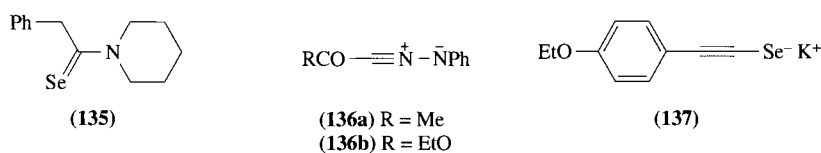
4.21.7.10 1,3,4-Selenadiazoles, 1,3,4-Selenadiazolines, and 1,3,4-Telluradiazolines

Very little work has been reported on the 1,3,4-selenadiazole system. Ring-opening of 1,3,4-oxadiazolium salts (132) with hydrogen selenide gives 1,2-disubstituted hydrazines (133) which are cyclized with perchloric or fluoroboric acid to give 1,3,4-selenadiazolium salts (134) (Scheme 9) (85ZOB2608).

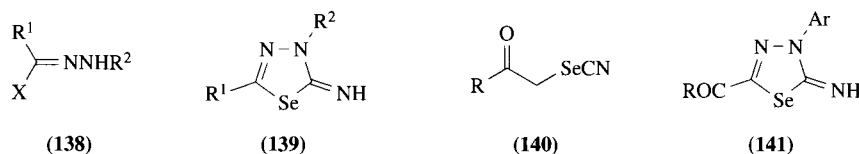


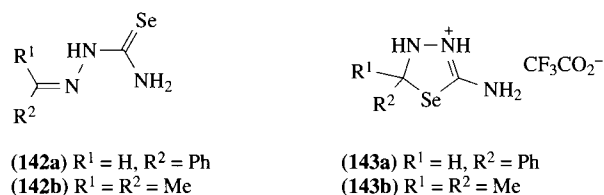
Scheme 9

[2 + 3]-Dipolar cycloaddition of the selenoamide (135) to the nitrileimine (136a) affords the 1,2,4-selenadiazoline (16) (90ZOR1129, 92ZOB1914). The alkyneselenolate (137) undergoes [2 + 3]-cycloaddition to the nitrile imine (136b) to give the 2-arylidene-1,2,4-selenadiazoline (15) (90ZOR2449). Crystal structure determinations of (15) and (16) have been carried out (see Section 4.21.3.1).

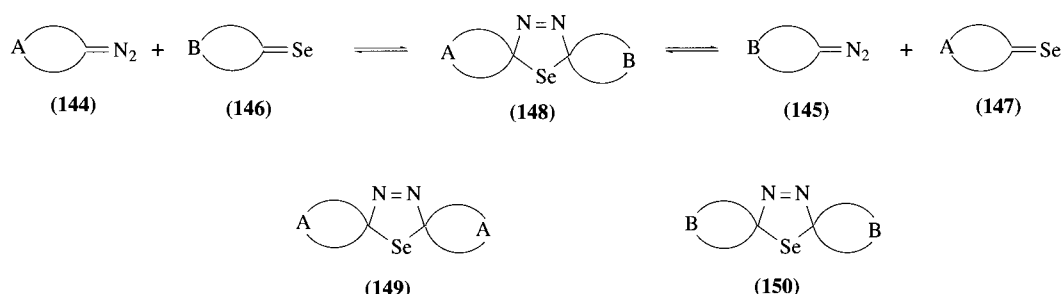


α -Halohydrazone (138) react with potassium selenocyanate to give 3,5-disubstituted-2-imino-1,3,4-selenadiazolines (139) (84CHEC-I(6)357). Further examples have been reported (88SUL93, 93JCR(S)76). Acylmethyl selenocyanates (140) react with arenediazonium salts to give 5-acyl-2-imino-1,3,4-selenadiazolines (141) (82G545, 84CHEC-I(6)357, 87ZN(B)613, 88SUL11, 90PS(53)403). The seleno-semicarbazones (142a) and (142b) are cyclized by trifluoroacetic acid to give the 2-amino-1,3,4-selenadiazolinium trifluoroacetates (143a) and (143b) (91KGS563).

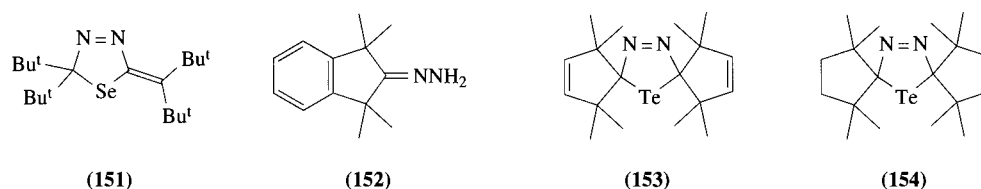




Symmetrical and unsymmetrical crowded 1,3,4-selenadiazolines are obtained by the cycloaddition of diazo compounds to selones (Scheme 10). Excessive crowding destabilizes the selenadiazoline and cycloreversion may occur with an equilibrium arising in which two diazo compounds (**144**) and (**145**) and two selones (**146**) and (**147**) equilibrate with three 1,3,4-selenadiazolines (**148**)–(**150**) $\langle 84\text{CB}277, 85\text{JCS(P1)}107, 85\text{T}4843, 91\text{JOC}3178 \rangle$. Cycloaddition of carbon diselenide to di-*t*-butyldiazomethane gives the 2-alkylidene-1,3,4-selenadiazoline (**151**) $\langle 89\text{ACS}885 \rangle$. Reaction of the hydrazone (**152**) with tellurium dichloride and triethylamine gave the 1,3,4-telluradiazoline (**118**). A similar procedure was used to prepare the 1,3,4-telluradiazolines (**153**) and (**154**). Compounds (**118**), (**153**) and (**154**) are the first derivatives of the 1,3,4-telluradiazole system to be prepared $\langle 93\text{CL}1047, 93\text{JA}7019 \rangle$.

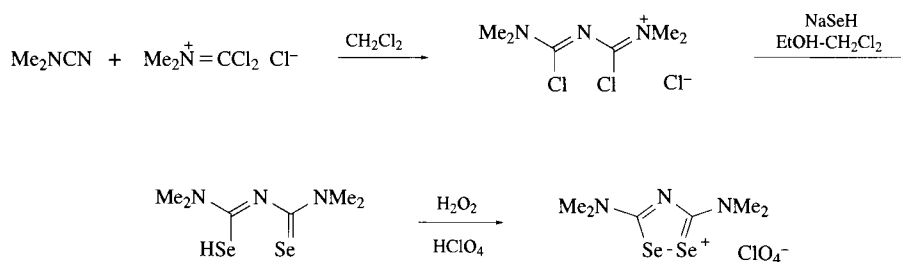


Scheme 10



4.21.7.11 1,2,4-Diselenazol-1-ylum Salts and 1,2,4-Dichalcogenazolines

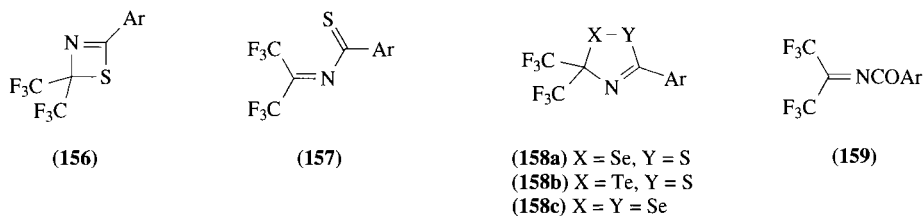
Primary selenoamides react with iodine to give iodides (**50**) $\langle 79\text{EGP}134093, 87\text{NKK}1691 \rangle$. Reaction of dimethylcyanamide with dichloromethylenedimethylammonium chloride and then NaSeH leads to tetramethyldiselenobiuret and thence to the salt (**46**) on oxidation (Scheme 11) $\langle 86\text{JAP}61205269, 87\text{BCJ}2686 \rangle$. Reaction of the Ni(II) complex (**155**) with diphosgene gives the salt (**17**) $\langle 92\text{ZAAC}61789 \rangle$.



Scheme 11

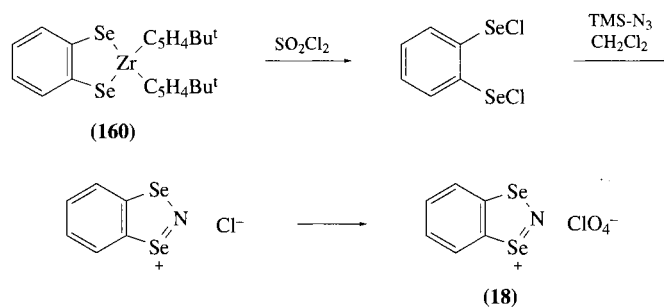
$$\left(\begin{array}{c} \text{Ph} \\ \diagup \quad \diagdown \\ \text{C}=\text{O} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{Se} \\ \diagup \quad \diagdown \\ \text{Et}_2\text{N} \end{array} \right)_2 \text{Ni} \quad (155)$$

Above 80 °C the thiazetes (**156**) are in equilibrium with the thioamide derivatives (**157**). Heating the mixture with P₄Se₁₀ converts (**157**) into the 1,2,4-thiaselenazolines (**158a**) <78S44, 80CB2699>. Prolonged reaction of (**157**) with Sb₂Te₃ affords the 1,2,4-thiatellurazolines (**158b**) <79CC80, 80CB2699>. Reaction of (**159**) with P₄Se₁₀ affords the 1,2,4-diselenazoline (**158c**) <80CB2699>. Selenourea reacts with hexafluorothioacetone dimer at room temperature to give (**14**). The structure of (**14**) has been established by x-ray crystallography (see Section 4.21.3.1) <90CB691>.



4.21.7.12 12⁴,3,2-Benzodiselenazol-1-ylum Salts

λ^4 ,3,2-Benzodiselenazol-1-ylum perchlorate (**18**) and other salts have been prepared from the zirconium heterocycle (**160**) (Scheme 12). The structure of (**18**) has been established by x-ray crystallography (see Section 4.21.3.1) $\langle 92\text{ZN(B)}675 \rangle$.

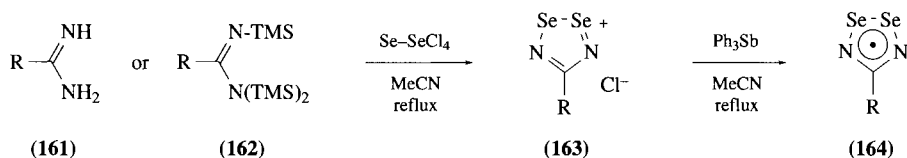


Scheme 12

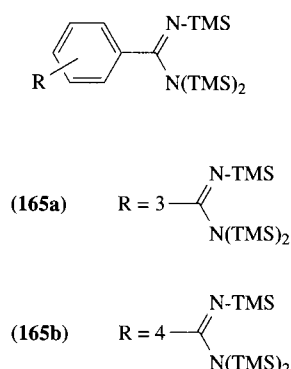
4.21.7.13 1λ⁴,2,3,5-Diselenadiazol-1-ylum Salts and 1,2,3,5-Diselenadiazolyl Radicals

Amidines (**161**) and tris(trimethylsilyl) amidines (**162**) react with a mixture of selenium and selenium tetrachloride to give $1\lambda^4,2,3,5$ -diselenadiazol-1-ylum chlorides (**163**), some of which are converted into other salts for characterization. These salts are reduced by triphenylantimony to give $1,2,3,5$ -diselenadiazolyl radicals (**164**) (Scheme 13). The salts (**23**) and (**43a**)–(**43d**) were thereby prepared and converted into the radicals (**21a**)–(**21e**) $\langle 89\text{JA}9276, 91\text{JA}582, 92\text{CC}1265, 92\text{IC}1802 \rangle$. The

silylated bis-amidines (**165a**) and (**165b**) were likewise employed to prepared the diradicals (**2**) and (**22**), respectively <91JA582, 91JA3559>. The structures of two of these salts and all the radicals have been determined by x-ray crystallography (see Section 4.21.3.1).

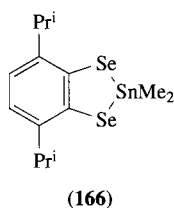


Scheme 13

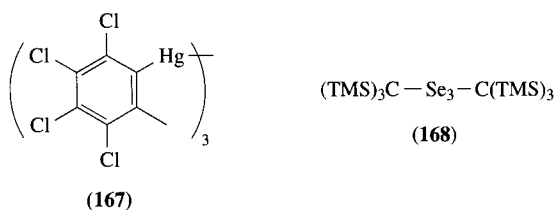


4.21.7.14 1,2,3-Triselenoles and Related Compounds

Reaction of the 1,3,2-benzodiselenastannole (**166**) with selenium tetrachloride gives the triselenole (**40**) which is converted into the triselenolium hexafluorophosphate (**20b**) by reaction with nitrosyl hexafluorophosphate <94CC1593>. Benzo[1,2-*d*][1,2,3]triselenolium chloride (**20c**) was obtained by reaction of 1,2-benzene-bis(selenenyl chloride) with selenium <92AG(E)779>. The structure of the trifluoromethanesulfonate (**20a**) has been established by x-ray crystallography (see Section 4.21.3.1).



The triselenole (**44**) has been prepared by heating the mercurial (**167**) with selenium <88PS(36)135>. Reaction of 2,5-dichloro-3,4-dilithiothiophene with selenium-selenium tetrachloride at -95°C afforded the thieno[3,4-*d*]triselenole (**45**) <89POL2817, 92POL395>. The triselenole (**39b**) and the thia-diselenole (**39a**) have been prepared from the 1,2,3-selenadiazole (**54**) (Scheme 1, Section 4.21.5.1) <88CL657>. Heating the triselenide (**168**) with copper powder gave the 1,2,4-triselenolane (**19**) whose structure has been determined (Section 4.21.3.1) <90CB2325>.



4.21.8 APPLICATIONS

The 1,2,4,5-oxatellurazoles (**47a**)–(**47c**), (**48**), and (**113**) are intermediates in the synthesis of tellurium heterocycles which possess fog-inhibiting properties in films <86USP4607000, 87USP4661438>. The salt (**46**) and related 1,2,4-diselenazol-1-ylum salts are patented for potential use as electroconductive materials and agrochemicals <86JAP61205269>. Several 1,2,3-selenadiazoles are reported to possess antibacterial activity <86MI 421-02, 86MI 421-03, 90JIC757, 90MI 421-02>. The 1,2,5-selenadiazole (**29i**) possesses anticarcinogenic activity against Ehrlich ascite tumour cells <84JAP(K)5920274>. A wide range of substituted 2,1,3-benzoselenadiazoles have been tested for pesticidal activity <88MI 421-02>. 2,1,3-Benzoselenadiazoles (**131**; $R^1 = \text{Br}$, $R^2 = \text{H}$, $R^3 = \text{CH}_2\text{NR}_2$) possess antibacterial activity <84IJC(B)180>. Antifungal properties are shown by many 2,1,3-benzoselenadiazoles <84IJC(B)180, 91KFZ49>. The condensed 1,2,5-selenadiazoles (**25a**) and (**25b**) are electron acceptors which form conducting radical–anion salts with suitable donors <87CL2285, 92JA3034>. Compound (**25b**) is patented as a photoreceptor for electrophotographic use <90JAP(K)0297964>. Compounds (**25a**), (**25b**), and (**27**) form CT complexes with alkyl substituted aromatic hydrocarbons. Selective CT formation enables particular isomers such as *p*-xylene and 2,6-dimethylnaphthalene to be separated from the corresponding isomer mixtures <89EUP346842, 92JA3034>. Crystals of the diradicals (**2**), which exists in two phases, and (**22**) are semiconductors <91JA582, 91JA3559, 92JA1729>.

4.22

Three or Four Heteroatoms including at least One Phosphorus

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4.22.1 INTRODUCTION

4.22.1.1 History

A great variety of heterophospholes have been developed during the last quarter of a century, from 1970 to 1995. They are covered in chapters 3.15 and 3.16, and in their majority in this chapter. The first representatives of heterophospholes, i.e. 2*H*-1,2,3-diazaphospholes were found in 1967 <67CHE601> and remained the only examples for seven more years. They are also the only heterophospholes in this chapter which are mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CH(1)523>.

4.22.1.2 Scope

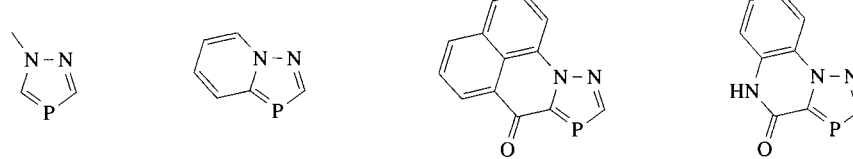
Heterophospholes are five-membered, 6 π -systems. To allow full cyclic conjugation their phosphorus ring member must be two-coordinate and contribute one π -electron (in this respect heterophospholes are different from phospholes, see Chapter 2.15). If the ring is neutral, it must therefore, in addition to the phosphorus, contain one member such as NR, O, or S contributing two π -electrons. Furthermore, the ring may contain one or more two-coordinate nitrogen atoms. Accordingly two aza-, oxa-, thiaphospholes, six diaza- oxaza-, thiaza- and six triaza-, oxadiazza-, thiadiazaphospholes, and two tetraza-, oxatriaza-, thiatriazaphospholes can be anticipated, in all 48 ring systems <B-89MI 422-01, B-90MI 422-01, 90PS(49/50)349>. The 1,2- and 1,3-azaphospholes, the 1,2- and 1,3-oxaphospholes, and the 1,2- and 1,3-thiaphospholes are covered in chapters 3.15 and 3.16. The remaining 42 systems are the subject of this chapter. Of them, 16 neutral representatives ((A–K) and (M–Q) in Figure 1) are known. Two more exist only as cations (L) and (R). The ring of a third cation, the tetrazaphospholium ion (S) consists of heteroatoms only and is thus beyond the scope of CHEC-II but should be mentioned in this context nevertheless.

In addition, five heterodiphospholes (T–X) are known and are also dealt with in this chapter. Within the scope of this chapter are five-membered rings with three and four phosphorus atoms but no other heteroatoms. In these systems, full cyclic conjugation can only be attained if all phosphorus atoms are two-coordinate. The ring consequently must be negatively charged as in the 1,2,4- and 1,2,3-triphospholides (Y, Z) and in the tetraphospholides (Æ). The pentaphospholide (Ø) is again beyond the definition but must not be excluded here.

Known benzo derivatives can only be conceived for 1,2,3- and 1,3,2-diheterophospholes (G, H) and (I–L), for 1,2,3- and 1,2,5-heterodiphospholes (U) and (W), as well as for 1,2,3-triphospholides (Z) (Figure 1). In every other case of anellation a nitrogen atom must occupy a ring junction position and becomes thus also a member of the anellated ring. Strictly speaking, these systems belong to Volume 8, but because they are so closely related to the monocyclic heterophospholes, they are covered in this chapter, too. Also included are bicyclic heterophospholes with heteroatoms in other than ring junction positions of the anellated ring.

In Figure 1, the known systems are ordered according to: (1) the number of phosphorus atoms in the five-membered ring; (2) the number of other heteroatoms; (3) the number of heteroatoms adjacent to phosphorus; (4) the number of heteroatoms adjacent to each other; (5) the nature of the

1,2,4-diazaphospholes (A)



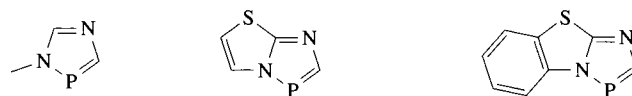
1,2,4-oxazaphospholes (B)



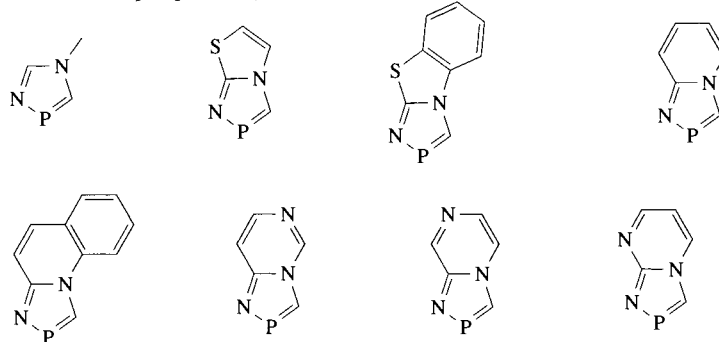
1,2,4-thiazaphospholes (C)



1H-1,4,2-diazaphospholes (D)



4H-1,4,2-diazaphospholes (E)



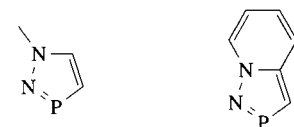
1,3,4-thiazaphospholes (F)



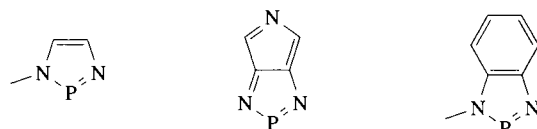
2H-1,2,3-diazaphospholes (G)



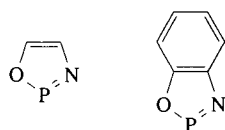
1H-1,2,3-diazaphospholes (H)



1,3,2-diazaphospholes (I)



1,3,2-oxazaphospholes (J)



1,3,2-thiazaphospholes (K)

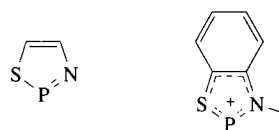
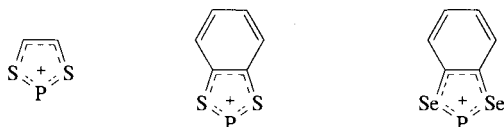


Figure 1 Known heterophospholes with two or more heteroatoms other than phosphorus and polyphospholides with three or more phosphorus atoms, as well as their annelated and oxo derivatives.

1,3,2-dithia/selenaphospholes (L)



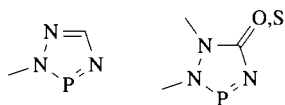
3H-1,2,3,4-triazaphospholes (M)



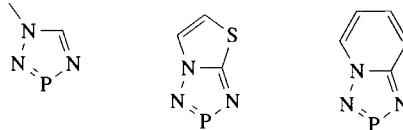
2H-1,2,3,4-triazaphospholes (N)



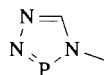
2H-1,2,4,3-triazaphospholes (O)



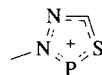
1H-1,2,4,3-triazaphospholes (P)



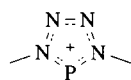
4H-1,2,4,3-triazaphospholes (Q)



3H-1,3,4,2-thiadiazaphospholium (R)



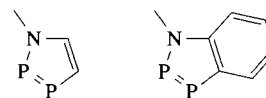
1,4H-tetrazaphospholium (S)



1,2,4-azadiphospholes (T)



1,2,3-azadiphospholes (U)



1,2,4-thiadiphospholes (V)



1,2,5-thiadiphospholes (W)



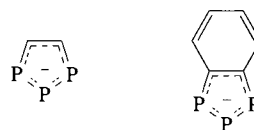
1,2,3,5-diazadiphospholes (X)



1,2,4-triphospholes and triphospholides (Y)



1,2,3-triphospholides (Z)



tetraphospholides (/E)

pentaphospholide (Φ)

Figure 1 (continued)

heteroatoms: N, O, S, Se; and (6) whether they are monocyclic, 4,5-anellated, or otherwise anellated. This order is also used to arrange the compounds in the sections of this chapter. While spectra, structure, and bonding can be discussed for them in general, reactivity and synthesis must be treated individually for each group of compounds of a section.

4.22.1.3 Reviews

A 1978 review <78S557> covers heterocycles containing a PNN-linkage and includes 1,2,3-diazaphospholes and 1,2,3,4-triazaphospholes. Azaphospholes and, more general, heterophospholes

have been reviewed in 1989 <B-89MI 422-01> and 1990 <B-90MI 422-01>, and anellated heterophospholes in 1994 <94T7675>. Azaphospholes are also contained in a review on cyclic mono- and diphosphazenes <90UK931>. Synthetic routes to heterophospholes have been surveyed <86PS(28)71> as has the use of α -aminocarbonyl compounds for the synthesis of 1,3,2-oxazaphospholes <92RHA25> and the use of 2-substituted cycloiminium salts for the synthesis of anellated azaphospholes <95S361>. Reviews on phosphalkynes <90CRV191, B-90MI 422-02, B-90MI 422-03> and a more general review on compounds containing phosphorus-carbon multiple bonds <94CRV1413> demonstrate their potential for heterophosphole synthesis. A review on the preparative use of metallophosphalkenes <96AG292> also includes the synthesis of 1,2,3-diazaphospholes. Polyphospholide anions are found in a review on phosphanes <93CRV1623> and in a review of their own <94CCR1, 95MI 422-01>. A list of compounds, complete up to mid 1987 is provided by a compilation of ^{31}P NMR shifts of heterocycles of two-coordinate phosphorus <88PS(36)217> and a comprehensive list of anellated heterophospholes is contained in the review mentioned above <94T7675>. Cycloaddition reactions of heterophospholes have been reviewed among those of other compounds with $\text{P}=\text{C}$ or $\text{P}=\text{N}$ bonds <86PS(26)203>.

A review <94MI 422-01> on 1,3-heterophospholes (Chapter 3.16) compares their reactivity to that of di- and triazaphospholes which are covered in this chapter. In contrast to 1,3-azaphospholes the latter contains two-coordinate nitrogen atoms in the ring. The RC/N exchange lowers the charge density at the phosphorus atom and facilitates the attack by hard nucleophiles.

4.22.2 SPECTRA, STRUCTURE, AND BONDING

4.22.2.1 Theoretical Methods

Quantum chemical calculations on different levels have been reported for 2*H*-1,2,3-diazaphospholes (**G**) <83T1507>, for 4,6-diamino-1,3,5-triaza-2-phosphapentalenes derived from 1,3,2-diazaphospholes (**I**) <86CB3213>, for the tetrazaphospholium ion (**S**) <93CB1513>, for 1*H*-1,2,3-azadiphosphole (**U**) <89NJC309>, and for 1*H*-1,2,3-benzazadiphosphole <93PS(76)45>. Planar and nonplanar structures of 2*H*-1,3,2-diazaphosphole and its 2-boryl derivative as well as of 4*H*-1,2,4-diazaphosphole and its 4-boryl and 3,5-diboryl derivatives are compared by correlated *ab initio* calculations <95JPC586>.

The electronic structure of 1,3-azaphospholes (chapter 3.16), of 1*H*- and 4*H*-1,2,4-diazaphospholes, and of 1*H*-, 2*H*-, 3*H*-, and 4*H*-1,2,3,4-triazaphospholes has been investigated by *ab initio* quantum chemical calculations and HeI ultraviolet photoelectron spectroscopy. According to the 4-31G(*) calculations, the total energy of the tautomers containing three-coordinate phosphorus is significantly higher (by 25–35 kcal mol⁻¹) than the total energy of those containing two-coordinate phosphorus. The aromatic stabilization—as measured by the heats of bond separation reactions—changes in a similar way. The calculated optimized geometries reveal that the rings containing two-coordinate phosphorus can be characterized by bond lengths between those of isolated single and double bonds. In the tautomers containing three-coordinate phosphorus, however, $\text{P}-\text{C}$ and $\text{P}-\text{N}$ bond lengths are much closer to the single-bond value, indicating that conjugation is in force only on the rest of the molecule. In order to assess the conjugative interaction between the $\text{P}=\text{C}$ moiety and the rest of the molecule, ring fragmentation reactions have been investigated. The heats of these reactions indicate that the conjugation of the $\text{P}=\text{C}$ moiety (and thus the aromatic stability) increases with the increasing number of nitrogen atoms in the ring. The photoelectron spectra of the investigated compounds are in accordance with the electronic structure of the compounds containing two-coordinate phosphorus. When the electron is removed from π -orbitals, ionization energies of azaphospholes are similar to those of the corresponding azoles <92JA9080>.

The comparison of π -ionization energies of compounds containing $\text{C}=\text{C}$, $\text{C}=\text{N}$, and $\text{C}=\text{P}$ double bonds reveals a more pronounced similarity between the carbon- and phosphorus-containing species than between the nitrogen- and phosphorus-containing species. Ring fragmentation reaction heats of the corresponding azaphospholes and azoles show a similar behavior. All these facts suggest that, although the strength of the two-coordinate $\text{P}=\text{C}$ bond is known to be significantly smaller than that of the $\text{C}=\text{C}$ or $\text{C}=\text{N}$ bond, in conjugative interactions two coordinate $\text{P}=\text{C}$ is more comparable to $\text{C}=\text{C}$ than to $\text{N}=\text{C}$ π -systems. By using perturbation arguments, earlier observations about the similarities in chemical reactions of the two coordinate $\text{P}=\text{C}$ and $\text{C}=\text{C}$ bonds become understandable <93JPC4011>.

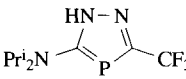
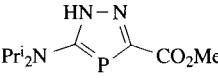
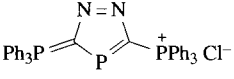
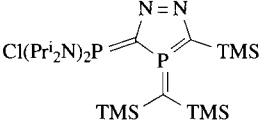
Phosphorus analogues of the cyclopentadienide anion, i.e. phospholide (chapter 2.15), 1,2-diphospholide (chapter 3.15), 1,3-diphospholide (chapter 3.16), 1,2,4-triphospholide (**Y**), 1,2,3-triphospholide (**Z**), tetraphospholide (**Æ**), and pentaphospholide (**Ø**) ions were examined by complete

structural optimization using the all-valence electron SCF-MO method SINDO1. Optimized geometries obtained with inclusion of d-orbitals on phosphorus show that the ring bond lengths CC, CP, and PP are in the ranges 137–142 pm, 174–177 pm, and 217–220 pm, respectively. These values are between those of the bond lengths of the respective single and double bonds and are in close agreement with the observed values of the ligated rings in complexes. The bond-order definition of aromaticity, based on the ring-current concept, reveals that the phosphorus analogues of cyclopentadienide anion in the above order retain 91, 86, 88, 96, 86, 95, and 100% aromaticity relative to the carbocyclic system $C_5H_5^-$. A rather dramatic result is that the pentaphosphorus analogue P_5^- is as aromatic as the carbocyclic anion $\langle 92JOC3694 \rangle$. Its structure and bonding have been discussed earlier $\langle 84CJC341, 89AG500, 89CB2121, 90PAC423 \rangle$.

4.22.2.2 X-ray and Electron Diffraction

The known molecular structures of the heterophospholes of this chapter are compiled in Tables 1–6. Except for two of them they were determined by x-ray diffraction. They have been reviewed $\langle 88MI\ 422-01, B-89MI\ 422-01, B-90MI\ 422-01 \rangle$.

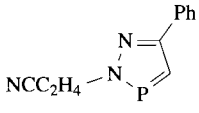
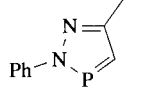
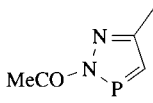
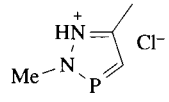
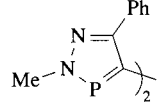
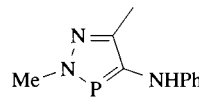
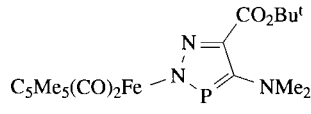
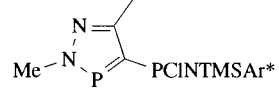
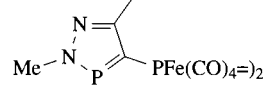
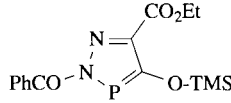
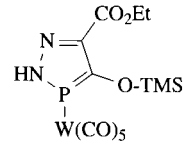
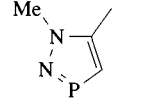
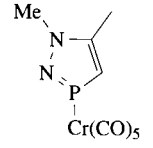
Table 1 Bond lengths (pm) in 1,2,4-diazaphosphole rings (A) and bond angle(s) at the phosphorus atom derived from x-ray analyses.

	Bonds					Angle(s)	Ref.
	1,2 NN	2,3 CN	3,4 PC	4,5 PC	1,5 CN		
	134.0	132.0	173.4	173.4	132.0	87.5°	B-89MI 422-01
	136.6	135.8	177.3	175.6	131.8	85.7°	92CB411
	135.2	136.2	177.1	174.2	133.8	86.2°	92CB411
	137.6	146.7	167.3	162.9	146.5	90.7°	96TH 422-01
	134.8	134.9	173.3	171.1	135.5	89.9° 135.7° 133.7°	93BSF757

All structures show a planar ring with averaged bond distances in accord with a delocalized π -bond system. The angle at the two-coordinate phosphorus atom in azaphospholes clearly increases with the number (n) of two-coordinate nitrogen atoms adjacent to phosphorus, $n = 0$: 86–92°, $n = 1$: 92–93°, $n = 2$: 97–100°. A comparatively large angle at a phosphorus atom is found in heterophospholes with a sulfur or with a second phosphorus ring member (Tables 3, 5, 6). The largest angle (103°) is found in a triphosphole. PC bond lengths in heterophospholes generally range from 170 pm to 175 pm as compared to mean values of 167 pm and 185 pm for the localized double and single PC bond in phosphalkenes $\langle 86ZOB2433, 88MI\ 422-01, B-90MI\ 422-04 \rangle$. PN bonds in azaphospholes are 162 pm to 170 pm long as compared to mean values of 156 pm and 167 pm for the more or less localized double and single bonds in amino(imino)phosphines $\langle 88MI\ 422-01, 88ZOB2045, B-90MI\ 422-05 \rangle$. PP bond lengths in 1,2,3-azadiphospholes are only slightly longer than in diphosphenes (200–204 pm) $\langle 88MI\ 422-01, B-90MI\ 422-06 \rangle$. The PS bond length in the 1,3,2-benzodithiaphospholium cation is the shortest non-terminal phosphorus(III)-sulfur bond reported up to 1995 $\langle 89IC144 \rangle$.

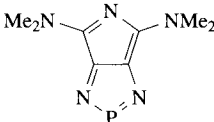
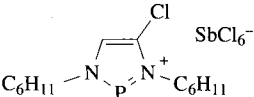
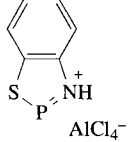
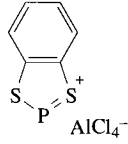
From the thiaza- and diazaphosphole molecular dimensions aromaticity indices were derived $\langle 90T5697 \rangle$.

Table 2 Bond lengths (pm) in 2*H*- and 1*H*-1,2,3-diazaphosphole rings (**G**, **H**) and bond angle(s) at the phosphorus atom derived from x-ray or electron diffraction.

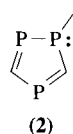
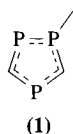
	Bonds					Angle	Ref.
	1,5 CN	1,2 NN	2,3 PN	3,4 PC	4,5 CC		
	134.3	134.4	167.6	170.2	140.7	88.8°	73DOK(211)1101
	132	132	164	175	142	92°	68DOK(183)95
	134	134	168	175	144	89°	71DOK(197)1081
	132.6	134.3	166.1	174.6	141.5	88.2°	78CB1558
	132.5	135.4	168.5	172.6	142.6	89.5°	88IZV150
	132.9	134.7	167.4	168.8	141.6	90.4°	83CB549
	134.6	134.2	170.3	174.6	142.5	91.0°	95OM581
	132.5	135.2	168.9	171.8	141.9	89.2°	93BSF726
	132.0 132.2	133.7 135.1	— —	171.3 171.4	142.3 141.0	88.7° 89.3°	88CC574
	132.2	134.5	171.9	172.0	143.3	86.6°	96TH 422-02
	134.3	134.0	166.0	169.5	141.4	91.7°	96TH 422-02
	135.6	133.0	165.4	172.3	138.1	92.9°	79AG442
	136.2	135.4	163.7	172.8	138.2	95.2°	80JOM(185)53

* Ar = 2,4,6-Bu₃C₆H₂.

Table 3 Bond lengths (pm) in 1,3,2-diaza-, thiaza-, and -dithiaphosphole rings (**I**, **K**, **L**) and bond angle(s) at the phosphorus atom derived from x-ray analyses.

	Bonds					Angle	Ref.
	4,5 CC	1,5 CN/S	1,2 PN/S	2,3 PN/S	3,4 CN/S		
	137.6	134.5	166.5	166.1	134.9	99.8°	86CB3213
	135.1	137.0	165.6	167.3	136.3	90.0°	90DOK(312)623
	137.8	137.8	163.8	164.8	138.0	91.3°	89AX(C)1485
	139.4	173.2	203.4	164.3	138.7	93.7°	90IC4938
	138.3	171.1	201.5	201.6	172.8	97.6°	89IC144

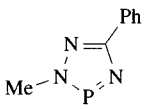
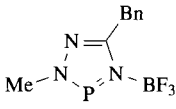
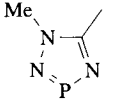
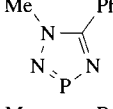
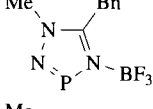
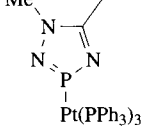
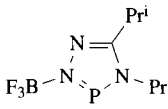
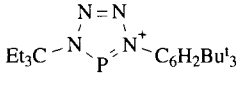
In *P*-coordinated azaphosphole complexes (Tables 2, 4) the metal atom lies strictly in the plane of the ring and the ring structure is not significantly different from that of the free azaphosphole. Of the 3,5-di-*i*-butyl-1,2,4-triphospholide ion both η^1 and η^5 complexes are known. In most of the η^1 complexes (Table 6) the metal atom is coplanar with the ring and the sum of bond angles around the ligating phosphorus atom P-1 is 360° in accord with bonding mode (1).



In the last complex of Table 6, however, the metal atom deviates from the plane of the ring and the arrangement about P-1 is pyramidal with a sum of angles equal to 348°. This situation is described by bonding mode (2) <89NJC353>. It also applies to the 1-alkyl triphosphole with a sum of angles around P-1 of 342° <95CC1611>.

Some azaphospholes are not stable as monomers but oligomerize. In other cases the complex formation or oxidation of monomeric azaphospholes is accompanied by an oligomerization. For the oligomerization the monomers add to each other by their P=N bonds forming a cyclophosphazane ring. Obviously for steric reasons the eight-membered cyclophosphazane ring and thus the tetramer is generally preferred. X-ray structure investigations have been reported of 1,2,4,3-triazaphosphole tetramers <84CJC43, 92JCS(P2)671> and of their [Cr(CO)₅]₂ complex <81AG420> as well as of their [Fe(CO)₄]₄ complex <84ZOB271>, and of the tetroxide <81MI 422-01, 92RHA25> and of a 1,3,2-oxazaphosphole tetramer. The sulfide of a 1,2,4,3-triazaphosphole was shown to have a trimeric structure was shown by ³¹P NMR spectroscopy <94HAC385>.

Table 4 Bond lengths (pm) in 2*H*-, 1*H*-, and 4*H*-1,3,2-thiazaphosphole rings (**O**, **P**, **Q**) and tetrazaphosphole ring (**S**) and bond angle(s) at the phosphorus atom, derived from x-ray analyses.

	Bonds					Angle	Ref.
	1,5 CN	1,2 NN	2,3 PN	3,4 PN	4,5 CN		
	132.8	135.4	166.8	161.6	135.7	92.4°	80CR(C)271
	131.6 130.4	136.2 136.4	164.4 163.1	164.4 163.2	135.6 136.1	86.6° 89.5°	89JCR(S)250
	134.2	133.2	163.8	163.6	134.1	96.9°	79CB3159
	135.8	135.1	162.7	165.4	132.0	97.0°	78CR(C)319
	134.3	135.7	162.2	170.1	133.5	93.1°	92PS(69)189
	132	139	164	163	131	96.5°	83JOM(256)375
	131.5	136.3	163.7	166.9	137.4	89.5°	92JCS(P2)671
	2,3 NN	1,2 NN	1,5 PN	4,5 PN	3,4 NN		
	126.5	136.8	165.4	165.3	137.4	86.7°	93CB1513

4.22.2.3 NMR Spectra

A compilation of ^{31}P NMR data is available for heterophospholes complete up to mid-1987 <88PS(36)217>, and for anellated heterophospholes up to 1993 <94T7675>. Some characteristic data is also found where more generally the ^{31}P NMR spectra of two-coordinate phosphorus compounds are treated <B-87MI 422-01, B-90MI 422-03, B-90MI 422-07, B-91MI 422-01>.

A low-field chemical shift is characteristic for heterophosphole phosphorus atoms. Its magnitude depends mainly on the ring members adjacent to phosphorus, but is also influenced by other factors. Even when neglecting single extreme values for the more common systems, only broad and overlapping ranges result.

Ring members adjacent to P	$\delta^{31}\text{P}$ Ranges in heterophospholes
C, C	50–180
C, N	160–270
C, P	240–360
C, S	180–310
N, N	220–300
N, P	300–350
N, O	230–270
N, S	≈ 320
S, S	≈ 410

Table 5 Bond lengths (pm) in 1,3,4-thiazaphosphole (**C**) and in 1,2,4- and 1,2,3-azadiphosphole (**I**, **U**) rings and bond angles at the two-coordinate phosphorus atoms, derived from x-ray analyses.

	Bonds					Angles CPN		Ref.
	1,2 CS	2,3 CN	3,4 PN	4,5 PC	1,5 CS	CPN		85AG125
	172.8	132.4	168.4	166.9	172.8	98.0°		
	1,2 PN	2,3 PC	3,4 PC	4,5 PC	1,5 CN	CPN	CPC	91HAC577
	181.4	169.9	177.8	175.4	126.5	99.7°	94.3°	
	174.1	172.1	176.2	172.9	133.5	94.7°	93.9°	
	1,2 PN	2,3 PP	3,4 PC	4,5 CC	1,5 CN	CPN	PPC	89NJC309
	170.6	206.3	174.0	136.4	137.3	95.4°	93.0°	
	168.5	205.5	183.0	130.9	142.0	95.8°	94.0°	88TL5867

Table 6 Bond lengths (pm) in 1,2,4-triphosphole rings (**Y**) and endocyclic angles at the phosphorus atoms, derived from x-ray analyses.

	Bonds					Angles			Ref.
	1,2 PP	2,3 PC	3,4 PC	4,5 PC	1,5 PC	P-1	P-2	P-4	
	209.8	171.8	176.3	172.0	173.4	105.8°	94.0°	101.8°	95CC1661
	208.6	175.8	173.7	172.1	173.8	107.4°	95.7°	107.8°	95CC1661
	209.0	172.3	174.3	174.2	171.2	104.7°	96.6°	102.8°	93JOM(462)319
	206.8	174.5	172.6	174.0	171.1	106.7°	95.4°	103.6°	88CC1615, 89NJC353
	201.0	173	181	169	176	108°	97°	104°	88CC1615
	209.8	172	175	172	172	104.5°	96.6°	103.4°	89NJC353
	210.9	175.7	174.4	173.9	174.8	99.7°	99.7°	101.6°	B-96MI 422-01
	207.8	175.2	169.0	172.1	171.4	100.2°	99.1	1.02.6°	94CCR(137)1
	207.6	175.6	172.7	174.7	175.3	98.9°	98.7°	97.6°	96ZN(B)1022

Electron-withdrawing substituents in the 4-position of 1,2,3-diazaphospholes cause a downfield ^{31}P shift. *N*-Deprotonation and *N*-protonation or alkylation in different heterophosphole systems give rise to shifts in opposite directions <88PS(36)217>. Correlations of the available data demonstrate that $\delta^{31}\text{P}$ in a heterophosphole is influenced in very much the same way as $\delta^{13}\text{C}$ or $\delta^{15}\text{N}$ in the corresponding position of the heterocycle with CH or nitrogen replacing phosphorus <86ZN(B)553, 88PS(36)217>. This suggests a rather congruent bonding situation in heterophospholes and in the better known non-phosphorus-containing five-membered heterocycles.

For many heterophospholes, $\delta^{13}\text{C}$ values are given and discussed, some $\delta^{14,15}\text{N}$ values are also available <77IZV532, 86ZN(B)553, 87JA627, 87JOM(319)49, 89JCR(S)250, 91MRC1045>.

Characteristic one bond ^{31}P , ^{13}C coupling constants are $^1J_{\text{PC}} = 30\text{--}70$ Hz. They are found to be negative <71DOK(197)1081, 78MI 422-01, 91MRC1045>. The observed coupling constants are larger than in phosphines and they extend to considerably higher values than in phosphinines <76JA5451, 79JMR(34)199>. The two bond coupling constant $^2J_{\text{PC}}$ to C-5 in 1,2,3-diazaphospholes ranges from 0 to -12 Hz <91MRC1045>.

One bond ^{31}P , ^{15}N coupling constants in heterophospholes are generally positive <91MRC1045>. Ranges and individual values are: $^1J_{\text{PN}} = 24$ to 83 Hz for 2*H*-1,2,3-diazaphospholes <77IZV532, 86ZN(B)553, 91MRC1045>, 92 to 97 Hz for 1*H*-1,2,3-diazaphospholes <86ZN(B)553>, 87 Hz for 1,2,3-diazaphospholium ions <91MRC1045>, 87 Hz and 89 Hz for 1,4,2-diazaphospholo[4,5-*a*]pyridines <91MRC1045>, 93 Hz for 1,3,2-oxazaphospholium ions <87JA627>, 79 Hz for 3*H*-1,2,3,4-triazaphospholes <91MRC1045>, and $79\text{--}89$ Hz for 1*H*- and 2*H*-1,2,4,3-triazaphospholes as well as for 4-BF₃ complexes thereof <89JCR(S)250>; $^2J_{\text{PN}} = 2\text{--}7$ Hz for 1,2,4-diazaphospholes <86ZN(B)553, 87JOM(319)49>, $6\text{--}9$ Hz for 1*H*- and 2*H*-1,2,3-diazaphospholes <86ZN(B)553, 91MRC1045>, 0.5 Hz and 2 Hz for 1,4,2-diazaphospholo[4,5-*a*]pyridines <B-90MI 422-01>, 0 Hz and $4\text{--}8$ Hz for 1*H*- and 2*H*-1,2,4,3-triazaphospholes and for 4-BF₃ complexes thereof <89JCR(S)250>.

As in α -unsubstituted phosphinines <66AG907, 83TL2645, B-90MI 422-08> and phosphalkenes with a hydrogen atom *trans* to the phosphorus substituent <84ZOB1520, B-90MI 422-07>, the two bond ^{31}P , ^1H coupling is large, $^2J_{\text{PCH}} = 29\text{--}57$ Hz. For 1,2,3-diazaphospholes it is found to be positive <71DOK(197)1081, 71MI 422-01>. A three bond phosphorus coupling to a carbon bonded ring hydrogen is in the range of $^3J_{\text{PH}} = 4\text{--}9$ Hz.

One bond ^{31}P , ^{31}P coupling in 1,2,3-azadiphospholes, $^1J_{\text{PP}} = 465\text{--}481$ Hz, is somewhat smaller than in diphosphines, $^1J_{\text{PP}} = 525\text{--}670$ Hz <86PS(29)73, B-90MI 422-06>. The $^2J_{\text{PP}}$ is found to be $47\text{--}59$ Hz in 1,2,4-thiadiphospholes <86AG570, 88TL4535> and $23\text{--}25$ Hz in 1,2,3,5-diazadiphospholes <85AG127>.

Proton and in some cases ^{13}C -, ^{15}N -, and ^{31}P -NMR spectroscopy have been used to study proton exchange in *N*-unsubstituted di- and triazaphospholes. The exchange is found to be rapid for 1,2,3-diazaphospholes <77IZV532, 77ZOB576, 84PS(21)335> and 1,2,4-diazaphospholes <86ZN(B)553, 87CB1645, 89JOM(338)329> but slow enough for 1,4,2-diazaphospholes <86PS(28)289> and 1,2,4,3-triazaphospholes <84CC183> to allow the individual tautomers to be observed. The 2*H*-tautomers are favoured in the case of 5-*t*-butyl-1,2,3,4-triazaphosphole <88AG1541> and 5-dimethylamino-1,2,4,3-triazaphosphole <80ZN(B)1222>. The two-coordinate phosphorus atom does not take part in the proton exchange <80ZN(B)1222, 86ZN(B)553>.

Phosphorus-31 solid state NMR of 1,3,2-benzodithiaphospholium and -thiazaphospholium salts has been studied <92IC3386>.

4.22.2.4 Other Spectroscopic Methods

For many heterophospholes UV spectra have been reported <81JA2465, 81ZN(B)1273, 82TL3643, 83JOM(258)257, 86CB3213, 88TL5867, 89NJC309>. The replacement of a pyridinic nitrogen atom in an azole for a phosphorus atom in a heterophosphole is generally accompanied by a bathochromic shift of λ_{max} <68DOK(183)95, 78TL441, 80ZC342, 85PS(25)345, 86TL5699>. As compared to pyrrole, imidazole, and oxazole, 1,3-azaphospholes like thiazoles show an additional $\pi \rightarrow \pi^*$ band <86TL5699>. 2-Aryl-1,3-benzoxaphospholes exhibit a strong blue fluorescence ($\lambda = 416$ nm) in the concentration range $10^{-2}\text{--}10^{-4}$ M <85PS(25)345>. The deep red color of the 4,6-diamino-1,3,5-triaza-2-phosphapentalenes is due to a CT band at 500 nm <86CB3213>. Electronic absorption and magnetic circular dichroism of 1,3,2-benzothiazaphospholium and -dithiaphospholium ions are compatible with a delocalized π -electron system over the heterocyclic moiety <90OM1085>.

Raman <68DOK(183)95, 71DOK(197)1081, 72JPR806> and IR spectra <68DOK(183)95, 71DOK(197)1081, 72JPR806, 84IZV1182, 84S591> of 1,2,3-diazaphospholes, IR spectra of 1,2,4-diazaphospholes <85ZN(B)1077, 86JOM(306)39>, 1,2,4-oxazaphospholes <85ZN(B)1077, 86JOM(306)39, 86S31>, 1,2,3,4-

triazaphospholes <85ZN(B)1077, 86JOM(306)39>, and 1,3,2-benzodithiaphospholium salts <88CC842, 89IC144> as well as mass spectra of various heterophospholes <71IZV2611, 78TL441, 80ZN(B)1222, 81ZN(B)1273, 86TL4415, 87CB1809, 89JOM(338)329> have been reported and discussed.

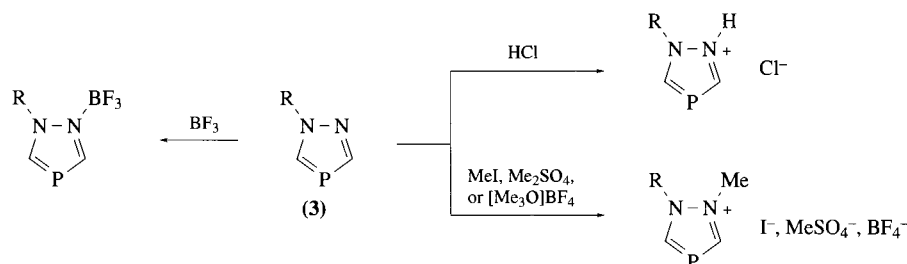
4.22.3 1,2,4-DIAZA-, 1,2,4-OXAZA-, AND 1,2,4-THIAZAPHOSPHOLES (A, B, C)

1,2,4-Diazaphospholes resemble in their chemical behaviour pyrazoles from which they derive formally by a CH/P-exchange in the 4-position. They differ for example, in their hydrolytic stability from 1,2,3-diazaphospholes (next section) which also derive from pyrazoles by this exchange but in the 3-position.

4.22.3.1 Reactivity

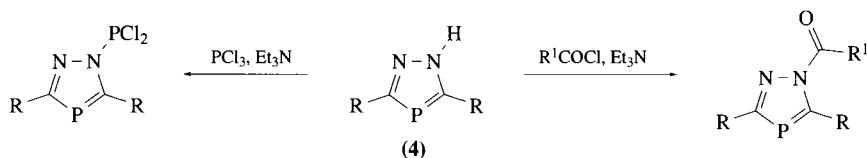
1,2,4-Diazaphospholes are colorless to pale yellow, distillable oils or crystalline solids which may exhibit a characteristic unpleasant penetrating smell <87TH 422-01>.

Monocyclic 1,2,4-diazaphospholes are fairly unreactive; no 1,2-additions to the P=C bond and no 1,1-additions to the phosphorus atom are known. They are stable to hydrolysis even by concentrated hydrochloric acid <84AG901>. They are degraded, however, by 30% aqueous hydrogen peroxide and bromine in dry media to phosphoric acid and PBr₃, respectively <87TH 422-01>. 1,2,4-Diazaphospholo[1,5-*a*]pyridines are rapidly oxidized in air <87TL1511>. 1,2,4-Diazaphospholes (3) (R = H, Me, Ph) are methylated and protonated at the pyridinic nitrogen atom and they add Lewis acids to this nitrogen as well (Scheme 1) <87TH 422-01>.



Scheme 1

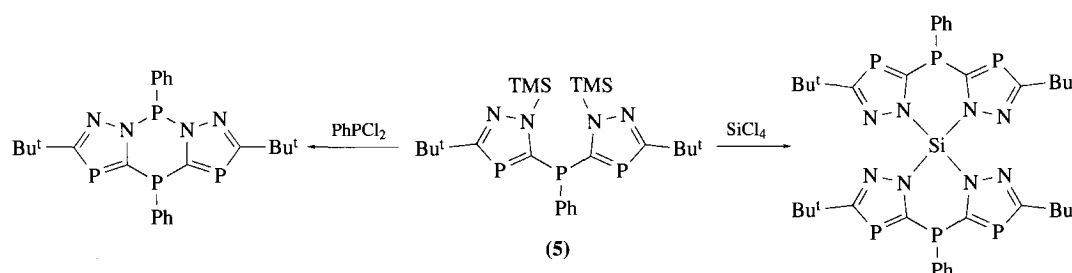
N-Unsubstituted 1,2,4-diazaphospholes (4) undergo *N*-alkylation by reaction with alkyl vinyl ether, sulfur ylides, and diazo compounds <95HAC403>. They react with acyl chlorides in a 2 : 1 molar ratio to give a mixture of the *N*-acylated diazaphosphole and the diazaphosphole hydrochloride. Preparative *N*-acylation is achieved in presence of a tertiary amine. Sulfonyl chlorides and phosphorus trichloride also give *N*-substitution reactions (Scheme 2) <87TH 422-01>.



Scheme 2

Conversely, 1-acyl <87CB1645, 87TH 422-01>, 1-phosphoryl <87CB1645>, and 1-(thio)phosphinyl <87CB1645, 87TH 422-01> groups are lost by methanolysis, hydrolysis, or aminolysis. The *N*-trimethylsilyl groups of a 1,2,4-diazaphosphole can be cleaved by hydrolysis or methanolysis to give the *N*-unsubstituted compound <87CB1645, 88ZN(B)1285, 89NIC359, 89S511>. On the other hand P(SiMe₃)₃ vice versa converts *N*-unsubstituted 1,2,4-diazaphospholes into the *N*-trimethylsilyl derivatives <87TH 422-01>. By substitution of the *N*-trimethylsilyl group other silyl, phosphino, arsino, and stibino

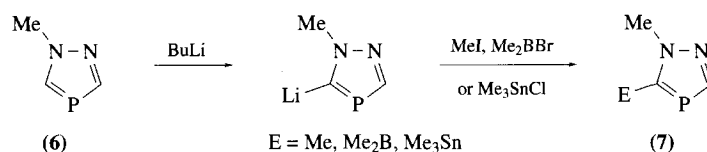
derivatives have been prepared and starting from a bis(1,2,4-diazaphospholyl)phosphine (**5**) polycyclic structures have been built in this way (Scheme 3) <88TL925>.



Scheme 3

1-Dimethylphosphoryl-1,2,4-diazaphospholes eliminate MeOPO_2 on heating to give the 1-methyl derivatives <87CB1645>. *N*-Unsubstituted 1,2,4-diazaphospholes (**4**) are deprotonated by aqueous sodium hydroxide <87TH 422-01> or butyllithium <84AG899, 87CB1809>; reprotonation and methylation <84AG899, 87CB1809, 87TH 422-01> take place at nitrogen.

1-Methyl-1,2,4-diazaphosphole (**6**) is metallated by butyllithium selectively in the 5-position <87JOM(319)49>. From the subsequent reaction with an electrophilic element halide, 5-methyl-, 5-stannyl-, and 5-boryldiazaphospholes (**7**) are obtained <87JOM(319)49, 87TH 422-01>. Catalytic amounts of potassium *t*-butoxide in acetonitrile- d_3 effect an H/D-exchange, fast in the 5-position and slow in the 3-position of 1-phenyl-1,2,4-diazaphosphole <87JOM(319)49>.



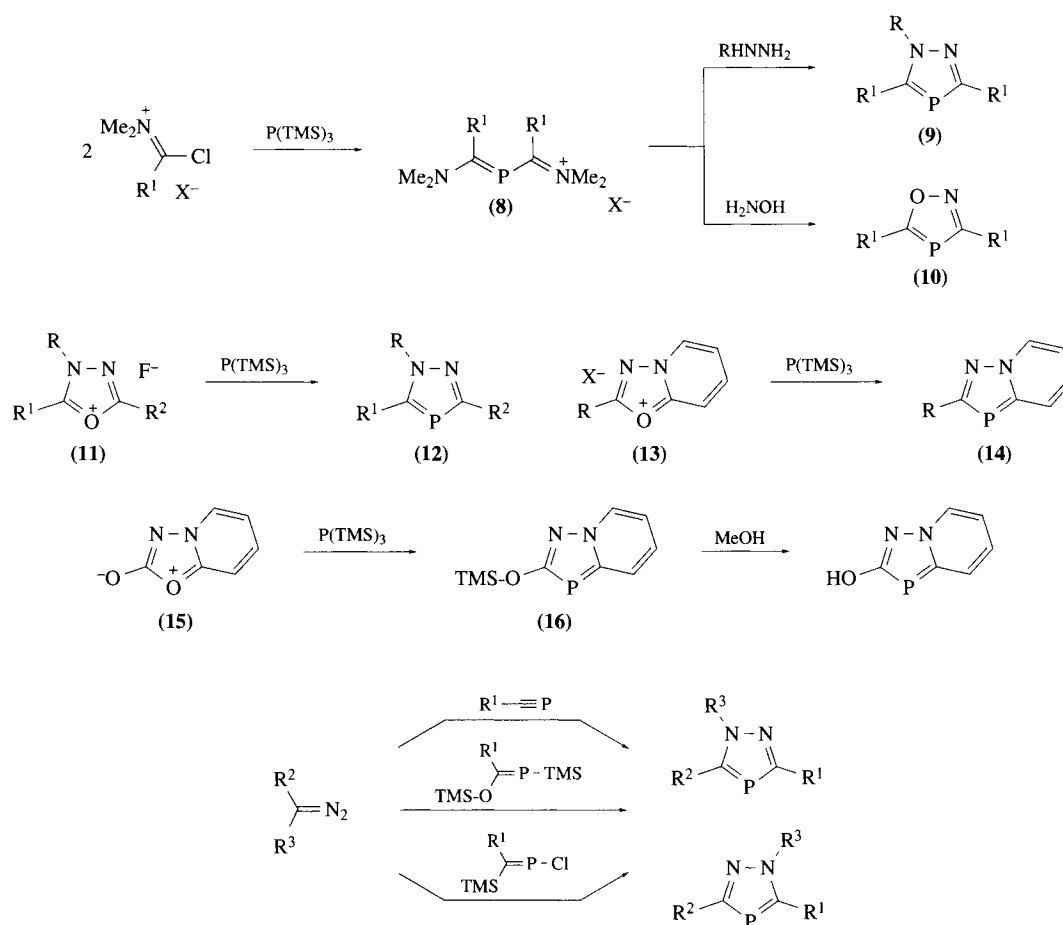
1,2,4-Oxaza- and 1,2,4-thiazaphospholes are colorless to pale yellow, air-stable oils or solids <88AG1541>. 2-Phenyl-5-*t*-butyl-1,2,4-thiazaphosphole is reported to be thermally stable up to 200°C . It does not hydrolyze in aqueous methanol <87S689>.

The [3 + 2] dipolar cycloaddition of nitrile oxides to the $\text{P}=\text{C}$ bond in 1,2,4-oxazaphospholes (**32**) <84CC1634, 87S689, 90PS(49/50)317> as mentioned in 4.22.3.2 is the only reaction described so far.

4.22.3.2 Syntheses

Condensation of 1,3-bis(dimethylamino)-2-phosphaallylic cations (**8**) ($\text{R}^1 = \text{H}$, Bu^t , Ph) with hydrazines and hydroxylamine gives 1,2,4-diazaphospholes (**9**), $\text{R} = \text{H}$, Me , Ph <84AG901>, and 1,2,4-oxazaphospholes (**10**) <86PS(28)71>. The unsubstituted 1,2,4-diazaphosphole is preparatively accessible only by this route so far (Scheme 4). Monocyclic (**12**), $\text{R} = \text{Me}$, Et , Ph ; R^1 , $\text{R}^2 = \text{H}$, Me , Pr^i , Bu^t , Ph <84AG901>, and bicyclic 1,2,4-diazaphospholes (**14**), $\text{R} = \text{Me}$, Pr^i , Bu^t , Ph and (**16**) <87TL1511>, are obtained from oxadiazolium cations (**11**), (**13**), and zwitterions (**15**) by condensation with tris(trimethylsilyl)phosphine <88TL3387>.

An important third route to 1,2,4-diazaphospholes is the [3 + 2] cycloaddition of phosphalkynes and diazoalkanes (Scheme 4). The necessary phosphalkynes are prepared separately ($\text{R}^1 = \text{neopentyl}$, Pr^i , Bu^t , other tertiary alkyl groups) or *in situ* ($\text{R}^1 = \text{Me}$, by flash vacuum pyrolysis of dichloro ethylphosphine) <89PS(46)31>. In most cases diazoalkanes add to phosphalkynes regio-specifically (except $\text{R}^1 = \text{H}$, NPr_2 , see Section 4.22.5.2) <88JOM(338)329, 92CB411> with the formation of a $\text{P}=\text{C}$ bond. The cycloaddition products of primary ($\text{R}^3 = \text{H}$) <84AG898, 84JCS(CC)1634, 86JOM(306)39, 86S31, 87CB1645, 88JOM(338)329>, silyl- ($\text{R}^3 = \text{SiMe}_3$) <88TL925>, phosphino- ($\text{R}^3 = \text{PPh}_2$, P(OMe)_2) <90AG316>, acyl- ($\text{R}^3 = \text{COMe}$, COPh , etc.), and phosphoryl-diazoalkanes ($\text{R}^3 = \text{POPh}_2$, PO(OMe)_2) <84AG898, 87CB1645, 87PS(30)479> rearrange to give 1,2,4-diazaphospholes. The isomer resulting from a 1,5-shift of R^3 is always formed; for $\text{R} = \text{aryl}$ a minor amount of the other isomer is formed in addition (For the reaction products of diazomethanes with $\text{R}^{2,3} = \text{alkyl}$, aryl see <87TL2693, 90T3859>).



Scheme 4

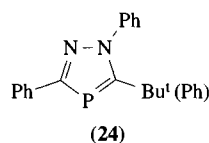
Bis- and tris(trimethylsilyl-diazomethyl)phosphines undergo a double and triple regiospecific cycloaddition with a phosphalkyne <88TL925>.

The stereochemistry of the [3 + 2] cycloaddition reaction between phosphacetylene and diazo-methane has been investigated by *ab initio* calculations. The regioisomeric intermediate leading to the 1,2,4-diazaphosphole was found to be slightly more stable than that leading to the 1,2,3-diazaphosphole <96MI 422-02>.

More 1,2,4-diazaphospholes ($\text{R}^3 = \text{H}$) result from primary diazoalkanes and a phosphalkene of type $\text{R}^1(\text{Me}_3\text{SiO})\text{C}=\text{PSiMe}_3$, $\text{R}^1 = \text{Bu}^t$ <85ZN(B)1077, 87CB1809>, 1-Ad <86S31> or a phosphalkene of type $\text{R}^1(\text{Me}_3\text{Si})\text{C}=\text{P}\text{Cl}$, $\text{R}^1 = \text{Ph}$ <84AG899, 88TL785>, SiMe_3 <84CC1640, 88ZN(B)1285, 88JOM(338)329>, CO_2Et <86TL5611>. In the reaction of lithio or other metallated diazomethanes (17) with *P*-chloro trimethylsilylphosphaethenes (18) the phosphavinyl diazoalkanes (19) can be isolated at -78°C as intermediates. During thawing phosphavinyl diazoalkanes undergo cyclisation to 1,2,4-diazaphospholes (20), including the tris(trimethylsilyl) derivative <88ZN(B)1285, 89NJC359, 89S511>. The intermediate with $\text{R}^2 = \text{Me}_3\text{Si}$ may react with $\text{Bu}^t\text{C}\equiv\text{P}$ in a cycloaddition as described above to produce a phosphalkenyl substituted 1,2,4-diazaphosphole (21) (Scheme 5) <89S511>. Further phosphalkyne equivalents for the reaction with ethyl diazoacetate in the synthesis of 1,2,4-diazaphospholes are 1,1-dichloroalkylphosphines (22), $\text{R}^1 = \text{Me}$, Pr^n , *n*-pentyl, allyl, PhCH_2 , Ph , PhS , Me_3Si , in the presence of pyridine or triethylamine <90PS(49/50)317, 92HAC337> or allyl dichlorophosphines (23), $\text{R}^1 = \text{CMe}=\text{CHCO}_2\text{Me}$, in the presence of the equimolar amount of dabco (Scheme 6) <90TL1147>.

Reactions of diphenylnitrile imine and the phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ <84AG898, 87S689, 88AG1541> or the phosphalkene $\text{Ph}(\text{Me}_3\text{Si})\text{C}=\text{P}\text{Cl}$ <88TL785> also give 1,2,4-diazaphospholes (24). If the nitrile imine has a methyl in place of the one of the phenyl groups, 2% of the isomeric 2*H*-1,2,3-diazaphosphole is formed along with the 1,2,4-diazaphosphole <88AG1541> (see Section 4.22.5.2).

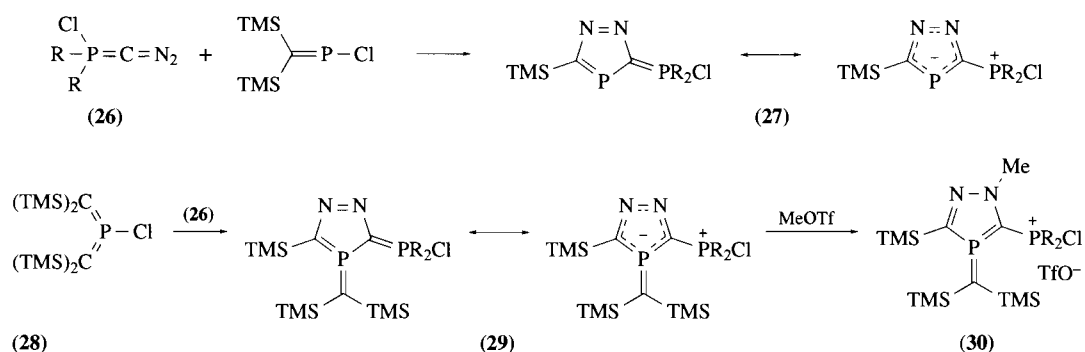
Sydones (25) provide another source for the CNN fragment. With a phosphalkyne <87CB1809> and with two types of phosphalkenes <86TL4415, 87CB1809> they also give 1,2,4-diazaphospholes


$$\begin{array}{c}
 \text{R} \\
 | \\
 \text{N}^+ = \text{N} \\
 | \\
 \text{R}^1 - \text{C} = \text{C} - \text{O}^- \\
 | \\
 \text{O}^- \\
 \text{(25)}
 \end{array}
 \xrightarrow[
 \begin{array}{c}
 \text{R}^1 - \text{C} \equiv \text{P} \quad \text{or} \quad \text{TMS-O} - \text{C}(\text{R}^1) = \text{P} - \text{TMS} \\
 \text{or} \quad \text{TMS} - \text{C}(\text{R}^1) = \text{P} - \text{Cl}
 \end{array}
]{}
 \begin{array}{c}
 \text{R} \\
 | \\
 \text{N} - \text{N} \\
 | \quad | \\
 \text{R}^1 \quad \text{P} \quad \text{Bu}^t, \text{Ph}
 \end{array}
 \quad
 \begin{array}{c}
 \text{Me} \\
 | \\
 \text{N} - \text{N} \\
 | \quad | \\
 \text{P} \quad \text{Bu}^t
 \end{array}$$

Scheme 7

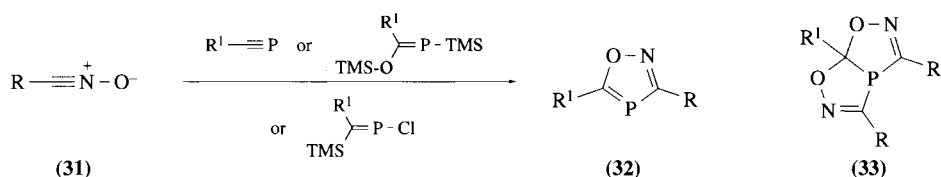
Another cationic 3-phosphonio-1,2,4-diazaphosphole derivative (molecular structure in Table 1) results from the reaction of $(\text{Ph}_3\text{PCl})_2$ with trimethylsilyl azide $\langle 96\text{TH } 422\text{-}01 \rangle$ (see Section 4.22.8.2).

Nitrile oxides (**31**) ($R = Bu^t$, Ph, and other aryl groups) and phosphalkynes ($R^1 = neopentyl$, Pr^i , Bu^t , other tertiary alkyl groups, and by *in situ* preparation also $R^1 = Me$) give 1,2,4-oxazaphospholes (**32**) $\langle 84AG898, 84CC1634, 86JOM(306)39, 86S31, 87S689, 88AG1541, 89PS(46)31 \rangle$ in a regiospecific addition (Scheme 9). In the case of sterically less demanding substituents the oxazaphosphole adds a second



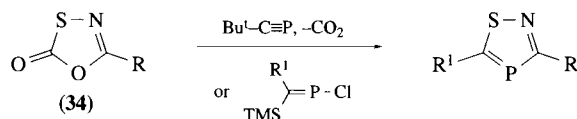
Scheme 8

molecule of nitrile oxide $\langle 87S689, 88JOM(338)329, 89PS(46)31 \rangle$ yielding a symmetrical bicyclic compound (33) (see Section 4.22.3.1). In place of phosphalkynes, certain phosphalkenes may also be used $\langle 84CC1640, 85ZN(B)1077, 88AG1541, 88TL785 \rangle$. Dichloromethylphosphine Cl_2CH-PH_2 may also serve as synthetic equivalent of phosphacetylene. Its reaction with benzonitrile oxide in pyridine leads to a transient 1,2,4-oxazaphosphole which as in the above examples immediately adds a second molecule of nitrile oxide $\langle 89CC988, 90PS(49/50)317 \rangle$.



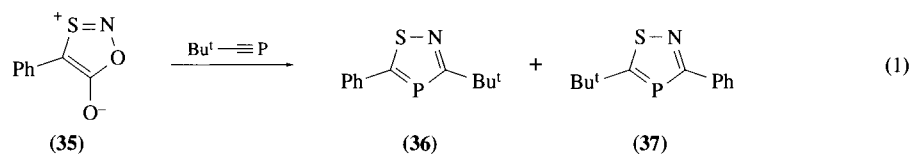
Scheme 9

Phenyl nitrile sulfide, from the thermolysis of an oxathiazolone (34) ($R = Ph$), adds with the same orientation as the nitrile oxides to $Bu^tC\equiv P$ (Scheme 10) $\langle 87S689, 88AG1541 \rangle$. More 1,2,4-thiazaphospholes are produced with phosphalkenes, $R = Ph$, 2- and 4-tolyl, $R^1 = Ph$, $SiMe_3$ $\langle 88TL4535 \rangle$; for side products of this reaction see Chapter 3.15 and Section 4.22.11.2.



Scheme 10

4-Phenyl oxathiazolium-olate (35) and the phosphalkyne $Bu^tC\equiv P$ react to yield two isomeric 1,2,4-thiazaphospholes. Besides the main product (36) with the expected order of substituents, 3% of the product (37) with the reversed order is found $\langle 87CB1809, 88AG1541 \rangle$.



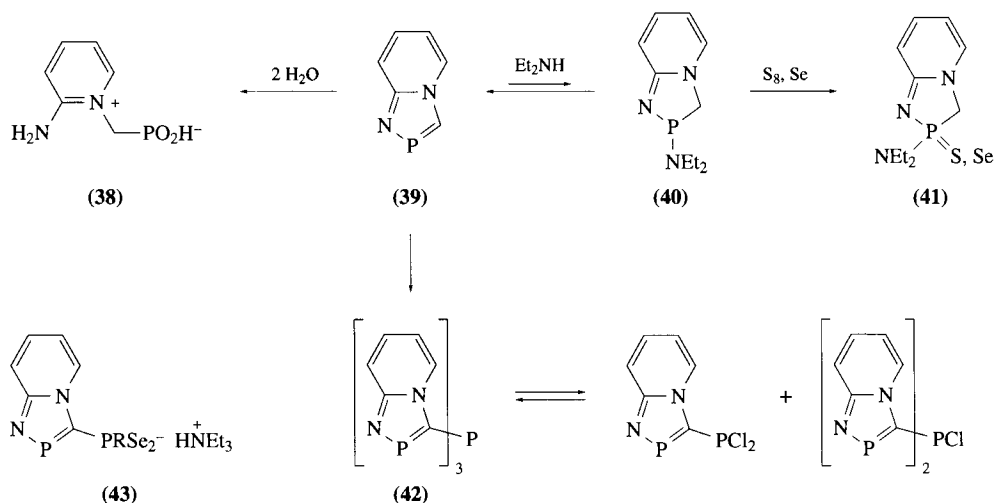
4.22.4 1,4,2-DIAZAPHOSPHOLES (D, E) AND 1,3,4-THIAZAPHOSPHOLES (F)

1,4,2-Diazaphospholes have sometimes been misnumbered as 1,3,4-diazaphospholes.

4.22.4.1 Reactivity

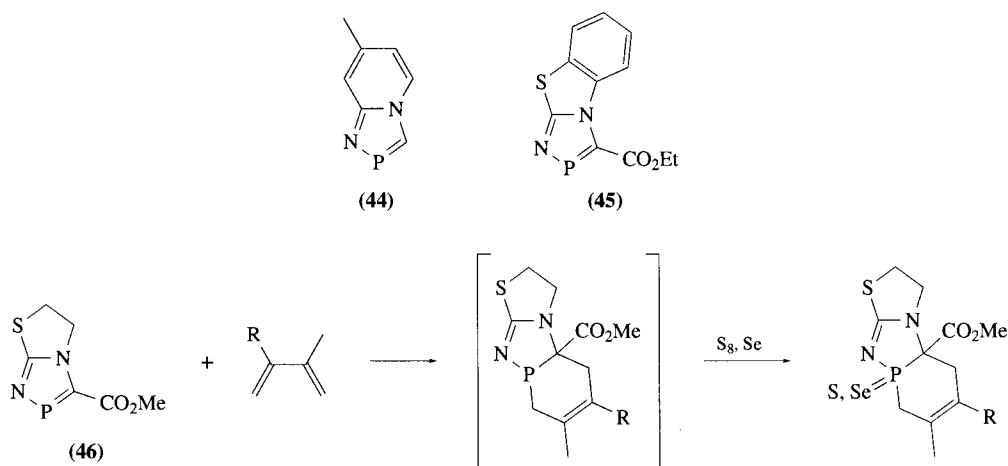
The 1,4,2-diazaphospholes are colorless to pale yellow crystalline solids and stable towards atmospheric oxygen. For reactions, mainly the 1,4,2-diazaphospholo[4,5-*a*]pyridines (39) were used.

They have a characteristic naphthalene-like smell <86PS(28)289>. They do not react with sulfur, selenium, or methyl iodide but with dimethyl sulfate, alkylation at the two-coordinate nitrogen occurs. Hydrolysis opens the diazaphosphole ring to give a zwitterionic 2-aminopyridinio-methylphosphonite (**38**) (Scheme 11). Methanol adds to the P=C bond. The adduct with diethylamine (**40**) is largely dissociated but its product of oxidation with sulfur or selenium (**41**) can be isolated. With Ph_2PCl , MePCl_2 , $\text{ClCH}_2\text{PCl}_2$, and PCl_3 substitution at the carbon atom next to phosphorus takes place. The tris(1,4,2-diazaphospholyl)phosphine (**42**), resulting in the latter case, and phosphorus trichloride take part in a substituent exchange equilibrium <86PS(28)289, 95CB581>. The reaction of 1,4,2-diazaphospholo[4,5-*a*]pyridine (**39**) with selenophosphonic acid anhydrides $(\text{RPSe}_2)_2$ ($\text{R} = \text{Ph}$, 4-MeOC₆H₄, 4-Me₂NC₆H₄) in the presence of NEt_3 leads to triethylammonium selenophosphinates (**43**) <93PS(77)235>.



Scheme 11

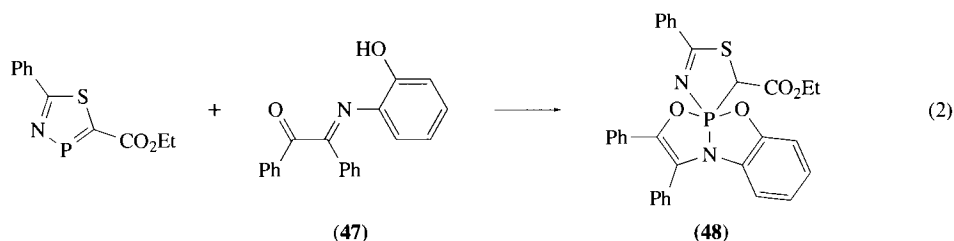
2,3-Dimethylbutadiene and isoprene undergo a [4 + 2] cycloaddition to the P=C bond of 1,4,2-diazaphospholo[4,5-*a*]pyridines (**44**) and [5,4-*b*]benzothiazoles (**45**) (Scheme 12) <86PS(28)289, 91HAC369>. 1,4,2-Diazaphospholo[5,4-*b*]thiazolines (**46**) react with 1,3-butadienes ($\text{R} = \text{H}$, Me) only in the presence of elemental sulfur or selenium. The cycloaddition of isoprene proceeds regioselectively <94T7675>. 1,4,2-Diazaphospholo[5,4-*b*]thiazoles do not react with methyl iodide but are alkylated by dimethyl sulfate at the nitrogen atom next to phosphorus <92S267>.



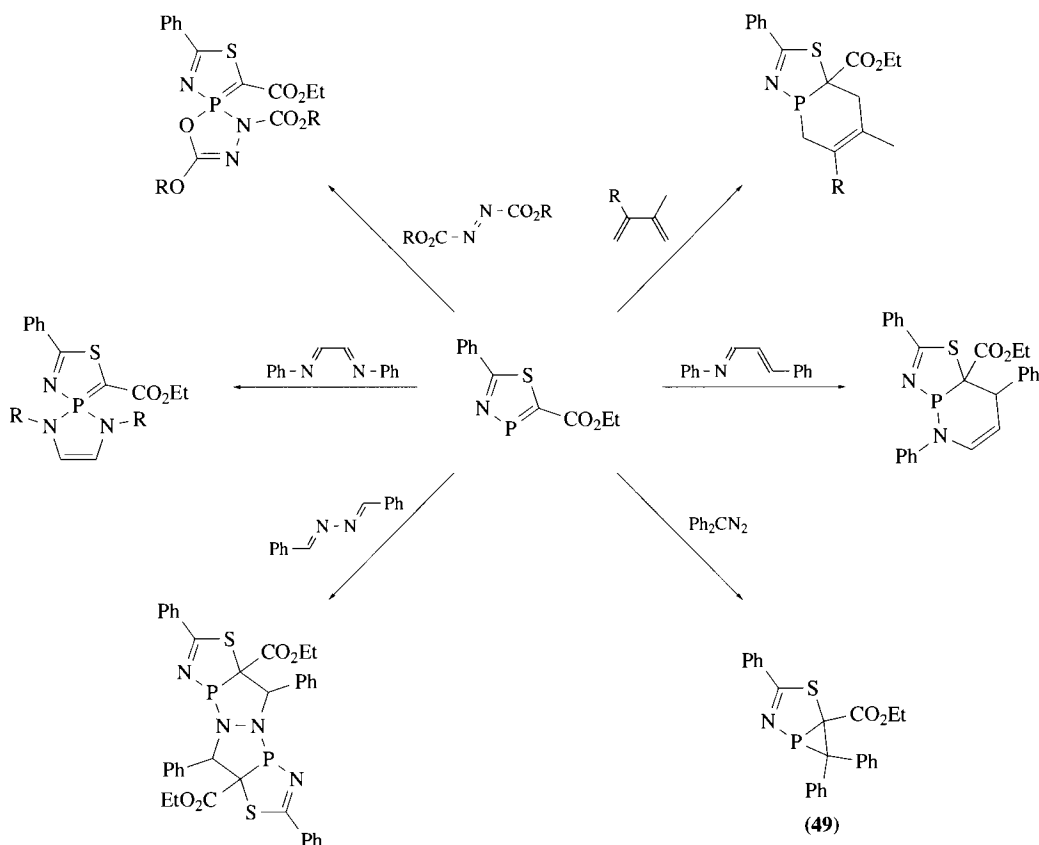
Scheme 12

The 1,3,4-thiazaphospholes are colorless, yellow, or red crystalline solids <85AG125>; the 2-phenyl derivative is a pale yellow liquid. They are not oxidized by atmospheric oxygen or sulfur <86PS(28)71>. Dimethyl sulfate or trimethyloxonium tetrafluoroborate methylates the nitrogen atom <85AG125>.

86PS(28)71> whereas methyl iodide does not react. Boron trifluoride coordinates to nitrogen <B-90MI 422-01>. Alcohols, thiols, water, and hydrogen chloride add to the P=C bond to give 4,5-dihydro-1,3,4-thiazaphospholes but diethylamine does not react <85AG125, 86PS(28)71>. Phenols (**47**) with a heterodiene moiety in the *ortho*-position react to yield tricyclopophosphoranes (**48**) (Equation 2) <B-90MI 422-01>.



Azodicarboxylic esters (R = Me, Et, Pr) and glyoxal bis(cyclohexyl)imine (R = C₆H₁₁) undergo [4 + 1] cycloaddition reactions to the phosphorus atom of a 1,3,4-thiazaphosphole. Butadienes (R = H, Me) and 1,4-diphenyl-1-azabutadiene give [4 + 2] cycloaddition reactions to the P=C bond (Scheme 13) <B-90MI 422-01>.



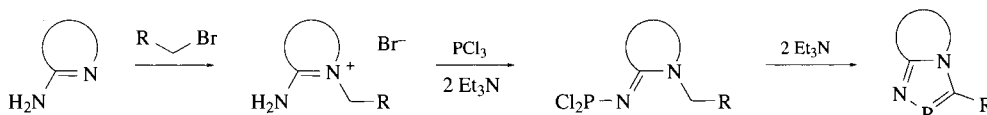
Scheme 13

With benzaldazine, a criss-cross-type cycloaddition takes place <B-90MI 422-01> and the reaction with diphenyldiazomethane yields a bicyclic phosphirane (**49**) among other products <87CB597>.

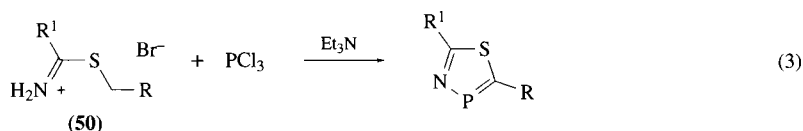
4.22.4.2 Syntheses

4,5-Anellated 1,4,2-diazaphospholes <92S267, 92ZN(B)373, 95S361> can be prepared in a condensation reaction from PCl₃ and partners with a four-membered chain and a suitable terminal reactivity. The latter have been obtained from 2-aminothiazoline, 2-aminothiazoles, 2-aminobenzothiazoles or

2-aminopyridines, and ethyl bromoacetate or phenacyl bromide. 2-Amino-1-(ethoxycarbonylmethyl)pyridinium bromides condense with phosphorus trichloride in the presence of triethylamine in acetonitrile to give 1-aza-2-phosphaindolizines ($R = \text{CO}_2\text{Et}$) (Scheme 14), i.e. [1,4,2]diazaphospholo[4,5-*a*]-pyridines. If the reaction is carried out in toluene, the intermediate (1-alkyl-1,2-dihydro-2-pyridylideneamino)dichlorophosphines can be observed and in some cases isolated. In the same way 3-substituted 5,6-dihydrothiazolo[3,2-*d*][1,4,2]diazaphospholes ($R = \text{CO}_2\text{Me}$, CO_2Et , CO_2Bu , COPh), thiazolo[3,2-*d*][1,4,2]diazaphosphole, and its benzo derivatives ($R = \text{CO}_2\text{Me}$, CO_2Et , COPh) are obtained. The salts from thioamides or thiourea (**50**) ($R^1 = \text{Me}$, Ph , NMe_2) and ethyl bromoacetate or benzyl bromides ($R = \text{CO}_2\text{Et}$, Ph , 4-substituted phenyl) correspondingly yield 1,3,4-thiazaphospholes from the condensation with PCl_3 <85AG125>.

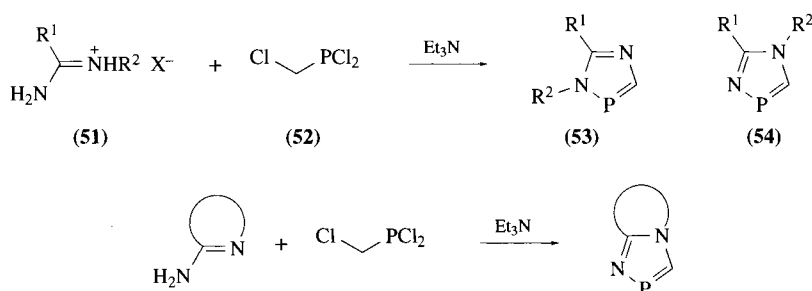


Scheme 14



5-Unsubstituted monocyclic and fused 1,4,2-diazaphospholes are synthesized by using chloromethyl dichlorophosphine (**52**) for condensation. With amidines (**51**) ($R^1/R^2 = \text{Me}/\text{H}$, Ph/H , Ph/Ph , SMe/Me) mixtures of 1*H*- and 3*H*-1,4,2-diazaphospholes (**53**) and (**54**) are obtained; for $R^2 = \text{H}$ they equilibrate by proton exchange <86PS(28)289, 90PS(49/50)349>.

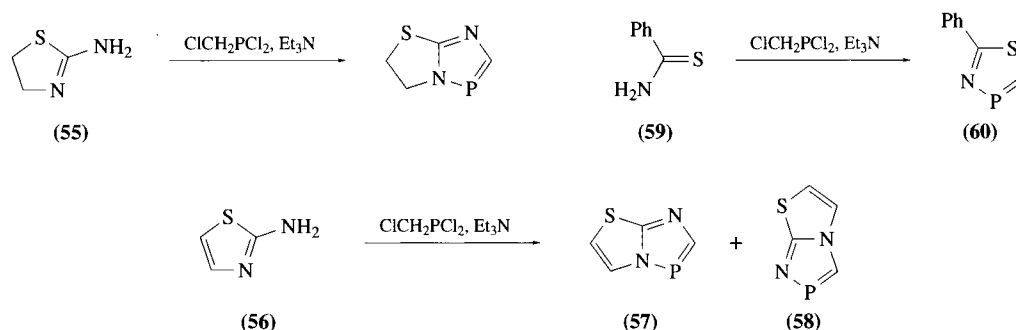
Condensation of 2-aminopyridines ($R = \text{H}$, Me), 2- and 4-aminopyrimidines ($R = \text{H}$, Me), 2-aminopyrazine, and 2-aminoquinoline with chloromethyl dichlorophosphine yields regiospecifically 1,4,2-diazaphospholo[4,5-*a*]pyridines, 1,4,2-diazaphospholo[4,5-*a*]pyrimidines, 1,4,2-diazaphospholo[4,5-*a*]pyrimidine, 1,4,2-diazaphospholo[4,5-*a*]pyrazine, and [1,4,2]diazaphospholo[4,5-*a*]quinoline, respectively (Scheme 15). In the case of 2-aminopyrimidines it has been possible to isolate a diazadiphosphetidine, as an intermediate. On treatment with NEt_3 it changes into the final product, presumably through intramolecular nucleophilic displacement of the chlorine atom by the pyridinic nitrogen atom accompanied by the rupture of the diazadiphosphetidine ring and loss of hydrogen chloride <86PS(28)71, 86PS(28)289, 91HAC369, 94T7675, 95CB581>.



Scheme 15

In the same way 2-aminothiazoline (**55**) can be condensed with chloromethyl dichlorophosphine (Scheme 16). The reaction is again regiospecific, but the orientation is reversed and the 5,6-dihydrothiazolo[3,2-*e*][1,2,4]diazaphosphole is obtained. In this case the reaction probably initiates at the ring nitrogen atom <86PS(28)289, 94T7675>. When 2-amino-1,3-thiazole or 2-amino-1,3-benzothiazoles are used for the cyclocondensation, mixtures of isomeric 1,5- and 4,5-anellated 1,4,2-diazaphospholes, resulting from both orientations of the CP unit with respect to the NCN fragment in the aminothiazole, are generally obtained. Thus, the reaction of 2-amino-1,3-thiazole (**56**) leads to thiazolo[2,3-*e*]-1,4,2-diazaphosphole (**57**) (70%) and thiazolo[3,2-*d*]-1,4,2-diazaphosphole (**58**) (10%). The ratio of the two isomers obtained from 2-aminobenzothiazoles strongly depends on the

substituents in the benzo ring ($R^1/R^2 = \text{H/H, H/OMe, Me/H}$) <94T7675, 95CB581>. The analogous condensation of thiobenzamide (**59**) with chloromethyl dichlorophosphine yields 2-phenyl-1,3,4-thiazaphosphole (**60**) <86PS(28)289>.



Scheme 16

4.22.5 1,2,3-DIAZAPHOSPHOLES (G, H)

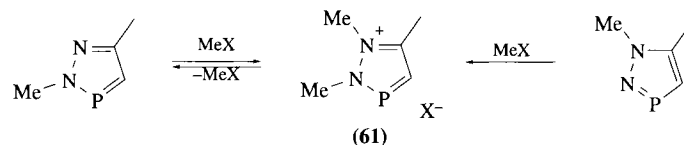
4.22.5.1 Reactivity

1,2,3-Diazaphospholes are colorless to pale yellow distillable liquids or crystalline solids <72JPR806, 80CB2278>. They are stable to oxidation by air and they do not react with elemental sulfur <67CHE601, 72JPR806, 81CR(C)187, 83CB549>. They are readily hydrolyzed <67CHE601, 72JPR806> to give the hydrazone from which they originate and phosphorous acid. The flash pyrolysis of some 2-methyl-1,2,3-diazaphospholes has been investigated <90PS(49/50)363>. While only a few reactions of 1*H*-1,2,3-diazaphospholes are reported, the chemistry of the 2*H*-isomers is well studied.

4.22.5.1.1 N-Coordination and N-substitution

Hydrogen halides give *N*-protonation of 2*H*-1,2,3-diazaphospholes (molecular structure of a hydrochloride in Table 2) but also add to the $\text{P}=\text{C}$ bond (see Section 4.22.5.1.2). Hydrolysis opens the $\text{P}=\text{N}$ bond of 1,2,3-diazaphospholo[1,5-*a*]pyridines <95S173>.

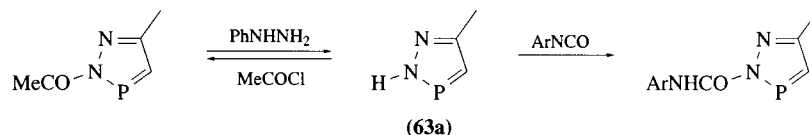
While alkyl halides do not react with 1*H*- and 2*H*-1,2,3-diazaphospholes, alkylation by dimethyl sulfate or trimethyloxonium tetrafluoroborate and protonation take place at the two-coordinate nitrogen atom and leave the phosphorus atom two-coordinate <67CHE601, 80CB2278, 83CB549, 95S173>. This is also true for the addition of BF_3 <80CB2278> and in some cases even for the coordination of transition metals (see Section 4.22.5.1.6). Methylation of both 2,5- and 1,5-dimethyl-1,2,3-diazaphosphole gives the same cation (**61**) ($\text{X} = \text{MeSO}_4, \text{BF}_4$), which on demethylation yields only the 2,5-isomer <80CB2278>.



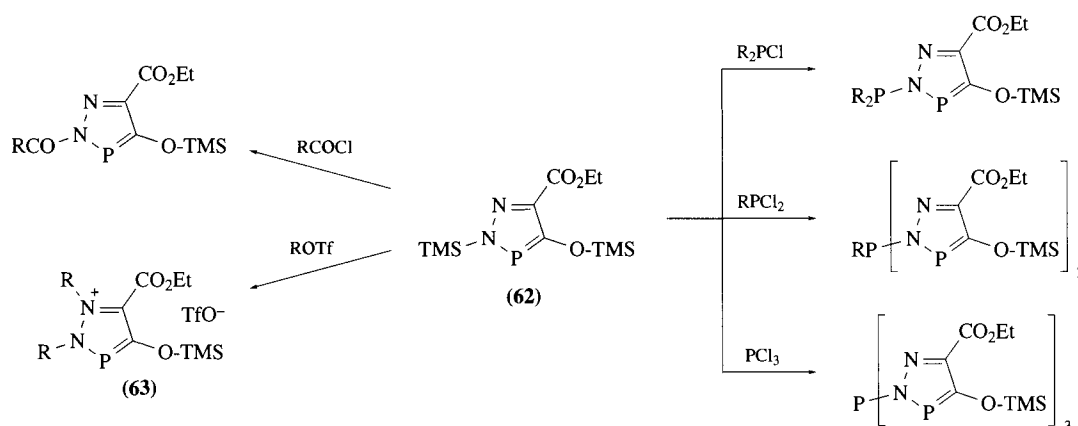
Scheme 17

Alkyltriflates react with 2-trimethylsilyl-1,2,3-diazaphospholes (**62**) exclusively in a 2:1 molar ratio and yield 1,2-dialkyl-1,2,3-diazaphospholium triflates (**63**) <96TH 422-02>. Methanolysis converts 2-trimethylsilyl-1,2,3-diazaphospholes to the *N*-unsubstituted compounds. In the latter the proton is bonded to N-2 and forms an intermolecular hydrogen bond to N-1 which allows a rapid exchange between the 2*H*- and the 1*H*-isomers <77ZOB576, 96TH 422-02>. The *N*-unsubstituted 5-methyl-1,2,3-diazaphosphole (**63a**) adds aryl isocyanates to N-2 <77IZV532> and is acylated reversibly <77IZV532, 77ZOB576>. 2-Acyl-1,2,3-diazaphospholes (molecular structure see Table 2) are readily obtained from the trimethylsilyl derivatives and acid chlorides <96TH 422-02>. More substitution

reactions are achieved with chlorophosphines, dichlorophosphines and phosphorus trichloride (Scheme 19) <83ZN(B)1484, 96TH 422-02>. The trimethylsilyl group is also replaced in the reaction with cyclopropenylium bromides or triphenyl chloromethane. Alkyl halides with less carbenium character do not react <96TH 422-02>.



Scheme 18

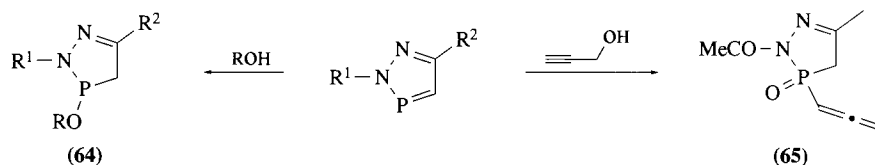


Scheme 19

4.22.5.1.2 Polar addition to the P=C bond and substitution at C-4

When a polar reagent adds to the P=C bond of a heterophosphole the more electronegative part generally becomes bonded to the phosphorus. The addition reactions are often reversible and the addition equilibria are more or less balanced.

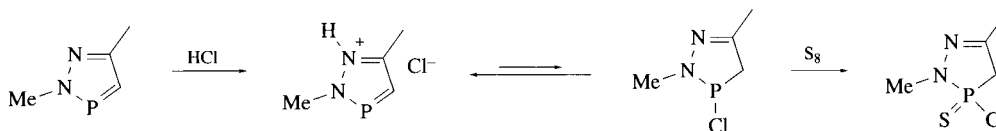
The equilibria from 2*H*-1,2,3-diazaphospholes and alcohols ROH depend on the nature of the *N*-substituent R¹. With R = Me <76ZOB590, 77ZOB576, 81CR(C)187, 84PS(21)335>, Et <67CHE601, 72JPR806, 76ZOB590>, CH₂Ph <76ZOB590>, the 3-alkoxy-3,4-dihydro-1,2,3-diazaphospholes (64) have been obtained. The addition is reversible <76ZOB590, 77ZOB576>; an excess of alcohol degrades the diazaphosphole to the hydrazone and P(OR)₃ <67CHE601, 72JPR806, 90ZOB35>. Addition of propynol to the 2-acetyl-5-methyl-1,2,3-diazaphosphole is followed by a rearrangement to the 3-allenyl-dihydrodiazaphosphole 3-oxide (65) <91PS(56)129>. Reaction with ethylene glycol gives a spirophosphorane <81CR(C)187, 84PS(21)335>, catechol degrades the ring completely <91PS(57)83>. Ammonia as well as primary and secondary amines do not react <67CHE601, 72JPR806, 85CB1621> except with 2-acetyl-5-methyl-1,2,3-diazaphosphole <72ZOB1939>. Water adds to 1,2,3-diazaphospholo[1,5-*a*]pyridines (as representatives of 1*H*-1,2,3-diazaphospholes) with rupture of the P=N bond <95S173>.



Scheme 20

The addition of hydrogen halides HX (X = Cl, Br, I) to a 2*H*-1,2,3-diazaphosphole yields the 3-halodihydrodiazaphosphole in equilibrium with the diazaphospholium halide see for example (Scheme 21). This equilibrium depends strongly on the substituent R¹ at nitrogen <80CB2278> and in particular on the substituent R² at C-4 <84S591>. For R¹/R² = Ph/H <72JPR806, 80CB2278>, COMe/H

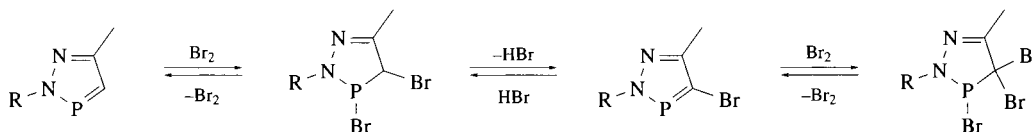
<72JPR806>, Me/Cl, Ph/Cl <84PS(21)97>, Me/Br, Ph/Br <84S591>, Me/I, Ph/I <84PS(21)97> the covalent addition product, for $R^1/R^2 = \text{Me/H}$ <80CB2278>, Me/Me, Me/SMe, Me/SPh <84S591> the ionic form is favored. In the latter cases the dihydrodiazaphosphole is present albeit in low equilibrium concentration, as shown by the reaction with sulfur (Scheme 21) <80CB2278>.



Scheme 21

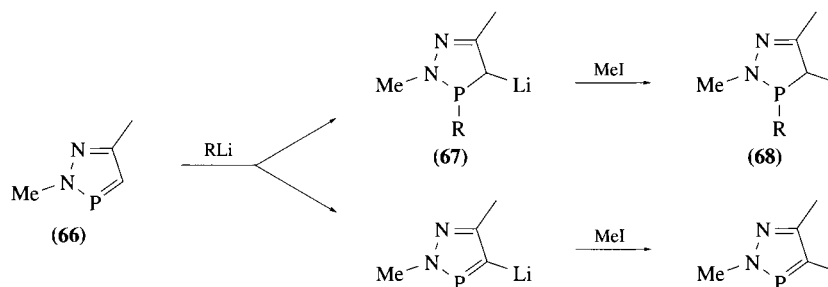
The 1,2-addition may be followed by a 1,2-elimination, thus restoring the diazaphosphole system. In the case of 4-unsubstituted 1,2,3-diazaphospholes this combination of addition and elimination will result in a substitution at C-4. The substitution was first shown for 2*H*-1,2,3-diazaphospholes with phosphorus(III) halides and thiophosphoryl halides <76CC887, 79AG442, 80CB2278>. The reaction rate increases in the order $\text{Ph}_2\text{PCl} < \text{PhPCl}_2 < \text{PCl}_3$. Likewise with $\text{P}(\text{CN})_3$ the 4-dicyanophosphinodiazaphosphole is obtained <80CB2278>. 1,2,3-Diazaphospholo[1,5-*a*]pyridines also undergo substitution in 4-position with PCl_3 <95S173>.

The reaction of 2*H*-1,2,3-diazaphospholes with bromine involves a sequence of 1,2-addition/elimination equilibria, $R = \text{Me, Ph}$ (Scheme 22) <85CB1621>. 4-Bromo-1,2,3-diazaphospholes become accessible this way. Similarly, 4-phenylthio- and 4-methylthio-1,2,3-diazaphospholes result from reactions with sulfenyl halides <84S591, 85CB1621>. Iodine chloride reacts to give both the 4-chloro- and the 4-iododiazaphosphole <84S591>. Chlorination and bromination of diazaphospholes at C-4 has been achieved also with SO_2Cl_2 and BrCN or NBS, respectively <84S591>.



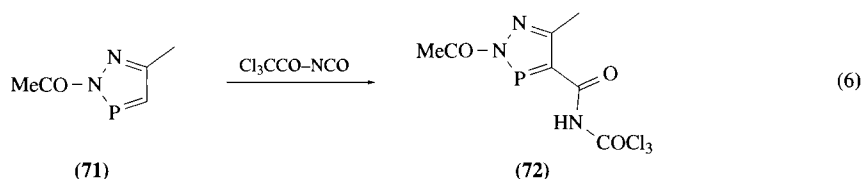
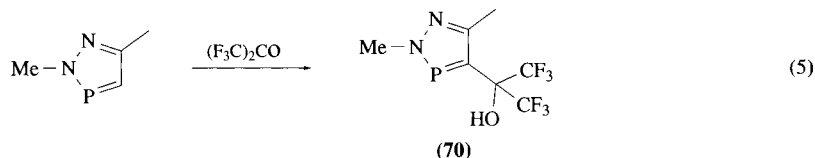
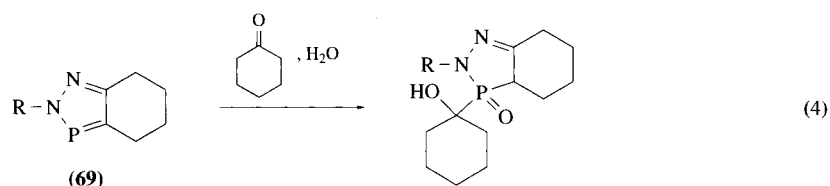
Scheme 22

Lithiumalkyls ($R = \text{Me, Bu, Bu}^t$) as well as lithium diisopropylamide ($R = \text{NPr}_2$) add readily to the $\text{P}=\text{C}$ bond of 2,5-dimethyl-1,2,3-diazaphosphole (**66**) <84PS(21)97, 87JOM(319)49>. With methyl iodide and organotin chlorides the adduct (**67**) yields 4-substituted dihydro-1,2,3-diazaphospholes (**68**). Only in the case of reaction of methyllithium ($R = \text{Me}$) is lithiation at C-4 observed as a minor side reaction (Scheme 23).

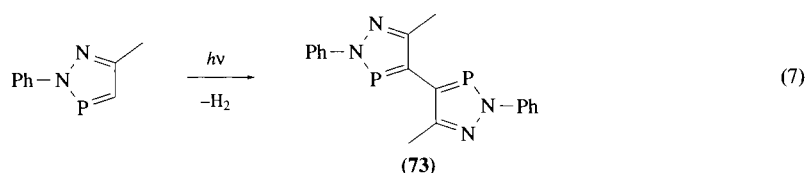


Scheme 23

1,2,3-Diazaphospholes generally do not react with aliphatic and aromatic aldehydes or ketones <67CHE601, 72JPR806>. A 4,5-tetramethylene 1,2,3-diazaphosphole (**69**) ($R = \text{cyclohexyl}$) adds cyclohexanone and water in a slow reaction (Equation (4)) <90ZOB35>. 2-Phenyl-5-methyl-1,2,3-diazaphosphole and aliphatic cyclic ketones condense to give the 4-alkenyl diazaphospholes and 4-hydroxyalkyl diazaphospholes <85ZOB1464, 91ZOB1063>. 2,5-Dimethyldiazaphosphole adds hexafluoroacetone giving the 4-hydroxy-alkyl derivative (**70**) (Equation (5)) <B-90M1 422-01>. 2-Acetyl-5-methyl-1,2,3-diazaphosphole (**71**) and an electron-poor isocyanate likewise yield the 4-carbamoyl derivative (**72**) (Equation (6)) <84IZV1182>.



2-Phenyl-5-methyl-1,2,3-diazaphosphole on irradiation loses hydrogen and yields the 4,4'-bis(diazaphospholyl) (73) (molecular structure in Table 2) (Equation (7)) <84IZV1182, 85ZOB1464, 88IZV150>.



4.22.5.1.3 Reactions with dienes and heterodienes

2,5-Dimethyl-1,2,3-diazaphosphole does not react with 2,3-dimethylbutadiene up to 90°C. [4 + 2] Cycloadditions to the P=C bond of 2-acetyl- and 2-phenyl-5-methyl-1,2,3-diazaphosphole are observed with isoprene <91S783>, 2,3-dimethylbutadiene <86BSF115>, cyclopentadiene, and pentachlorocyclopentadiene <79DOK(244)117> as well as with 1-vinyl-3,3-dimethylallenyl diethylphosphonate <92ZOB1505>. The addition of isoprene is regioselective, that of the vinylallene is not. The cycloaddition of cyclopentadiene is reversible. Under kinetic control the *endo*-cycloadduct (74) is formed, which on heating converts to the more stable *exo*-isomer <86BSF115>. Tetrahalo-benzoquinones add selectively to the P=C bond of 5-ethoxycarbonyl-2-trimethylsilyl-4-trimethylsiloxy-1,2,3-diazaphosphole (62) to give adducts (75) <96TH 422-02>. With diacetyl dipropyldiimine, [4 + 1] cycloaddition to the phosphorus of 2-acetyl-5-methyl-1,2,3-diazaphosphole takes place with formation of a spirocyclic ylide (76) <86TL2971>. Azodicarbonic acid dimethyl ester adds to 5-ethoxycarbonyl-2-trimethylsilyl-4-trimethylsiloxy-1,2,3-triazaphosphole in a 2:1 molar ratio to give a spirotricyclic zwitterion <96TH 422-02>.

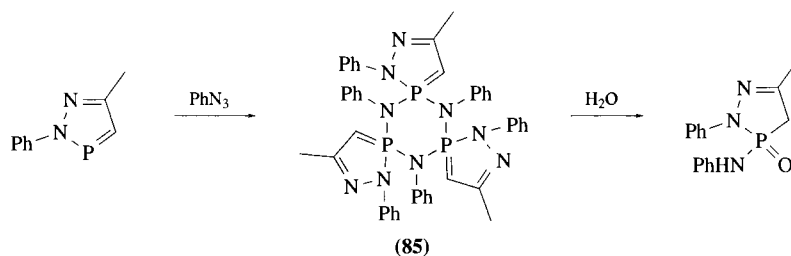
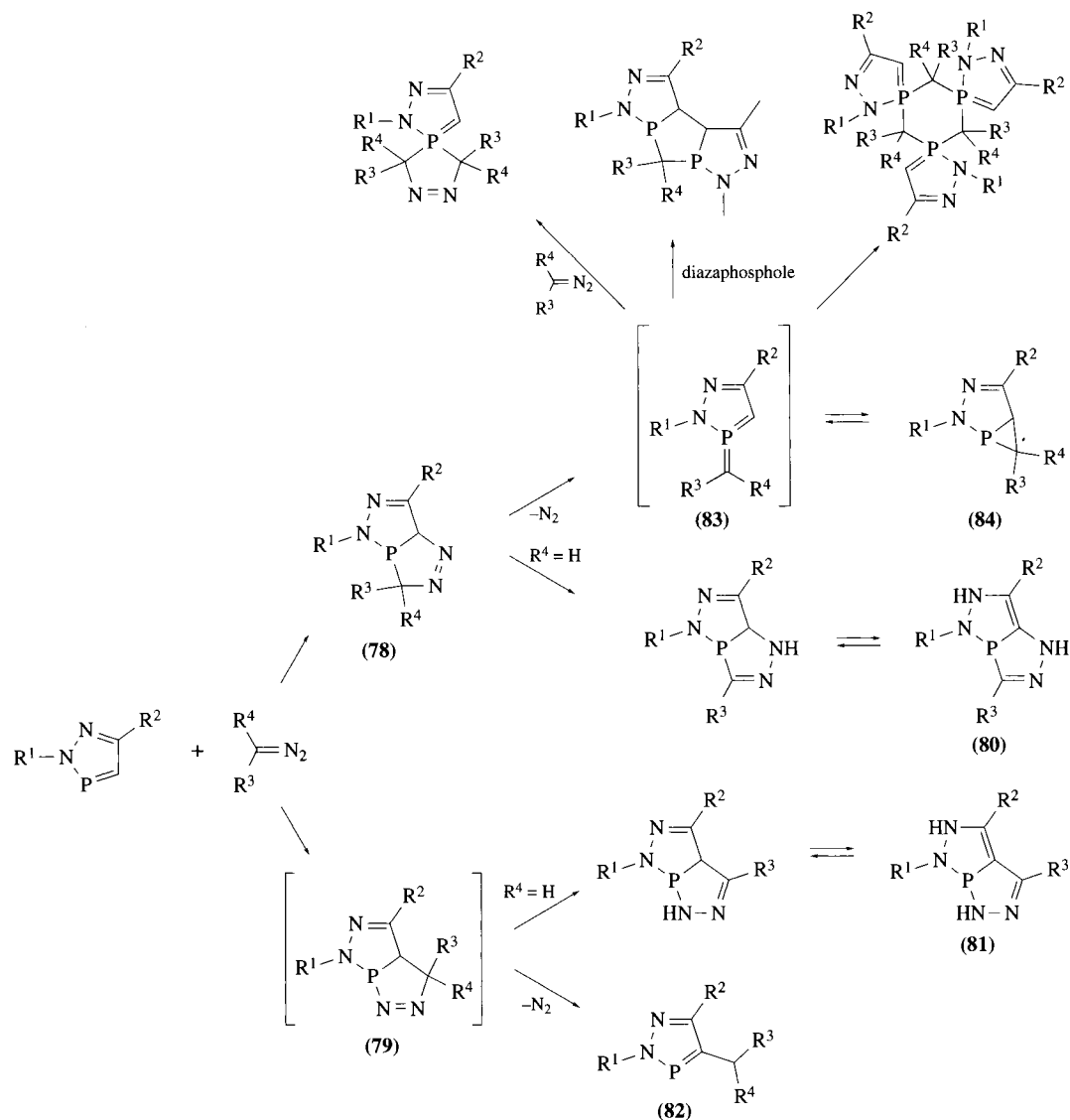
4.22.5.1.4 Reactions with 1,3-dipoles

Dipolar [3 + 2] cycloaddition reactions are covered in a review <86PS(26)203>. Nitrile ylides <83CJC1105>, nitrile imines <83CB549>, and nitrile oxides <81CC1131, 83T1507> add to the P=C bond of 2*H*-1,2,3-diazaphospholes with the nitrile carbon atom becoming bonded to the phosphorus atom. The reaction has also been found for the cycloaddition of these dipoles to phosphalkenes <86PS(26)203, B-90MI 422-04> and phosphalkynes <88AG1541, B-90MI 422-02> (Scheme 25). The nitrile imine cycloadduct on heating loses benzonitrile and yields the 4-anilinodiazaphosphole (77) <83CB549>.



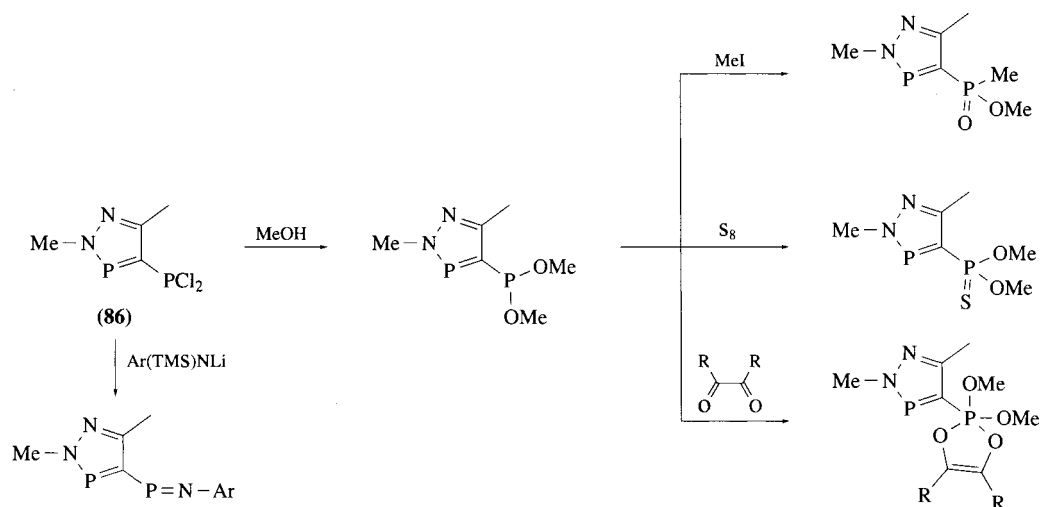
Phenyl azide reacts with 2*H*-1,2,3-diazaphospholes with loss of nitrogen to give a cyclic trimer (**85**) of the diazaphosphole *P*-imide which is suggested as an intermediate (Scheme 27) (81IZV1600, 90ZOB35).

The PCl_2 group of 4-dichlorophosphino-1,2,3-diazaphospholes (**86**) can be transformed by substitution and oxidation reactions as usual for dichlorophosphines $\langle 80\text{CB}2278 \rangle$ and it provides access to a diazaphospholyl aryliminophosphine (Scheme 28) ($\text{Ar} = 2,4,6\text{-Bu}_3\text{C}_6\text{H}_2$) $\langle 93\text{BSF}726 \rangle$ (For the molecular structure of an intermediate see Table 2).



4.22.5.1.6 Formation of transition metal complexes

Low valent transition metal centers coordinate preferentially to the phosphorus atom of azaphospholes. *P*-Coordinated complexes of 2,5-dimethyl-1,2,3-diazaphosphole with $\text{Cr}(\text{CO})_5$ (molecular structure in Table 2), $\text{W}(\text{CO})_5$, $\text{Fe}(\text{CO})_4$, $\text{MnC}_3\text{H}_4\text{Me}(\text{CO})_2$ <80JOM(185)53>, and $\text{Pt}(\text{PPh}_3)_3$ <83JOM(256)375>, of 2,5-dimethyl-4-(dimethylthiophosphoryl)- <80CB2278> and 1,5-dimethyl-1,2,3-



Scheme 28

diazaphosphole <80JOM(185)53> with $\text{Cr}(\text{CO})_5$ and of 5-ethoxycarbonyl-4-trimethylsiloxy-1,2,3-diazaphosphole with $\text{W}(\text{CO})_5$ (molecular structure in Table 2) <96TH 422-02> have been prepared. The 1,5-dimethyl-1,2,3-diazaphosphole can be displaced from its $\text{Cr}(\text{CO})_5$ complex by tetra-alkylammonium iodide or bromide or by phosphorus trichloride <80JOM(185)53>.

With Pd^{II} , Pt^{II} , and Au^{III} , *P*- and *N*-coordination is observed: 2,5-dimethyl-1,2,3-diazaphosphole with $\text{PtCl}_2\text{PEt}_3$ gives only the *cis*-*P*-coordinated complex, with $\text{PdCl}_2\text{PEt}_3$ only the *trans*-*N*-coordinated complex <84ICA33, 88IC2612>, and with $\text{P}(\text{Bu})_2\text{PEt}_3$ both of them in a ratio 1:2 <88IC2612>. Likewise, 1,2,3-diazaphospholes give *cis*-*N*- or *cis*-*P*-coordinated AuMe_2Cl -complexes, depending on the azaphosphole substituents <80ICA167>. Stable, insoluble 1:1 complexes with AuClCO , AuCl_3 <80ICA167>, and CuI <67CHE601> have also been reported.

2,5-Dimethyl-1,2,3-diazaphospholes with a 4-phosphino group coordinate to transition metals only by this substituent, as shown by the reaction of the 4-dichlorophosphino derivative with $\text{Cr}(\text{CO})_5$ <80CB2278>, $\text{HFeW}(\text{CO})_9^-$ <89OM244>, and $\text{HFe}(\text{CO})_4^-$ <88CC574>; in the latter cases in addition a Cl/H exchange and reduction to the diphosphene is found. The molecular structure of the bis- $\text{Fe}(\text{CO})_4$ complex of the bis(diazaphospholyl)diphosphene is given in Table 2.

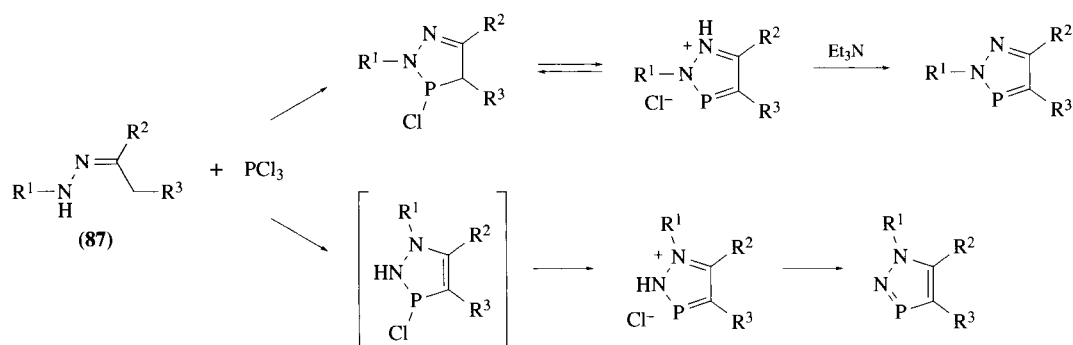
The diazaphospholyl iminophosphine (see above) uses alternatively *N*-1, *P*-3, or the side group phosphorus atom for transition metal complexation <93BSF726>.

4.22.5.2 Syntheses

2*H*-1,2,3-Diazaphospholes are easily accessible by the PCl_3 condensation of alkylketone hydrazones (87) (Scheme 29). A wide variety of hydrazones have been used: R^1 , R^2 , $\text{R}^3 = \text{H}$, alkyl, aryl, and in addition $\text{R}^1 = \text{acyl}$, $\text{R}^3 = \text{Ph}_2\text{PO}$ <67CHE601, 70ZOB1501, 72JPR806, 72ZOB1939, 76AG91, 76CC887, 77ZOB576, 78CB1558, 79AG442, 80CB2278, 81CR(C)187, 83ZAAC(501)57, 84PS(21)335, 91S783>. Condensation may be achieved by refluxing in benzene. Depending on the nature of R^1 , the intermediate reached after the loss of two moles of HCl is covalent, $\text{R}^1 = \text{MeCO}$, Ph , pyridyl <70ZOB1501, 72JPR806, 72ZOB1939, 74PS(4)197, 76AG91, 76CC887, 77ZOB576, 78CB1558, 80CB2278>, or ionic, $\text{R}^1 = \text{Me}$ <78CB1558, 80CB2278>. The third mole of HCl is lost on further refluxing or with the help of a base. From ketone hydrazones with two different alkyl groups of similar reactivity (e.g. methyl ethyl ketone) two isomeric products (e.g. R^2 , $\text{R}^3 = \text{Me}$ and $\text{R}^2 = \text{Et}$, $\text{R}^3 = \text{H}$) are obtained <72JPR806, 72ZOB1939>. In some cases (e.g. R^1 , $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$) besides the 2*H*-, the 1*H*-1,2,3-diazaphosphole is found as a second product <79AG442>.

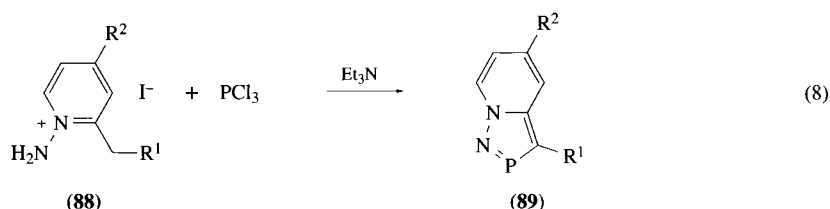
A cyclic silyl hydrazone derivative <83ZAAC(501)57> as well as azo compounds isomeric to hydrazones <74PS197> have also been used for the synthesis of 2*H*-1,2,3-diazaphospholes by the PCl_3 condensation. 2,4,5-Triphenyl-1,2,3-diazaphosphole is best prepared from the respective azoalkene and a fused benzothiadiphosphole as phosphorus donating reagent <95TL447>.

Treatment of a 2-acetyl-3-methoxy-3,4-dihydro-1,2,3-diazaphosphole with phenylhydrazine gives the 2-phenyl derivative in addition to the deacylated 1,2,3-diazaphosphole <77ZOB576>.

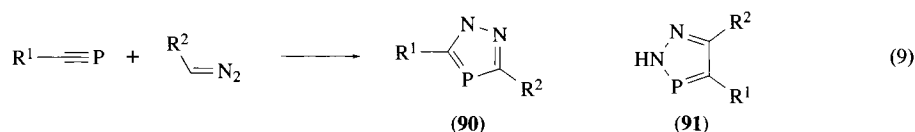


Scheme 29

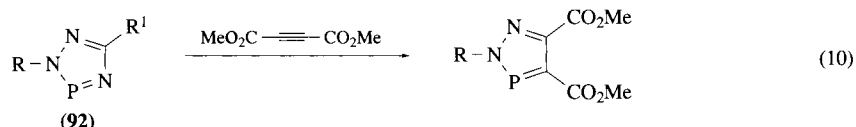
2-Alkyl-1-aminopyridinium iodides (**88**) condense with PCl_3 in presence of NEt_3 to give 1,2,3-diazaphospholo[1,5-*a*]pyridines (**89**). 2-Methyl-1-aminopyridinium iodide, on reacting with two equivalents PCl_3 under these conditions, forms 1-dichlorophosphino-1,2,3-diazaphospholo[1,5-*a*]pyridine (**89**), $\text{R}^1 = \text{PCl}_2$ (Equation (8)) <95S173>.



1,2,4-Diazaphospholes (**90**) are generally preferred over the 1,2,3-isomers (**91**) as products of the 1,3-dipolar cycloaddition of diazo compounds to phosphalkynes (**91**) and often the reaction is regioselective (Section 4.22.3.2). 1,2,3-Diazaphospholes are found as minor products, however, from the cycloaddition of $\text{HC}\equiv\text{P}$ to a diazo ester (15%) <88JOM(338)329>, as well as of $\text{Bu}^t\text{C}\equiv\text{P}$ to nitrile imines (2%) <87S689> and to a sydnone (13%) <88AG1541>. 4-Aminosubstituted 1,2,3-diazaphospholes ($\text{R}^1 = \text{Pr}_2\text{N}$) are obtained from $\text{Pr}_2\text{NC}\equiv\text{P}$ and methyl diazoacetate or trifluoromethyl diazomethane as a 1:4 and 1:2 mixture with the corresponding 1,2,4-diazaphospholes <92CB411, 93PS(76)5>. Treatment of the metallophosphalkene $(\text{Me}_2\text{N})_2\text{C}=\text{P}-\text{Fe}(\text{CO})_2\text{Cp}^*$ with ethyl or *t*-butyl diazoacetate affords the 2-metallated 1,2,3-diazaphosphole <95OM581>.



Acetylene dicarboxylic esters and (less easily) acetylene monocarboxylic esters replace nitriles from the 4,5-positions of 1,2,4,3-triazaphosphole rings (**92**) to give carboxyl derivatives of 1,2,3-diazaphospholes, presumably by a cycloaddition/cycloreversion mechanism, $\text{R}/\text{R}^1 = \text{Me}/\text{Ph}$, $\text{SiMe}_3/\text{NMe}_2$ <83ZN(B)1484>.



4.22.5.3 Application

Hydrochlorides of 2*H*-1,2,3-diazaphospholes (Section 4.22.5.1.2) i.e. 3-chloro-3,4-dihydro-2*H*-1,2,3-diazaphospholes generated *in situ* from a ketone hydrazone and PCl_3 (see Section 4.22.5.2) are

useful intermediates for the synthesis of indoles <87T2755, 88JCS(P1)971>, pyrroles <89JCS(P1)1053>, pyrrolylacetates and 1,2-dihydro-2-alkenyl-3*H*-pyrazol-3-ones <91CC34, 92JCS(P1)1729, 93HAC497>.

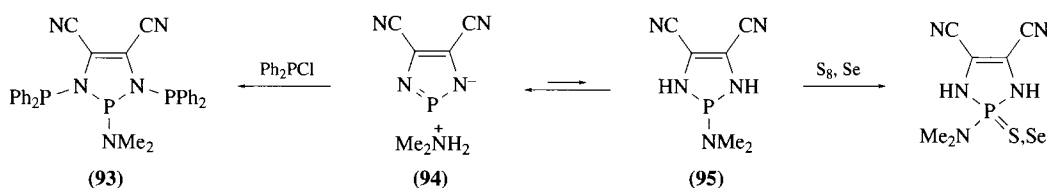
The usual synthesis from a hydrazone and PCl_3 has been applied to prepare *p*-(1,2,3-diazaphosphol-5-yl)benzylphosphonates, analogues to Fostedil in which the benzothiazol unit is replaced by a diazaphosphole ring. However, their activity to inhibit calcium transfer through biological membranes is weak <93PS(85)225>.

4.22.6 1,3,2-DIAZA-, 1,3,2-OXAZA-, AND 1,3,2-THIAZAPHOSPHOLES (I, J, K)

1,3,5-Triazaphosphapentalenes, 1,3,2-benzodiazaphospholes, 1,3,2-benzoxazaphospholes, and 1,3,2-benzothiazaphospholes are contained in a review on anellated heterophospholes <94T7675>. The synthesis of 1,3,2-oxazaphospholes from α -aminocarbonyl compounds has also been reviewed <92RHA25>.

4.22.6.1 Reactivity

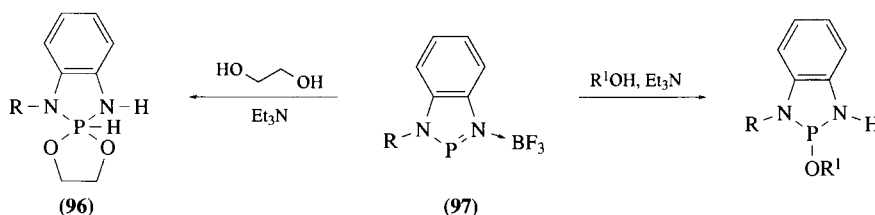
The salts of the 4,5-dicyano-1,3,2-diazaphospholyl anion are colorless crystalline solids <81ZN(B)1273, 83TL2137>. The anion can be alkylated <81ZN(B)1273, 84CC183, 86CB410> and silylated <86CB410> at nitrogen. Boron trifluoride becomes *N*-coordinated as well. Solutions of the dimethylammonium salt (**94**) contain a low equilibrium concentration of the isomeric 2-dimethylamino-2,3-dihydrodiazaphosphole (**95**), as shown by the oxidation with sulfur or selenium (Scheme 30) <B-90MI 422-01>.



Scheme 30

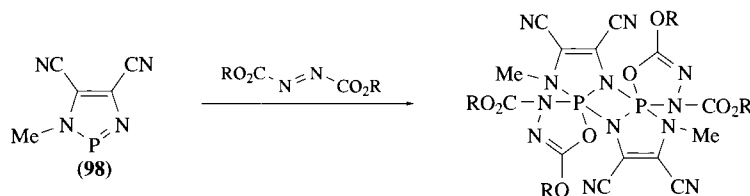
Reactions of (**94**) with methanol and hydrogen chloride yield the 2-methoxy- and 2-chloro-2,3-dihydro derivatives; an excess, however, degrades the products to DAMN and P(OMe)_3 or PCl_3 , respectively <83TL2137>. With tetramethylethylene glycol a spiroposphorane is formed <83TL2137>. Diphenylchlorophosphine reacts in a 1:2 ratio and gives the poorly-soluble 1,3-bis(diphenylphosphino)-2-dimethylamino-2,3-dihydrodiazaphosphole (**93**) <B-90MI 422-01>. Dialkylamines react at the cyano groups giving 4,6-diamino-1,3,5-triaza-2-phosphapentalenes (see Section 4.22.6.2).

The 1,3,2-diazaphospholes are colorless to pale yellow distillable liquids or crystalline solids <81ZN(B)1273, 86CB410, 86PS(28)71>. They are stable to oxidation by air and do not react with sulfur. For the reactions mostly the 1-methyl-4,5-dicyano derivative was used which is degraded to PBr_3 by bromine. It readily adds water, alcohols, or phenols to the $\text{P}=\text{N}$ bond yielding the 2,3-dihydrodiazaphospholes <B-90MI 422-01>. The BF_3 -adduct of 1-benzyl-1,3,2-benzodiazaphosphole (**97**) adds diethylamine or alcohols in the same way; with butanol a 1,1-addition to the phosphorus atom is observed <84CJC43>. In the reaction with diols, 1,2-addition of one hydroxy group is followed by 1,1-addition of the other to yield a spirocyclic phosphorane (**96**) (Scheme 31) <84CJC43>.



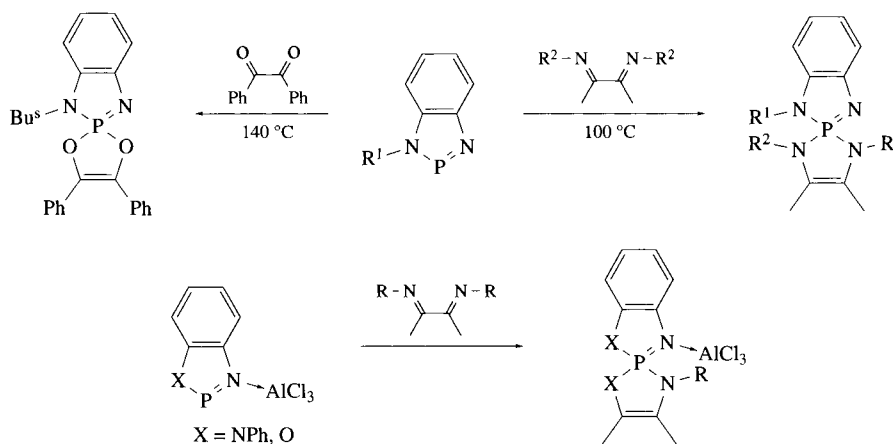
Scheme 31

The [4 + 2]cycloaddition of 4,5-dicyano-1,3,2-diazaphospholes and acetylenes yields 1,2-azaphospholes (Chapter 3.15). Azodicarboxylic esters ($R = \text{Et}, \text{Pr}^i$) give a 1,1-addition accompanied by a dimerization of the product (Scheme 32) <B-90MI 422-01>.



Scheme 32

1,3,2-Benzodiazaphospholes (thermally generated from their tetramers) as well as the 1-phenyl-1,3,2-benzodiazaphosphole and 1,3,2-benzoxazaphosphole AlCl_3 adducts and α -diimines or benzil also undergo [4 + 1] cycloadditions; here the products remain monomeric (Scheme 33) <84TL5521, 86TL2971>.



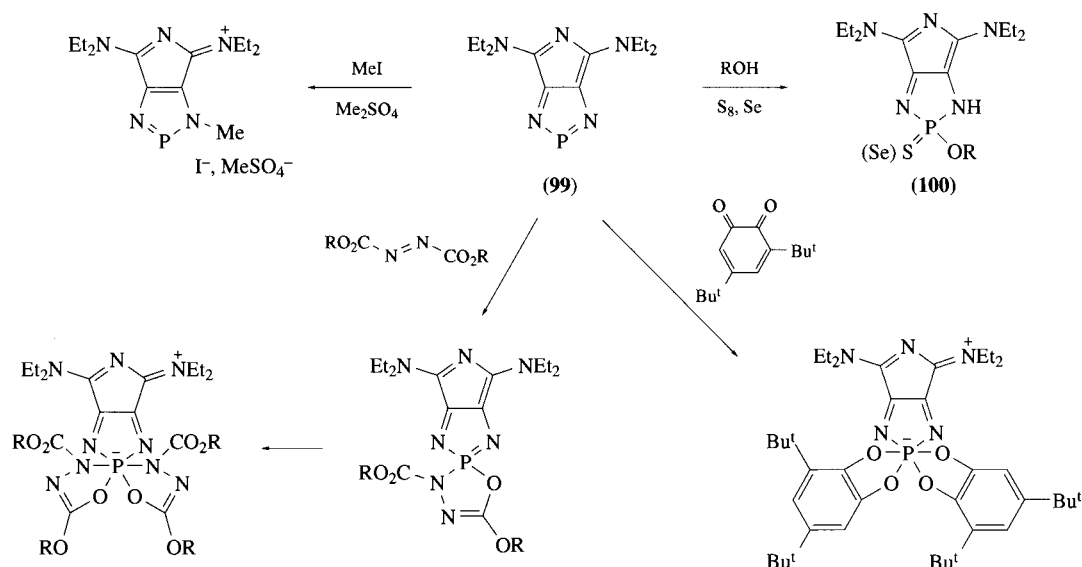
Scheme 33

The 4,6-diamino-1,3,5-triaza-2-phosphapentalenes are deep red crystalline solids. For reactions, the 4,6-bis(diethylamino) derivative (**99**) was used (Scheme 34). The compound is not oxidized by air and does not react with sulfur or selenium. Alkylation takes place at the nitrogen atom adjacent to phosphorus. With diethylamine and alcohols no reaction is observed <86CB3213, 87PS(30)780>. On simultaneous oxidation by sulfur or selenium, however, alcohols add to the $\text{P}=\text{N}$ bond yielding 1,2-dihydropentalene 2-sulfides or 2-selenides (**100**) <86PS(28)71>. Azodicarboxylic esters, $R = \text{Et}, \text{Pr}^i$, and 2,4-di(*t*-butyl)benzoquinone undergo a double [4 + 1] cycloaddition to the phosphorus atom resulting in zwitterionic products with six-coordinate <87PS(30)780> phosphorus (Scheme 34).

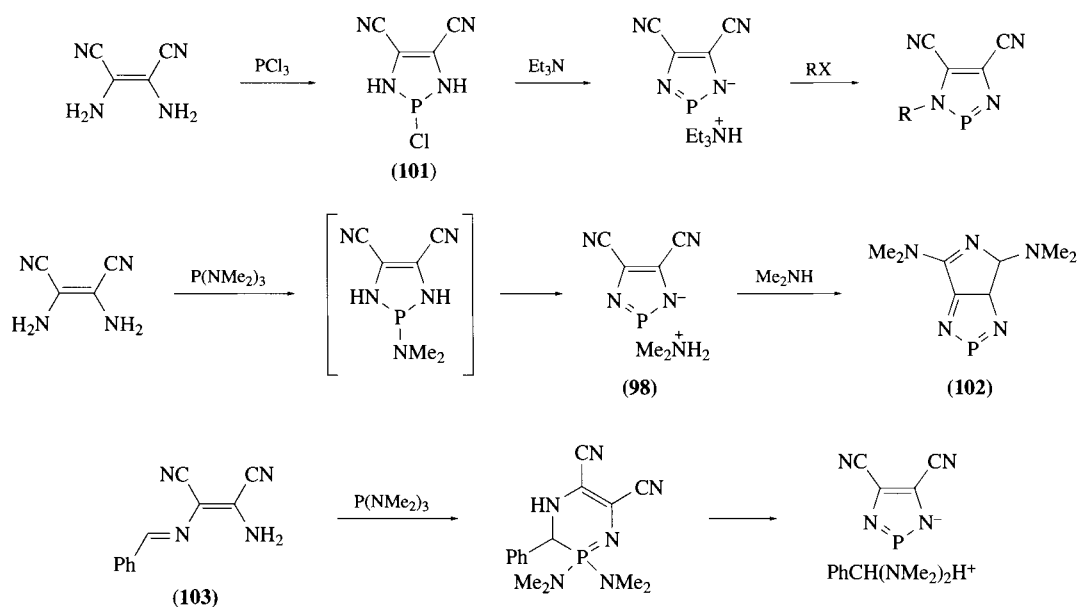
4.22.6.2 Syntheses

Diaminomaleodinitrile and PCl_3 in refluxing acetonitrile yield a cyclic chlorophosphine (**101**) which gives the diazaphospholes by treating with a tertiary base and then with an alkylating agent, $R = \text{Me}, \text{Et}, \text{CH}_2\text{C}_2\text{H}_5, \text{CH}_2\text{Ph}, \text{CH}_2\text{COPh}, \text{CH}_2\text{CO}_2\text{Et}$ <83TL2137, 86CB410>. Condensation of the diaminomaleodinitrile with $\text{P}(\text{NMe}_2)_3$ gives a product which is not the cyclic aminophosphine but already the isomeric dimethylammonium diazaphospholate (**94**) <81ZN(B)1273, 83TL2137>. Further heating converts it to the 4,6-bis(dimethylamino)-1,3,5-triaza-2-phosphapentalene (**102**) (Scheme 35) (molecular structure in Table 2). Other secondary amines react analogously <86CB3213>. The benzaldehyde derivative of DAMN (**103**) may also be used for condensation <84CC183>.

The transamination product of sarcosine nitrile and $\text{P}(\text{NMe}_2)_3$ rearranges to a cyclic aminophosphine (**104**) which on thermolysis ($120^\circ\text{C}/20 \text{ mbar}$) yields the diazaphosphole (**105**) <86PS(28)71>. Condensation of a 1,2-diiminoethane ($R = \text{cyclohexyl}$) with PCl_3 yields a 2,4-dichlorodihydro-1,3,2-diazaphosphole (**106**) <88DOK(298)369> which is converted to the 1,3,2-diazaphospholium ion (**107**)



Scheme 34



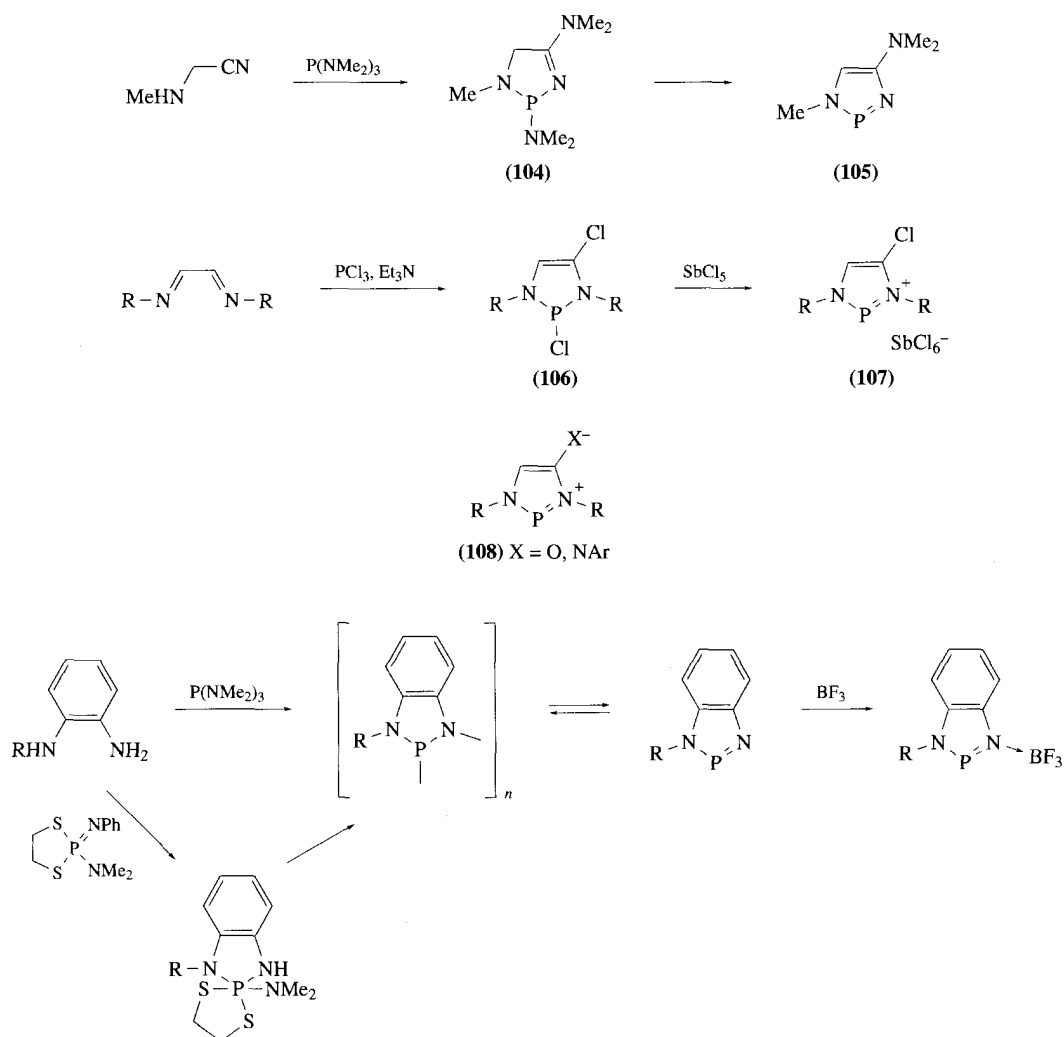
Scheme 35

by antimony pentachloride <90DOK(312)623>. The 4-unsubstituted compound analogous to (106) R = *t*-butyl is prepared via the corresponding dichlorosilane and is found to be ionic in solution and in the solid state.

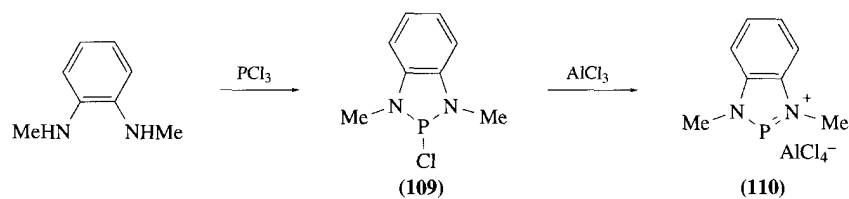
Mesoionic 1,3,2-diazaphospholium-4-olates (108) (X = O, NR) have been considered <96PS(111)197>.

1,3,2-Benzodiazaphospholes from the condensation of *o*-phenylenediamines, R = H, alkyl, Ph with P(NMe₂)₃, prove to be tetrameric or polymeric. They monomerize, however, on heating or as BF₃⁻ or AlCl₃-complexes <79TL447, 84CJC43, 93PS(75)245, 93T4651>. One representative (R = CH₂Ph) has been prepared using an iminodithiophosphate for condensation by a subsequent reductive elimination of disulfide (Scheme 36) <80TL1307>.

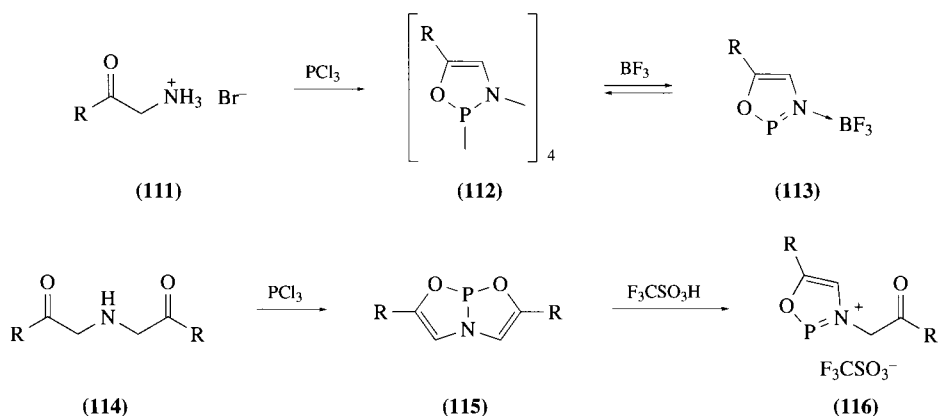
4,5-Diaminopyrimidine is reported to react with triphenylphosphite to give 1,3,2-diazaphospholo[1,5-*d*]pyrimidine. Formation of 1,3,2-diazaphospholopyridines from diaminopyridines under similar conditions is also claimed <79MI 422-01>. In both cases, however, the physical properties of the isolated materials are in accord with oligomers rather than with monomeric azaphospholes.



The 1,3-dimethyl-1,3,2-benzodiazaphospholium cation (**110**) (molecular structure in Table 3) can be prepared as tetrachloroaluminate <89AX(C)1485> from the 2-chloro-1,3-dimethyl-2,3-dihydro-1*H*-1,3,2-diazaphosphole (**109**); the latter is obtained from the condensation of PCl_3 with *N,N*-dimethyl *o*-phenylene diamine <81JCS(P2)1411>. PCl_3 condensation of a 2-aminoketone hydrobromide (**111**) yields the tetramer of a 1,3,2-oxazaphosphole (**112**) <81ZOB475, 84ZOB271>. Boiling with Et_2OBF_3 in benzene gives a complex of the monomer with the boron trifluoride (**113**) most probably coordinated to the nitrogen. Starting from a diketo amine (**114**) ($\text{R} = \text{Bu}^t$), a bicyclic product (**115**) (with a planar phosphorus coordination) is obtained. Protonation opens one ring and gives a 1,3,2-oxazaphospholium cation (**116**) (Scheme 37) <87JA627>.

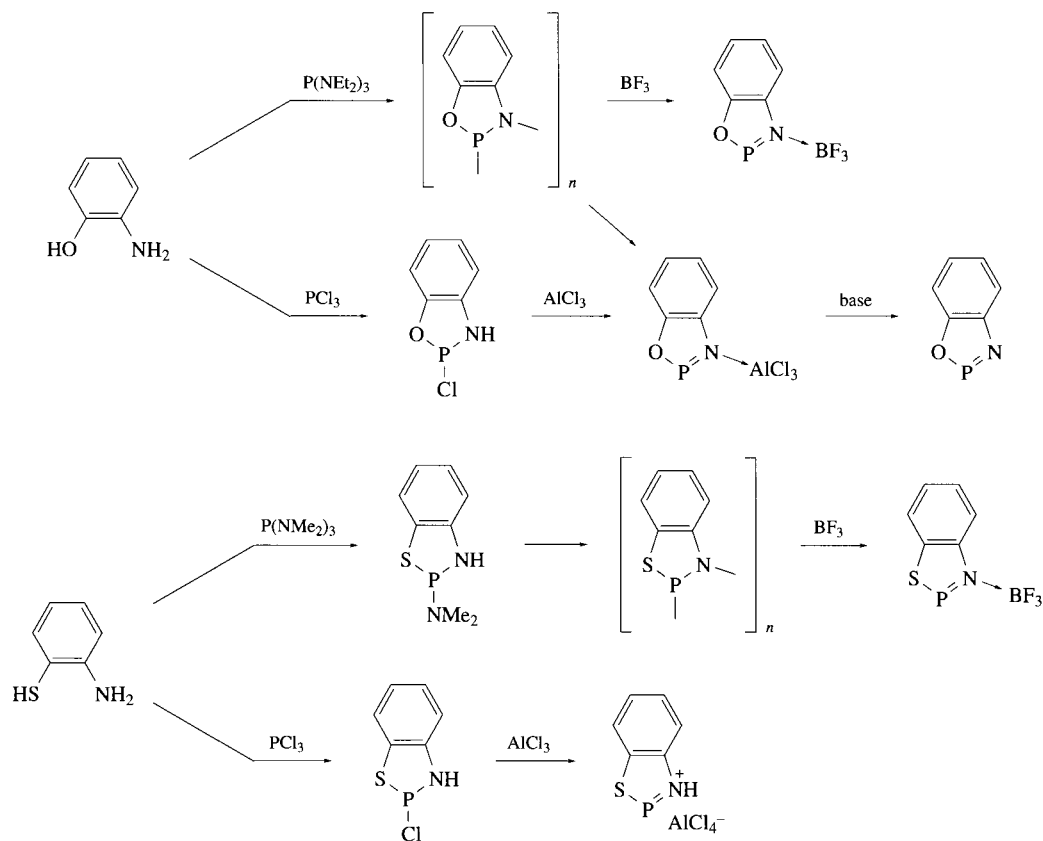


Condensation of *o*-aminophenol and *o*-aminothiophenol with PCl_3 , $\text{P}(\text{NMe}_2)_3$ or $\text{P}(\text{NEt}_2)_3$ gives covalent hydrochlorides and tetramers, respectively, of 1,3,2-benzoxazaphosphole and 1,3,2-benzothiazaphosphole <B-81MI 422-02>. Action of a Lewis acid converts them in each case to the heterophospholium ion <88CC842, 89IC144, 90IC4938> (molecular structure of the 1,3,2-benzo-



Scheme 37

thiazaphospholium ion in Table 3). Their aromatic character is best shown for the 1,3,2-benzothiazaphospholium ions (Scheme 38) <90OM1085, 92IC3386>. The reported 2,2-dichloro-1,3,2 λ^5 -benzodiazaphospholium, -benzoxazaphospholium, and -benzothiazaphospholium hexachloroantimonates are formally the chlorination products of the aromatic systems <91PS(55)255, 93PS(82)211>. 1,3,2 λ^5 -benzoxazaphospholes are dimeric. They have been prepared by quite a number of different routes <B-87MI 422-02>.

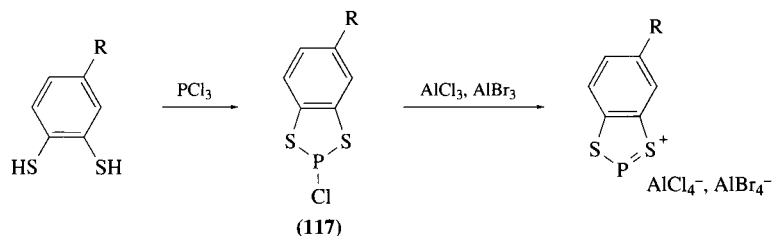


Scheme 38

4.22.7 1,3,2-DITHIA- AND 1,3,2-DISELENAPHOSPHOLIUM SALTS (L)

Only benzo derivatives of 1,3,2-dithia- and 1,3,2-diselenaphospholium salts (L) compounds are known. They are covered in a review on anellated heterophospholes <94T7675>. The method used

for the generation of 1,3,2-benzodiaza- and -thiazaphospholium cations has been extended to benzodithiaphospholium cations <88CC842, 89IC144, 89PS(41)37> (molecular structure in Table 3). Starting compounds are the 2-chloro-1,3,2-benzodithiaphospholes (**117**), which are obtained from the condensation of *o*-phenylenedithiols with PCl_3 (Scheme 39) <73ZN(B)363>.



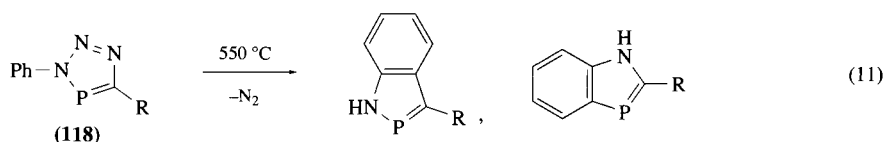
Scheme 39

The Lewis acidity of the cation towards pyridine has been determined using $\delta^{13}\text{C}$ of C-4 in the pyridine ring as a probe for the complexation equilibrium <92HAC157>. The 1,3,2-benzodiselenophospholium ion has been mentioned as an unpublished result <90IC4938>. 2,2-Dichloro-1,3,2 λ^5 -benzodioxaphospholium and -benzodithiaphospholium hexachloroantimonates have been described <78JCS(D)1465, 90ZAAC(585)197, 93PS(82)211>.

4.22.8 1,2,3,4-TRIAZAPHOSPHOLES (N, O) AND TETRAZAPHOSPHOLIUM SALTS (S)

4.22.8.1 Reactivity

The 1,2,3,4-triazaphospholes are colorless distillable liquids or crystalline solids <84CC1634, 86JOM(306)39, 87T3247, 88TL785>. The hydrolysis of 2-trimethylsilyl-5-*t*-butyl-1,2,3,4-triazaphosphole gives the corresponding NH compound. The flash vacuum pyrolysis of the 3-phenyl (**118**) and 3-naphthyl derivatives <87T3247, 89PS(46)31> leads to a mixture of 1,2- and 1,3-benzazaphospholes ($\text{R} = \text{Me}, \text{Bu}^t$) as the major and minor reaction products (Equation (11)) (see chapters 3.15 and 3.16).



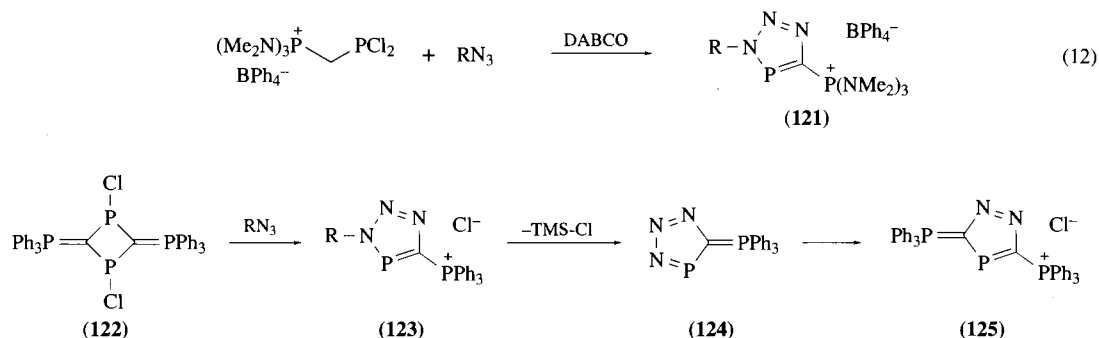
4.22.8.2 Synthesis

The 1,2,3,4-triazaphosphole ring may be generated from the combination of $\text{PC} + \text{NNN}$ or of $\text{PN} + \text{CNN}$ fragments. According to the first pattern the regiospecific cycloaddition of phosphalkynes, $\text{R}^1\text{-C}\equiv\text{P}$, $\text{R}^1 = \text{H}$, neopentyl, secondary and tertiary alkyl, Mes <86JOM(306)39, 86S31, 87T3247, 88AG1541>, or Me, if prepared *in situ* <89PS(46)31> and of phosphalkenes $\text{R}^1(\text{Me}_3\text{Si})\text{C}=\text{P}\text{Cl}$, $\text{R}^1 = \text{Me}$, Pr^n , *n*-pentyl, allyl, PhCH_2 <92HAC337>, Ph <88TL785>, SiMe_3 <84CC1640, 92HAC337>, to azides ($\text{R} = \text{H}$ and a wide variety of substituents) gives 3*H*-1,2,3,4-triazaphospholes (**119**). In the case of $\text{R} = \text{H}$ <88AG1541> and SiMe_3 <87T3247> they rearrange to give the 2*H*-isomers (**120**). The synthesis from phosphalkenes $\text{R}^1(\text{Me}_3\text{SiO})\text{C}=\text{PSiMe}_3$ is not successful here <85ZN(B)1077>.



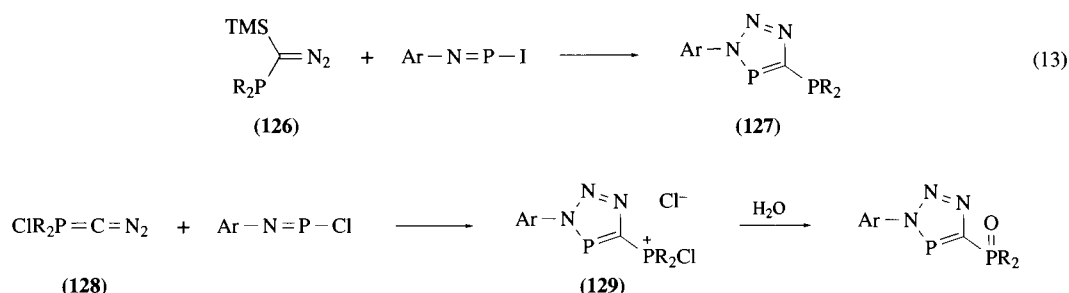
A 5-phosphonio-substituted 1,2,3,4-triazaphosphole (**121**) results from a dichlorophosphinomethyl-phosphonium salt, an excess of DABCO and mesityl azide. The 2-phosphonio-1-

phosphaethyne is suggested to be the key intermediate <91CC302>. From bis(triphenylphosphorane-diyl)-dichloro-1,3-diphosphetane (**122**) and phenyl or trimethylsilyl azide, 5-phosphonio-1,2,3,4-triazaphospholes (**123**) are obtained. In the case of $R = \text{Me}_3\text{Si}$, the product loses trimethylchlorosilane and gives the triphenylphosphorane-diyl-1,2,3,4-triazaphosphole (**124**) (or triphenylphosphonio-1,2,3,4-triazaphospholide) which finally converts to a 1,2,4-diazaphosphole (**125**) (see Section 4.22.3.2) <96TH 422-01>.



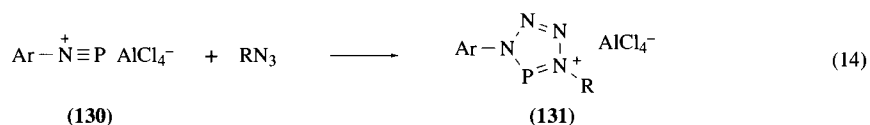
Scheme 40

According to the PN + CNN pattern, the reaction of a phosphino diazomethane (**126**) ($R = \text{dicyclohexylamino}$) and a *P*-iodo iminophosphine <94BSF748> and also the reaction of a phosphorane-diyl diazomethane (**128**) ($R = \text{Pr}^t_2\text{N}$) and a *P*-chloro iminophosphine <93BSF757> give the corresponding phosphino and phosphonio 1,2,3,4-triazaphospholes (**127**) and (**129**) ($\text{Ar} = 2,4,5\text{-Bu}^t_3\text{C}_6\text{H}_2$), respectively. The chlorophosphonio substituent in the second case is converted to a phosphoryl substituent by hydrolysis.



Scheme 41

The cycloaddition of an iminophosphonium ion (**130**) ($\text{Ar} = 2,4,6\text{-Bu}^t_3\text{C}_6\text{H}_2$) to azides ($R = \text{Bu}^t$, CEt_3) yields tetrazaphospholium ions (**131**) (Equation (14)) <93CB1513>.



4.22.9 1,2,4,3-TRIAZAPHOSPHOLES (O, P, Q) AND 1,3,4,2-THIADIAZAPHOSPHOLIUM SALTS (R)

1,2,4,3-Triazaphospholes are related to 1,2,4-triazoles by a CH/P exchange and to tetrazoles by a N/P exchange; they have been compared to these analogues with respect to their electronic structure and NMR spectra <89JCR(S)250>. The 1*H*-, 2*H*- and 4*H*-1,2,4,3-triazaphospholes differ considerably in their behavior. 1,2,4,3- λ^5 -Triazaphospholes, -oxadiazaphospholes and -thiadiazaphospholes are covered in a review on cyclophosphazanes with five- and six-coordinate phosphorus <B-87MI 422-02>.

4.22.9.1 Reactivity of 1,2,4,3-triazaphospholes

The 1,2,4,3-triazaphospholes are colorless or pale yellow distillable liquids or crystalline solids <76T2039, 80ZN(B)1222>. They are not oxidized by air and are reluctant to react with sulfur. The flash thermolysis of two 1,2,4,3-triazaphospholes has been investigated <90PS(49/50)363>.

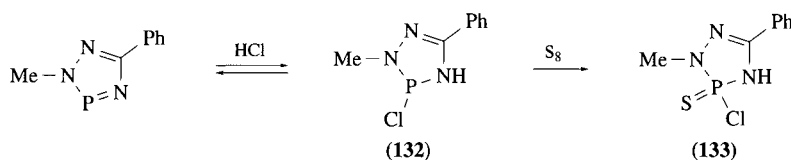
4.22.9.1.1 Reaction at a nitrogen ring member

The *N*-unsubstituted 5-dimethylamino-1,2,4,3-triazaphosphole is converted to its anion by sodium, potassium, or their hydrides <80ZN(B)1222>. Boryl <86PS(28)71>, silyl <80ZN(B)1222>, stannyl, phosphino, and (thio)phosphinyl <80ZN(B)1222> derivatives have been prepared mostly by reaction of the triazaphosphole with the corresponding chloride; the substituents become attached to N-2.

1*H*- and 2*H*-1,2,4,3-triazaphospholes are not alkylated by methyl iodide and not protonated by acetic or trichloroacetic acid; they are, however, decomposed by trifluoroacetic acid <74CR(C)355, 76T2039>. They are protonated by triflic or tetrafluoroboric acid and methylated by methyl triflate or trimethyloxonium tetrafluoroborate at N-4 <91TL501, 92MI 422-01>. Boron trifluoride coordinates to the same nitrogen <76T2039, 87TL6049, 89JCR(S)250>; in a 4*H*-1,2,4,3-triazaphosphole it coordinates to N-2. The molecular structure of the BF₃-complex of an example of each of the three isomeric 1,2,4,3-triazaphospholes is shown in Table 4.

4.22.9.1.2 Addition to the P=N bond

Hydrogen chloride adds to the P=N bond to give 3-chloro-dihydro-1,2,4,3-triazaphospholes (132) which may be converted to the thiochloride (133) (Scheme 42) <94HAC385>.



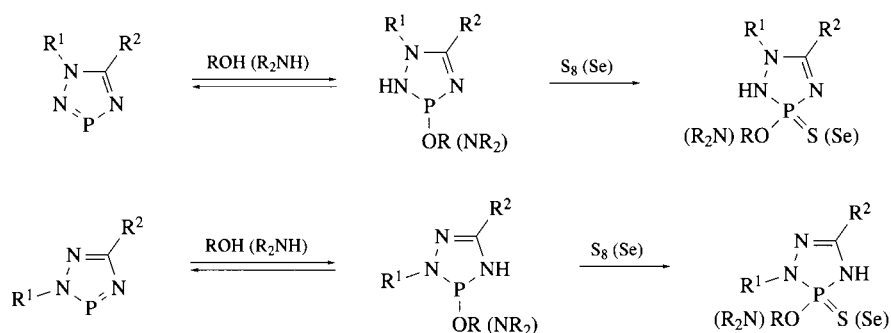
Scheme 42

The tendency of the three 1,2,4,3-triazaphosphole isomers to give 1,2-additions is quite different and decreases in the order 4*H* > 2*H* > 1*H*. Thus the 2*H*-isomers readily add water <84PS(20)333>, alcohols and phenols <74CR(C)355, 76T2039, 84PS(20)333>, or amines <74CR(C)355, 76T2039, 84CC183, 87TL6049> and yield 3,4-dihydrotriazaphospholes. An excess of water or alcohol degrades them to the amidrazone and H₃PO₃ or P(OR)₃, respectively <84PS(20)333>. In contrast, the 1*H*-isomers are reported not to react with alcohols or amines <76T2039>. In fact, however, they give a balanced equilibrium with alcohols and are degraded to P(OR)₃ by an excess <92MI 422-01>.

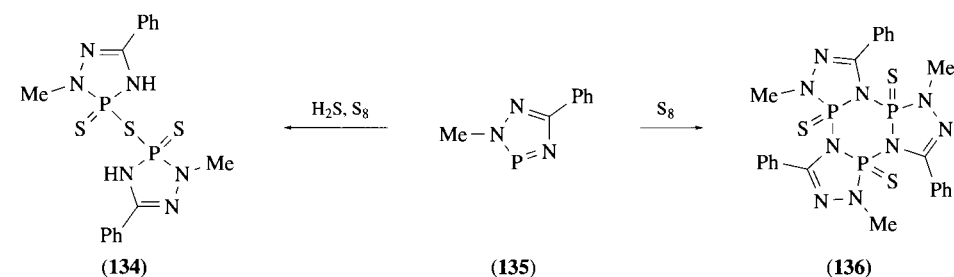
The said tendency also holds for the oligomerization: 1*H*-1,2,4,3-triazaphospholes are monomeric and the 2*H*-isomers are so too, although for some of them (mainly with RO or RS as 5-substituents) tetramers (or other oligomers) are reported to exist in a temperature controlled equilibrium with the monomers <87TL6049, B-90MI 422-01, 91CC23, 93CJC1200>. Finally, 4*H*-1,2,4,3-triazaphospholes are not known at all as such, but only in the form of their 2,3-dihydro derivatives, i.e. their tetramers and adducts (see Section 4.22.9.3).

Regardless of the differences in the addition equilibria, the combined action of an alcohol, ammonia or an amine and of sulfur or selenium on 1*H*- or 2*H*-1,2,4,3-triazaphospholes gives the dihydro-triazaphosphole-3-chalcogenides <92MI 422-01, 93CJC1200, 94HAC385>. This applies also to [1,5]-anellated 1,2,4,3-triazaphospholes (Scheme 43) <92MI 422-01, 94PS(93/94)381, 95ZN(B)558>. Hydrogen sulfide and sulfur together react with 2-methyl-5-phenyl-1,2,4,3-triazaphosphole (135) to give the dihydro triazaphosphole sesquisulfide (134). Sulfur alone gives in a slow reaction the trimeric triazaphosphole sulfide (136) <94HAC385, 94PS(93/94)383>. Grignard reagents add to the P=N bond

as well. Protonation or alkylation of the resulting anion yields 3,4-dihydro-triazaphospholes <84PS(20)333>.



Scheme 43

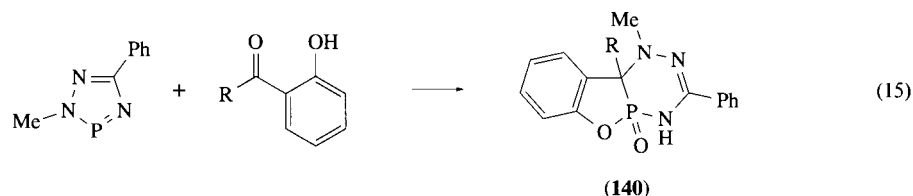


Scheme 44

Some further reactions with difunctional partners obviously involve the addition of the protic part to the P=N bond as the initial step. The reaction of 2H-triazaphospholes with glycols <74CR(C)355, 76T2039, 84CC183, 87TL6049> gives hydridospirophosphorane (137). Another example of this type provides the 2:1 condensation products from N³-amidrazones and P(NMe₂)₃ mentioned in Section 4.22.9.3.

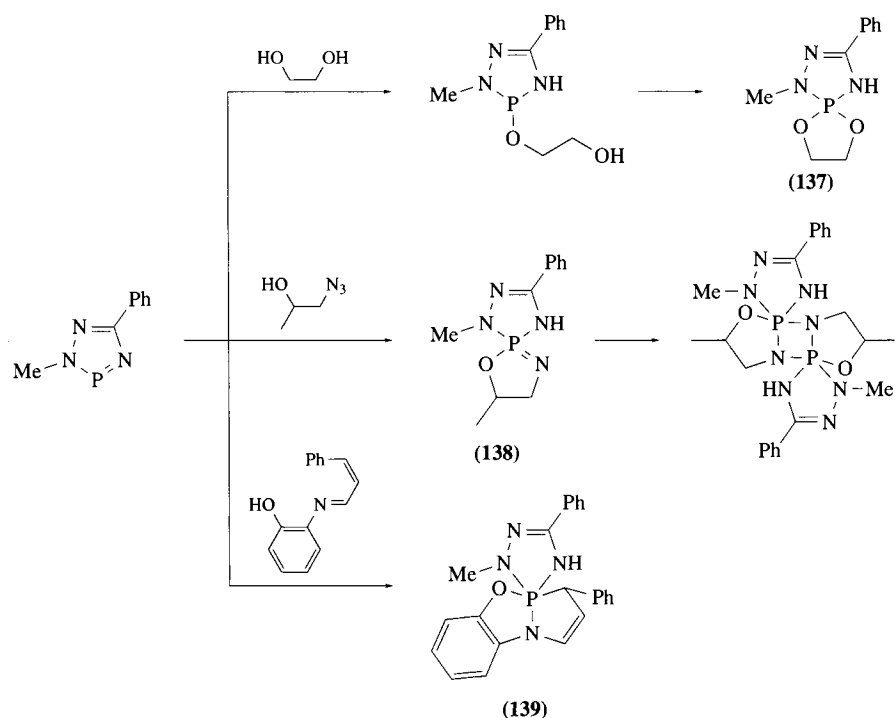
The spirocyclic phosphazenes (138) resulting from the reaction with 2-azidoalcohols dimerize <82TL853>. In the adducts of phenols with a heterodiene function in the 2-position <77ZN(B)841> the phosphorus atom also becomes the center of a tricyclic system (139) (Scheme 45).

In the reaction with 2-hydroxy derivatives of benzaldehyde, acetophenone, and benzophenone, the phenol group adds to the P=N bond, the carbon atom of the carbonyl group inserts into the P-NMe bond, and the phosphorus atom becomes oxidized to give (140) (Equation (15)) <96CB>.



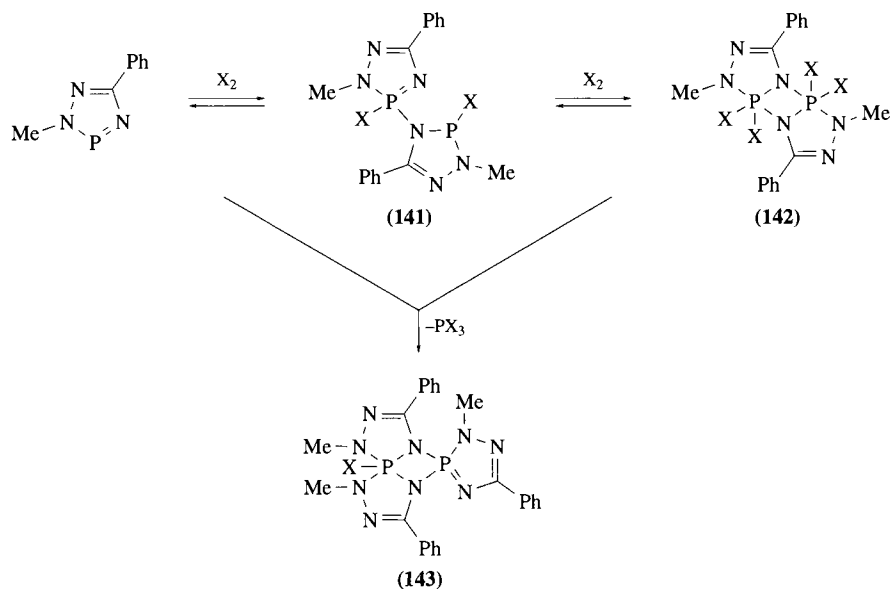
4.22.9.1.3 Oxidative addition to the phosphorus ring member

On chlorination or bromination of 2H-1,2,4,3-triazaphospholes, a 1,1-addition of the halogen to the phosphorus atom takes place, accompanied by a dimerization <77AG554, 81ZAAC(475)211>. The dichloride can also be obtained directly from the amidrazone and PCl₅ (see Section 4.22.9.3), and can be converted to the difluoride by SbF₃ <81IC1222, 81ZAAC(475)211>. With half a mole of bromine <86PS(28)71>, or if the triazaphosphole is reacted with its dibromide <83IC3696>, a dimer (141) with



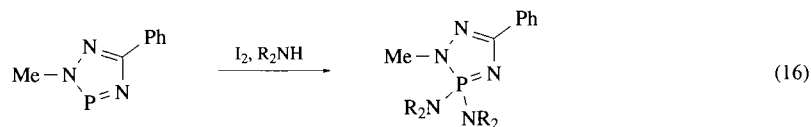
Scheme 45

mixed phosphorus oxidation states is formed. An equimolar mixture of the triazaphosphole and the dimer of its dihalide (**142**) slowly loses phosphorus trihalide and results in a product (**143**) in which three triazaphosphole rings are fused (82IC3916). Even more complex polycyclic triazaphospholes are formed from such mixtures ($\text{X} = \text{Cl}, \text{Br}$) (Scheme 46) (B-87MI 422-02).



Scheme 46

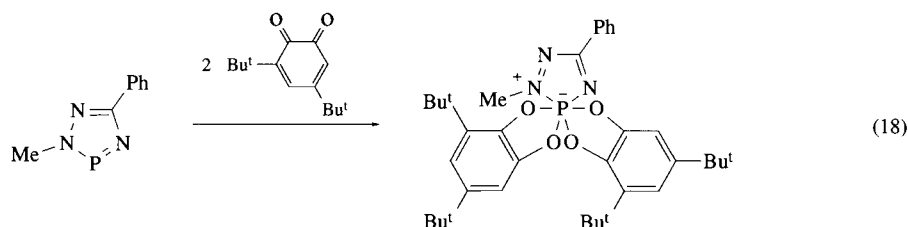
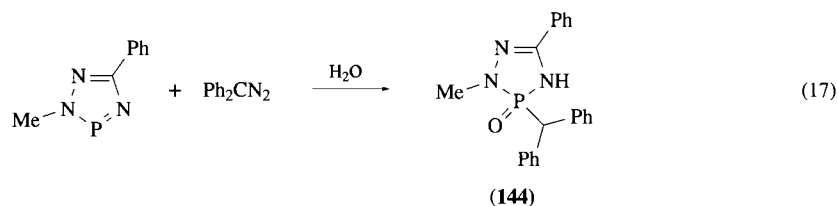
2H-1,2,4,3-Triazaphospholes do not react with iodine alone but yield the 3,3-diamino-1,2,4,3 λ^5 -triazaphospholes on the combined action of iodine and a primary or secondary amine (Equation (16)) (91PS(56)17, 92MI 422-01).



4.22.9.1.4 Cycloaddition reaction

2*H*-1,2,4,3-Triazaphospholes are reported not to react with phenyl azide, phenyl benzoyl-diazomethane, maleic acid anhydride, and tetracyanoethylene <76T2039>. From the [4 + 2] cycloaddition with electron-poor acetylenes, 1,2,3-diazaphospholes are obtained (see Section 4.22.5.2). [2 + 3] Cycloaddition of 2-methyl-5-phenyltriaazaphosphole with diphenyl-diazomethane yields, after hydrolysis, the 3,4-dihydrotriaazaphosphole-3-oxide (**144**), presumably via the *P*-ylide as an intermediate <86PS(26)203>. With α -diimines, $\text{R} = \text{Pr}^n$, Ph [4 + 1] cycloadducts are formed <86TL2971, 87TL6049, 93CJC1200>, which are similar in structure and bonding to the products of a 2 : 1 reaction of amidrazone hydrochloride and phosphorus pentachloride (see Section 4.22.9.2) <83CB1468, 91PS(56)17>. A comparable spirocyclic derivative results from the addition of 1,2-diaminopyridines under simultaneous oxidation <93JPR458>. The [4 + 1] cycloadducts with azodicarboxylic esters, $\text{R} = \text{Me}$, Et, Pr^i , CH_2Ph , <81CB825> and 1,2-diketones, $\text{R} = \text{Me}$, Ph, <84TL5521> are dimeric (Scheme 47).

The double [4 + 1] cycloaddition with tetrachloro- and 3,5-di(*t*-butyl)-*o*-benzoquinone results in zwitterionic products with six-coordinate phosphorus (Equation (18)) <84TL5521>.

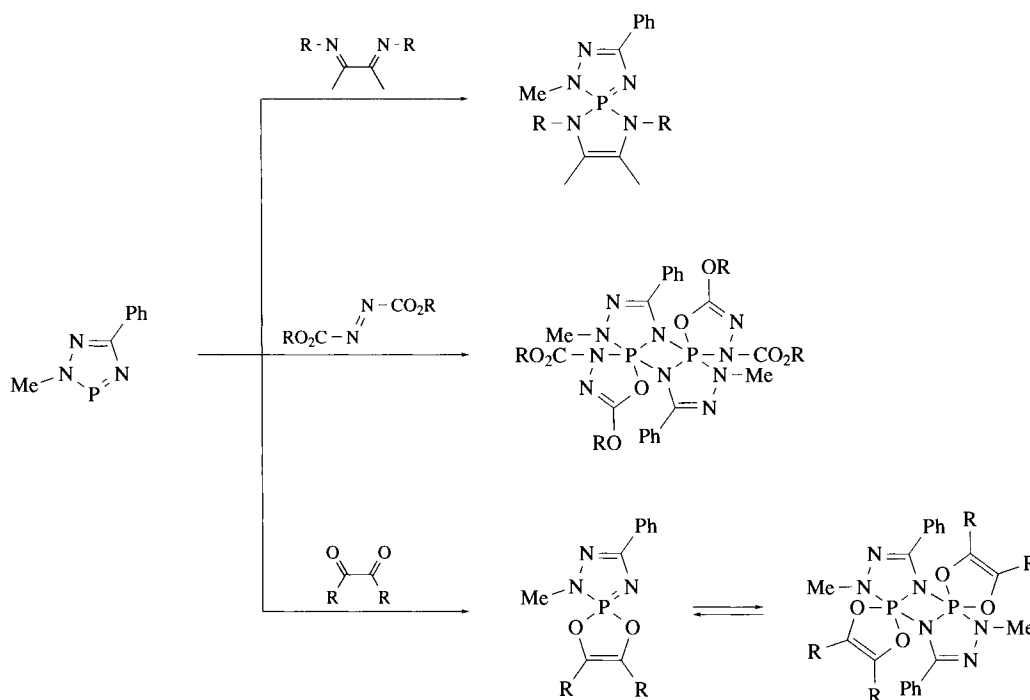


4.22.9.1.5 Formation of transition metal complexes

Triazaphospholes and Cu^I , Hg^{II} , and Cd^{II} salts yield solid products <76T2039>. *P*-Coordinated complexes of 2-methyl-5-phenyl- and 1,5-dimethyl-triazaphosphole with $\text{Cr}(\text{CO})_5$ and $\text{Mo}(\text{CO})_5$ <80JOM(185)53> and of the latter with $\text{Pt}(\text{PPh}_3)_3$ <83JOM(256)375> have been prepared. The molecular structure of this complex is shown in Table 4. With $\text{PtCl}_2(\text{PEt}_3)$ only the *trans*-N-4- is obtained, with $\text{PtBr}_2(\text{PEt}_3)$ both the *cis*-*P*- and the *trans*-N-4-coordinated complexes are obtained <84ICA33, 88IC2612>. A *cis*-N-2 or -N-4 coordinated complex of 1,5-dimethyltriaazaphosphole with Me_2AuCl and a poorly soluble 1 : 1 complex with ClAuCO have also been reported <80ICA167>. *P*-Coordination of the transition metal may induce an addition to the $\text{P}=\text{N}$ bond <81AG420, 84ICA33, 88IC2612>.

4.22.9.2 Reactivity of 1,3,4,2-Thiadiazaphospholium Ions

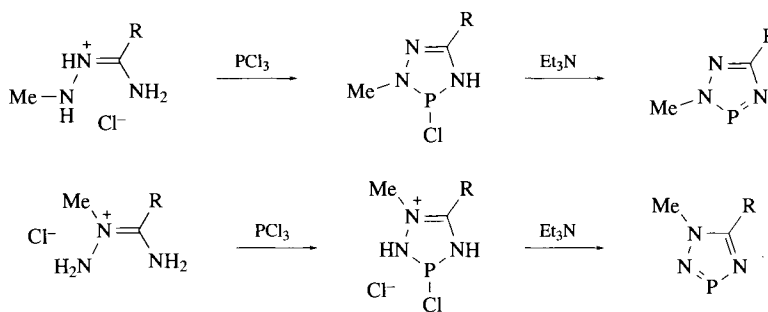
The phosphorus ring member has phosphenium character. It adds tetrachloro *ortho*-quinone and 2,3-butanedione and it also reacts with dimethylaniline and anisole in a *para*-substitution <93PS(76)79>.



Scheme 47

4.22.9.3 Synthesis

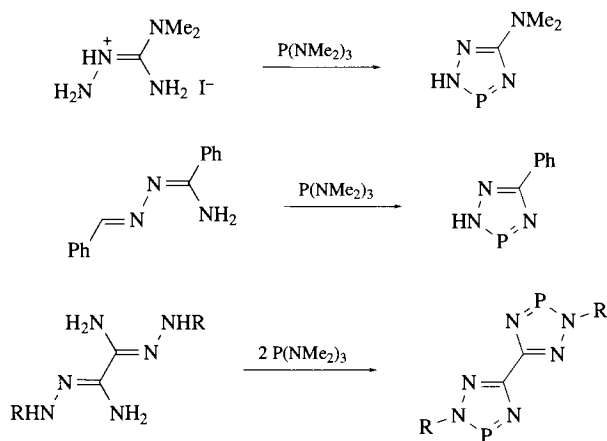
1,2,4,3-Triazaphospholes are always synthesized by condensation reactions. The first examples were obtained according to the pattern $\text{PNC} + \text{NN}$, most of them according to $\text{NCNN} + \text{P}$ from amidrazones or their heterocyclic equivalents and a phosphorus(III) partner such as PCl_3 or $\text{P}(\text{NMe}_2)_3$ or a phosphorus(V) partner and subsequent reduction. PCl_3 condensation of N^1 - and N^2 -methylamidrazones gives 2- and 1-methyl-1,2,4,3-triazaphospholes ($\text{R} = \text{Me}, \text{Ph}$). The first step is achieved in refluxing benzene, the second with the help of NEt_3 [86PS(28)71] (Scheme 48).



Scheme 48

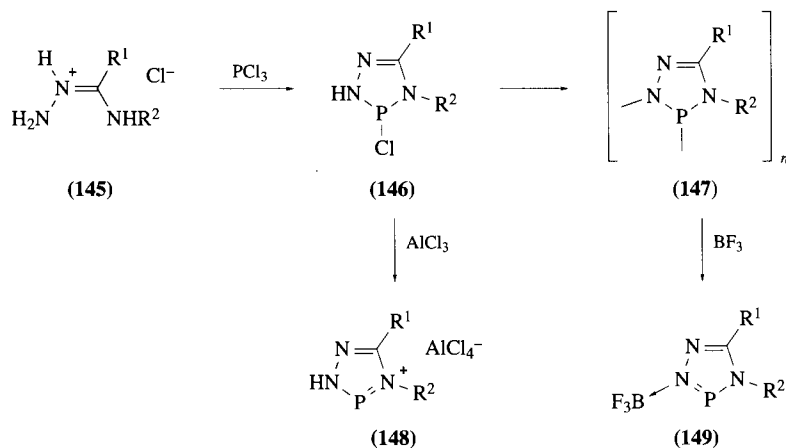
By condensation of an amidrazone hydrochloride or hydroiodide or an amidrazone benzaldehyde derivative with $\text{P}(\text{NMe}_2)_3$, N -unsubstituted as well as 1- and 2-substituted triazaphospholes are obtained [74CR(C)355, 76T2039, 80ZN(B)1222, 84CC183, 92PS(69)189]. 5,5'-Bis(1,2,4,3-triazaphospholyl)s have also been obtained this way [87TL6049] (Scheme 49).

4*H*-1,2,4,3-Triazaphospholes (**146**) are obtained from N^3 -substituted amidrazones (**145**) by reaction with PCl_3 , $\text{R}^1/\text{R}^2 = \text{Ph}/\text{Me}$ [86TL2971], Ph/Ph [92MI 422-01], or with tris(dimethylamino)phosphine, $\text{R}^1 = \text{Me}, \text{Pr}^i, \text{CH}_2\text{Ph}, \text{Ph}$; $\text{R}^2 = \text{Me}, \text{Pr}^i, \text{Bu}^s, \text{neopentyl}, \text{CH}_2\text{Ph}, \text{Ph}$ [92JCS(P2)671]. They are oligomeric (**147**) (however, see Section 4.22.2.2) and no monomeric representative has yet been prepared [80ZN(B)1222, 84CC183, 92JCS(P2)671]. Primary products of the reaction of N^3 -substituted amidrazones with PCl_3 are the 3-chloro-dihydro-1,2,4,3-triazaphospholes (**146**) which are converted to the 1,2,4,3-triazaphospholium tetrachloroaluminates (**148**) by aluminum trichloride [92MI 422-

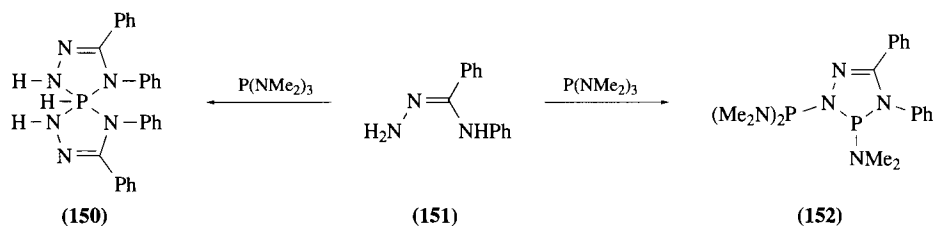


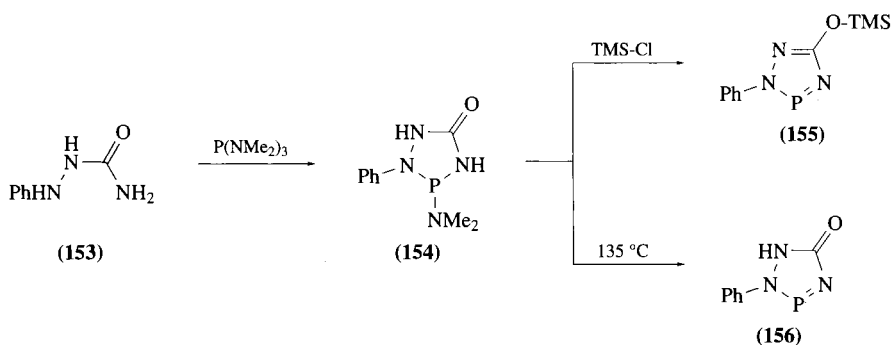
Scheme 49

01). The molecular structure of a 4,5-disubstituted 1,2,4,3-triazaphosphole tetramer has been elucidated by x-ray analysis (92JCS(P2)671). Treating the tetramers with BF_3OEt_2 or AlCl_3 affords the 2- BF_3 (149) or 2- AlCl_3 complexes of the monomers (86TL2971, 92JCS(P2)671, 92MI 422-01) (molecular structure of a BF_3 complex, $\text{R}^1 = \text{R}^2 = \text{Pr}^i$, in Table 4).

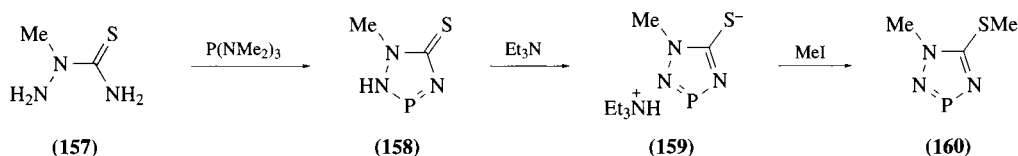


Spirocyclic (150) and phosphino substituted dihydro-1,2,4,3-triazaphospholes (152) result from the reaction of N^3 -substituted amidrazones and $\text{P}(\text{NMe}_2)_3$ in a 2 : 1 and 1 : 2 molar ratio (80ZN(B)1222, 92JCS(P2)671, 92MI 422-01). The semicarbazide (153) reacts with $\text{P}(\text{NMe}_2)_3$ in boiling acetonitrile to give the 3-dimethylamino-5-oxo-1,2,4,3-triazaphospholane (154). It is converted by trimethylchlorosilane to the 5-trimethylsiloxy-triazaphosphole (155) which exists in a temperature-controlled equilibrium with its tetramer. At higher temperatures the condensation affords the 5-oxo-dihydro-1,2,4,3-triazaphosphole (156) (91CC23). The 5-thioxo-dihydro-1,2,3,4-triazaphosphole (158) is obtained from the thiosemicarbazide (157) in the same way; (158) PBr_3 gives the hydrobromide. With an amine they both give the respective ammonium 1,2,4,3-triazaphosphole-5-thiolate (159) which is readily methylated to the 1-methyl-5-methylthio-1,2,4,3-triazaphosphole (160) (91CC23, 93CJC1200).

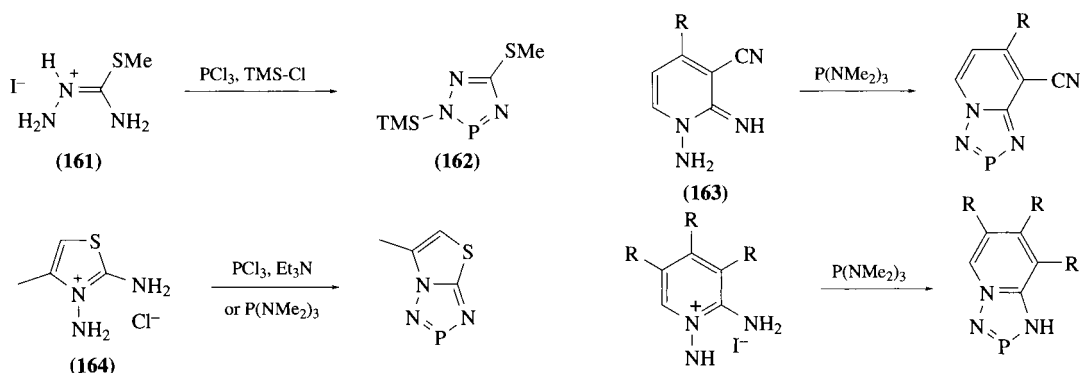




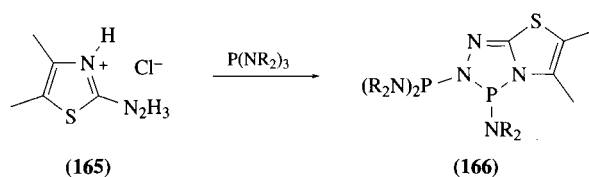
Scheme 50

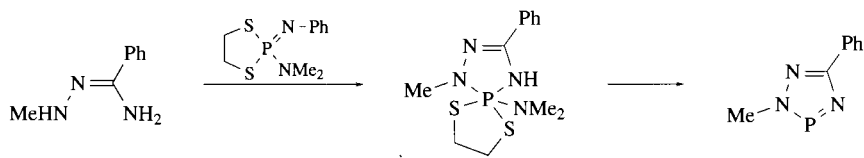


The *N*-unsubstituted *S*-methylthiosemicarbazide hydroiodide (**161**) affords the 2-trimethylsilyl-5-methylthio-1,2,4,3-triazaphosphole (**162**) from its reaction with PCl_3 and Me_3SiCl <B-90MI 422-01> or with $P(NMe_2)_3$ and $(Me_3Si)_2NH$ <93CJC1200>. The *N*¹-phenyl-, *N*²-methyl-, *N*³-methyl- and *N*³-ethyl-substituted *S*-methylthiosemicarbazide hydroiodides have also been used for condensation with $P(NMe_2)_3$. The results correspond to those obtained with other amidrazones <93CJC1200>. [1,5]Anellated 1,2,4,3-triazaphospholes are also prepared by condensation with PCl_3 or $P(NMe_2)_3$ <95S361>. Examples involve 1-amino-2-iminopyridines (**163**) <93JPR458> or their hydroiodides, i.e. 1,2-diaminopyridinium iodides $R = H, Me$ <94PS(93/94)381, 95ZN(B)558> and 2,3-diaminothiazolium chloride (**164**) <93JPR458>.



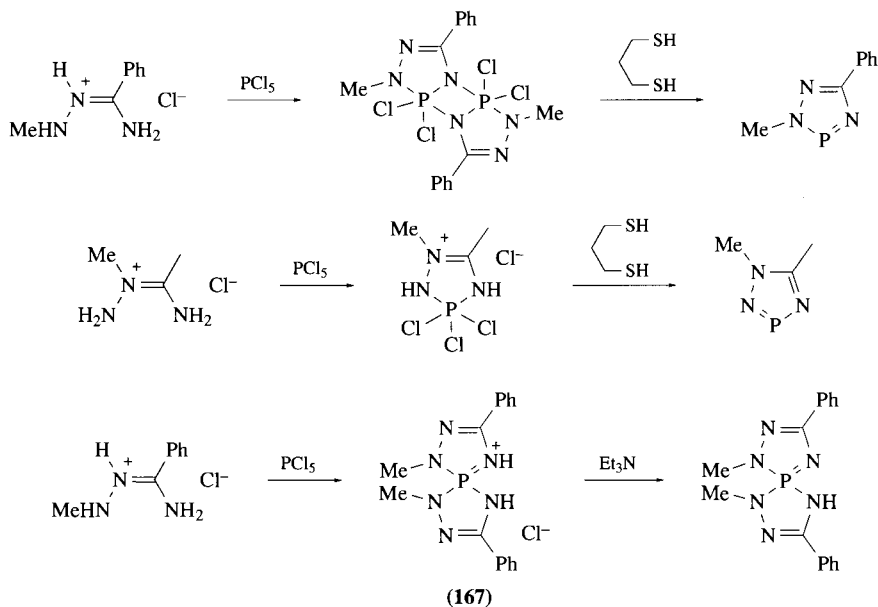
[4,5]Anellated 1,2,4,3-triazaphospholes (which are of 4*H*-type) cannot be obtained this way, however. The condensation of a 2-hydrazinobenzothiazole (**165**) <90PS(47)173> or of the 2-hydrazinobenzothiazole <85S1067> with tris(dialkylamino)phosphines lead instead to dihydro derivatives (**166**). Similar to 1,3,2-benzodiazaphospholes (Section 4.22.6.2), 1,2,4,3-triazaphospholes can be prepared *via* a pentavalent phosphorus compound which eliminates a disulfide (Scheme 51) <80TL1307>.





Scheme 51

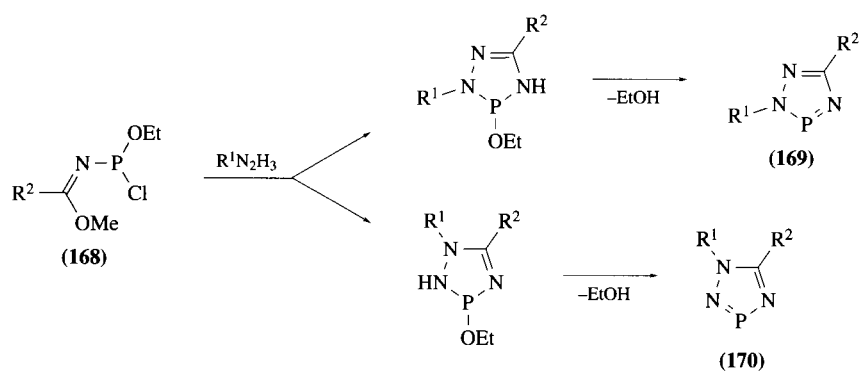
The equimolar condensation of N^1 - and N^2 -methylamidrazones with phosphorus pentachloride yields dimers and hydrochlorides of 3,3-dichloro-1,2,4,3 λ^5 -triazaphospholes (Scheme 52) <77AG554, 811C1222, 81ZAAC(475)211>. The former also result from the chlorination of the triazaphospholes (see Section 4.22.9.1) and can be reduced to them again by reaction with propanedithiol <77AG554>. The 2:1 condensation of amidrazones and phosphorus pentachloride gives spirocyclic 1,2,4,3 λ^5 -triazaphospholes (**167**) (see Section 4.22.9.1) (Scheme 52) <83CB1468>.



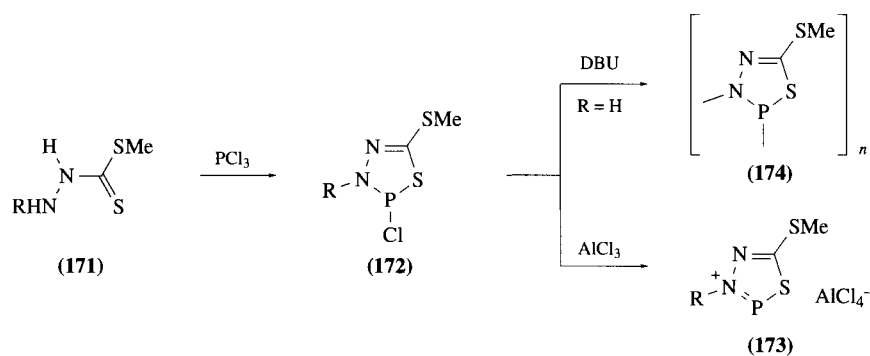
Scheme 52

1,2,4,3-Triazaphospholes, $R^1 = \text{Me, Ph}$; $R^2 = \text{Bu}^t, \text{CH}_2\text{Ph, Ph}$, are also synthesized from imidatochlorophosphines (**168**) by reaction with hydrazines (Scheme 53) <74CR(C)355, 76T2039>. Rather different conditions are necessary to eliminate ethanol from the cyclic ethoxyphosphine intermediates for the different isomers: 1*H*-1,2,4,3-triazaphospholes (**170**) form easily at room temperature, while the 2*H*-isomers (**169**) require 100°C or an OEt/Cl-exchange and subsequent elimination of HCl by base. Methyl esters of dithiocarbamic acids (**171**) and PCl_3 react in boiling benzene to give 2-chlorodihydro-1,3,4,2-thiadiazaphospholes (**172**). Aluminum trichloride abstracts chloride from them and yields the 1,3,4,2-thiadiazaphospholium salts (**173**), $R = \text{H, Ph, Ac}$ (Scheme 54) <93PS(76)79, 94ZOB149, 95PS(104)33>. Elimination of HCl in the case of $R = \text{H}$ does not give the monomeric 1,3,4,2-thiadiazaphosphole but an oligomer thereof (**174**) for which $n = 2$ is suggested (but seems rather doubtful) <95PS(104)33>.

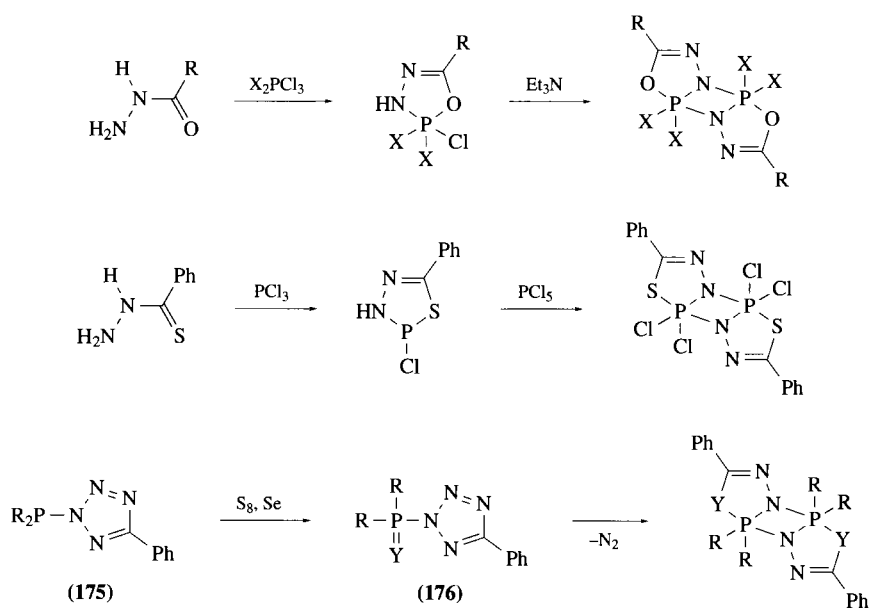
1,3,4,2 λ^5 -Oxadiazaphospholes, 1,3,4,2 λ^5 -thiadiazaphospholes and 1,3,4,2 λ^5 -selenadiazaphospholes are known with a variety of phosphorus substituents X and are in every case dimeric <B-87MI 422-02>. They are prepared starting from carboxylic and thiocarboxylic acid hydrazides (Scheme 55) <69AG707, 75CB820, 77CB1124, 77ZN(B)845, 811C1222, 82PS(14)49>. Alternatively, 2-phosphino-tetrazoles (**175**) are converted to thiophosphinoyl and selenophosphinoyl tetrazoles (**176**) (Scheme 55) ($Y = \text{S, Se}$) and the latter are thermolyzed at 100°C <93ZN(B)93>.



Scheme 53



Scheme 54

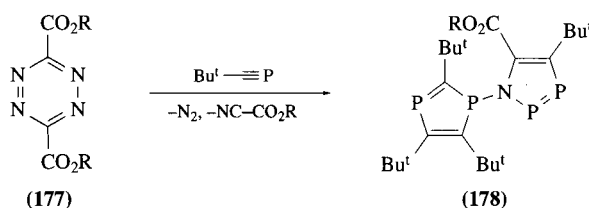


Scheme 55

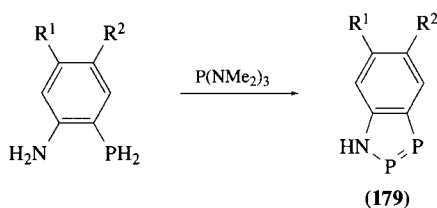
4.22.10 1,2,3-AZA-, 1,2,4-AZA- AND 1,2,3,5-DIAZADIPHOSPHOLES (U, T, X)

4.22.10.1 1,2,3-Azadiphospholes

1,3-Diphospholyl substituted 1,2,3-azadiphospholes (**178**) are formed by reaction of 1,2,4,5-tetrazine-dicarboxylates (**177**) with four moles of *t*-butylphosphaethyne in an unusual reaction sequence <88TL5867>. They are yellow liquids and they readily add hydrogen chloride or methanol to the P=C bond of the diphospholyl substituent to yield pale yellow crystalline products <88TL5867>. The molecular structure with R = Me is given in Table 6. Pyrolysis of crude bis(diisopropylamino)-phosphine yields, among other products, 1-isopropyl-5-methyl-1,2,3-azadiphosphole, a colorless pyrophoric solid <89NJC309>. Its molecular structure is given in Table 6. As compared to acyclic diphosphenes which adopt the *trans* configuration the 1,2,3-azadiphospholes contain a *cis*-diphosphene unit and as a consequence of the cyclic π -conjugation the P=P bond is slightly elongated.

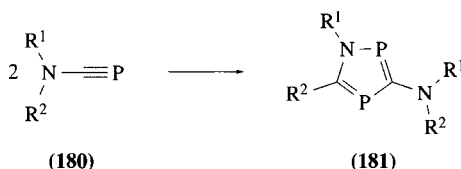


N-Unsubstituted 1,2,3-benzazadiphospholes (**179**) ($\text{R}^1, \text{R}^2 = \text{H, Me, Cl}$) are yellow solids and result from a synthesis analogous to that used for 1,3-benzazaphospholes (chapter 3.16) as yellow solids <90TL4463, 93PS(76)45>. They are converted to the anions by a strong base. 1,3-Dienes such as 2,3-dimethylbutadiene give a [2 + 4] cycloaddition to the P=P bond <90TL4463>.



4.22.10.2 1,2,4-Azadiphospholes

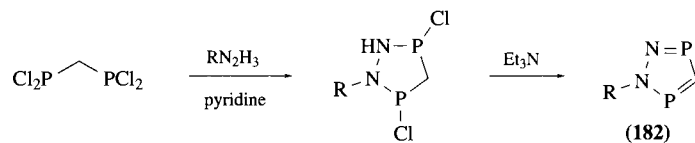
Aminophosphaethynes (**180**), $\text{R}^1/\text{R}^2 = \text{Bu}^t/\text{H}, \text{Bu}^t/\text{SiMe}_3, \text{cyclohexyl}/\text{SiMe}_3$ dimerize in alkaline medium to give 3-amino-1,2,4-azadiphospholes (**181**) <91HAC577, 92HAC435>. The molecular structure for $\text{R}^1 = \text{Bu}^t, \text{R}^2 = \text{H}$ is given in Table 5.



4.22.10.3 1,2,3,5-Diazadiphospholes

1,2,3,5-Diazadiphospholes (**182**) ($\text{R} = \text{Me, Ph}$) are obtained from the condensation of methylene bis(dichlorophosphine) and a hydrazine (Scheme 56) <85AG127>. 1-Phenyl-1,2,3,5-diazadiphosphole is a colorless, air-sensitive liquid. It is not alkylated by methyl iodide or trimethyloxonium tetra-

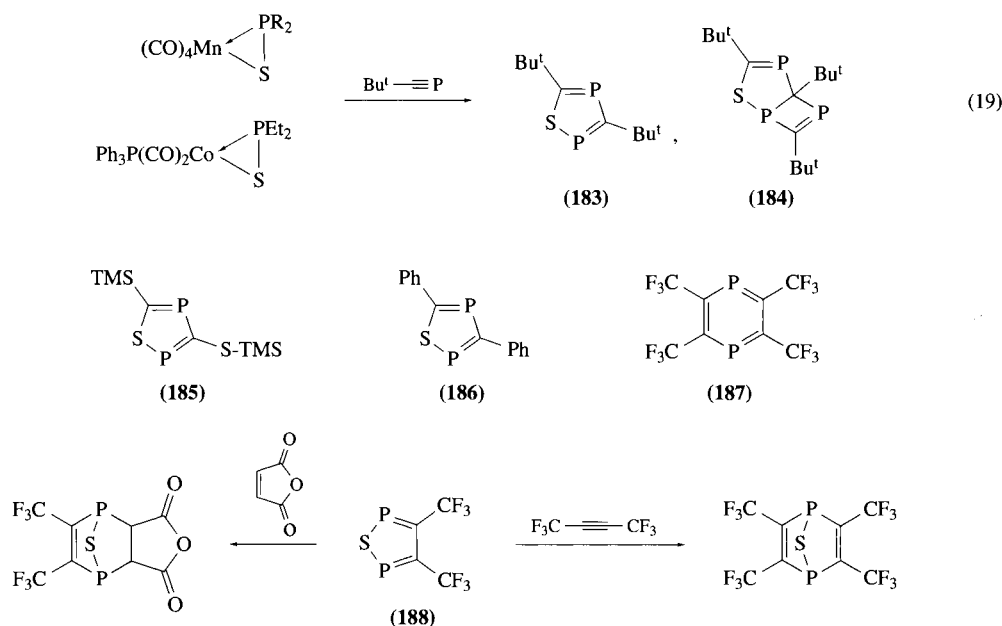
fluoroborate and it does not react with biacetyl and *o*-naphthoquinone. Additions of hydrogen chloride, methanol, and diethylamine always take place at both the P=C and P=N bond and yield the tetrahydro derivatives <85AG127>.



Scheme 56

4.22.11 1,2,4-THIADIPHOSPHOLES AND 1,2,5-THIADIPHOSPHOLES (V, W)

Thiophosphinato manganese ($R = \text{Me}$, cyclohexyl, Ph) and cobalt complexes and *t*-butyl phosphaethyne give in high yields the 1,2,4-thiadiphosphole (**183**) as a colorless, stable liquid. For $R = \text{Ph}$ in addition the bicyclic product (**184**) containing one more molecule of the phosphaethyne is observed (Equation (19)) <93AG1521, 94JOM(464)C31>. The adamantyl phosphaethyne has also been used for the synthesis of a 1,2,4-thiadiphosphole. From the condensation of lithium bis(trimethylsilyl)phosphide with carbon disulfide 3-trimethylsilylthio-5-trimethylsilyl-1,2,4-thiadiphosphole (**185**) is obtained as a distillable yellow liquid <86AG570>. Diphenyl-1,2,4-thiadiphosphole (**186**) is found in 2–4% yield as crystalline side product from the reaction of the phosphalkene $\text{Ph}(\text{Me}_3\text{Si})\text{C}=\text{P}\text{Cl}$ with an oxathiazolone (**34**) $R = \text{Ph}$, 2-MeC₆H₄, 2,6-Cl₂C₆H₃ <88TL4535>. The reaction of tetrakis(trifluoromethyl)-1,4-diphosphinine (**187**) with elemental sulfur results in the correspondingly substituted 1,4-diphosphabarrelene and 1,2,5-thiadiphosphole (**188**) is an air-sensitive oil. It behaves as a diene and undergoes [4 + 2] cycloadditions with bis(trifluoromethyl)-acetylene and maleic anhydride <81JA2465>.



Scheme 57

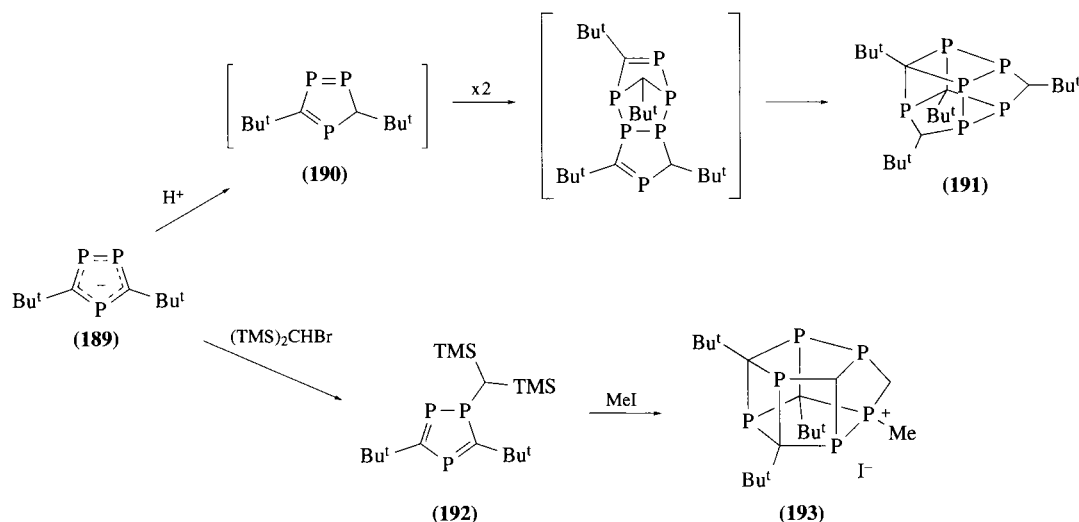
4.22.12 1,2,3-TRI- (Y), 1,2,4-TRI- (Z), TETRA- AND PENTAPHOSPHOLIDES (Æ, Ø)

The chemistry of polyphospholide anions is covered in reviews <93CRV1623, 94CCR1, 95CCR201>; their aromaticity has been evaluated <92JOC3694>. A review on “Rings with Phosphorus Carbon Multiple Bonds” <B-89MI 422-02> also includes tri- and tetraphospholes. Pentaphospholide complexes are contained in further reviews <87MI 422-03, 90AG1137>.

4.22.12.1 Reactivity

4.22.12.1.1 Protonation, alkylation and oxidation

The protonation of the 3,5-di-*t*-butyl-1,2,4-triphospholide ion (**189**) takes place at carbon. The resulting 1,2,4-triphospha-cyclopenta-1,3-diene (**190**) dimerizes via successive [4 + 2] and [2 + 2] cycloadditions to give a dihomocubane-structured cage molecule (**191**) containing five directly bonded phosphorus atoms and no C—C bond (Scheme 58) <89CC1046, 90PS(49/50)463>. The triphospha-cyclopentadiene is stable as η^4 -ligand in a cobalt complex <88CC819>.



Scheme 58

By contrast, alkylation of the 1,2,4-triphospholide ion by bis(trimethylsilyl)bromomethane takes place at P-1 and affords a stable 1,2,4-triphosphole (**192**) which is isolated as orange crystals <95CC1661>. It gives a *t*-PtCl₂PET₃ complex in which the triphosphole is attached via P-4 (molecular structures of the triphosphole and its complex in Table 6). By reaction with methyl iodide the triphosphole is converted to a homopentaprismane-structured phosphonium iodide (**193**) <94CCR1>.

The oxidative coupling of the 1,2,4-triphospholide ion $(Bu^tC)_2P_3^-$ with the 1,3-diphospholide ion $(Bu^tC)_3P_2^-$ by FeCl₃ or CoBr₂ results in a hexacyclic neutral cage product $(Bu^tC)_5P_5$ <89JOM(375)C31, 90PS(49/50)463>.

The solutions of alkali pentaphospholides MP_5 are gold-orange to red in color and are extremely sensitive to oxidation. The pentaphospholide ion P_5^- reacts with alkyl halides RBr and RI. The alkyl pentaphospholes RP_5 which are to be assumed as the primary products are non-aromatic and unstable, however, and rearrange to alkyl polyphosphines such as R_3P_7 and R_3P_9 <88AG288>. The trimethylsilyl pentaphosphole is known as a complex ligand (see Section 4.22.12.1.2).

4.22.12.1.2 Formation of transition and main group metal complexes

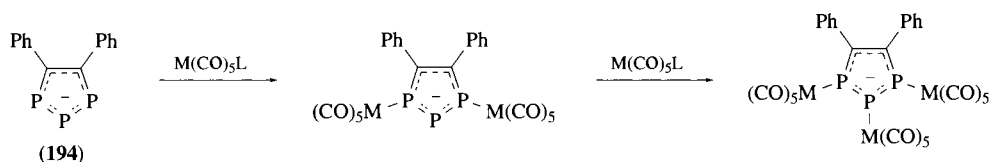
As has been mentioned in Section 4.22.12.1.1, the only known 1*H*-1,2,4-triphosphole forms an η^1 -complex by P-4 coordination.

Several types of 1,2,4-triphospholide transition metal complexes are known, that is complexes with η^1 -coordination of P-1 (in rare cases of P-4) to one or two metal centers and sometimes additional η^4 -coordination of the remaining four ring members, as well as with η^5 -coordination and sometimes additional η^1 -coordination of P-1 and P-2 <94CCR1, 95CCR201>. η^1 -Complexes are fluxional in solution as the metal atom undergoes an intramolecular shift between P-1 and P-2. The structural consequences of two bonding modes (**1**, **2**) for η^1 -complexes are mentioned in Section 4.22.2.2, molecular structures of four examples are found in Table 6.

η^5 -Complexes of the di-*t*-butyl-1,2,4-triphospholide encompass Yb, V, Cr, Mo, W, Fe, Ru, Co, Rh, Ir, and Ni, as well as Tl, Sn, and Pb derivatives. Most of the complexes are prepared from an alkali metal 1,2,4-triphospholide <89JOM(373)C17, 89JOM(375)C31, 90CC472, 90CC1307, 94CCR1, 95CCR201>.

but some have also been obtained from the phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ by metal vapour synthesis <87JOM(334)C35, 94MI 422-02, 94MI 422-03, 95CCR201>.

The 4,5-diphenyl-1,2,3-triphospholide ion (**194**) coordinates molybdenum and tungsten pentacarbonyl in two steps to P-1,3 and to P-2 <94BSF397>. With FeCl_2 a sandwich complex is obtained <93PS(77)254>.



Scheme 59

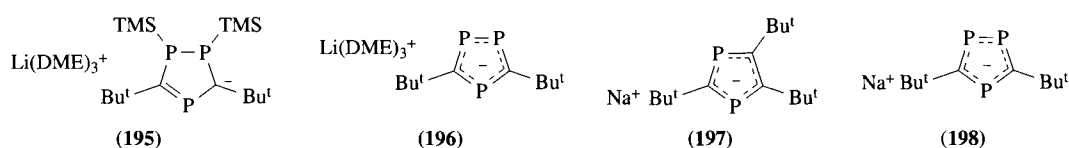
Of the pentaphospholide ion only η^5 -coordination is known, sometimes with additional η^1 -coordination. A characteristic feature is the formation of triple-decker complexes with P_5 as the middle deck <94CCR1>. Their electronic structure has been explored <89JA2030>.

Pentaphospholide sandwich complexes of Fe, Ru, and Cr cyclopentadienide units are obtained by cothermolysis of white phosphorus and the appropriate substrate complexes <87MI 422-03, 90AG1137> and also directly from LiP_5 , LiC_5Me_5 and FeCl_2 <88AG288>. A third approach involves a PCl_3 complex as the building block for the $\eta^5\text{-P}_5$ unit <93AG641>. The triple-decker complexes ($\eta^5\text{-C}_5\text{H}_5\text{Cr}$) $_2\text{P}_5$ and ($\eta^5\text{-C}_5\text{Me}_5\text{Cr}$) $_2\text{P}_5$ have been prepared from white phosphorus <86AG349, 90JCS(D)977>.

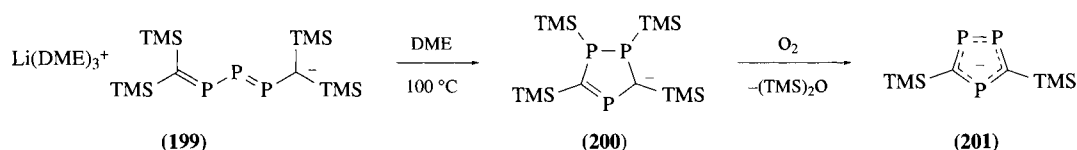
A series of anionic and neutral η^5 -pentaphospholyl metal tricarbonyl complexes [$\eta^5\text{-P}_5\text{M}(\text{CO})_3$] $^-$, $\text{M} = \text{Cr}, \text{Mo}, \text{W}$, and $\eta^5\text{-P}_5\text{Mn}(\text{CO})_3$ have been prepared from alkali pentaphospholides. $\text{K}(\text{DMF})_3[\eta^5\text{-P}_5\text{W}(\text{CO})_3]$ is silylated by Me_3SiCl to give the $\text{W}(\text{CO})_3$ complex of trimethylsilyl pentaphosphole Me_3SiP_5 <91AG590>.

4.22.12.2 Synthesis

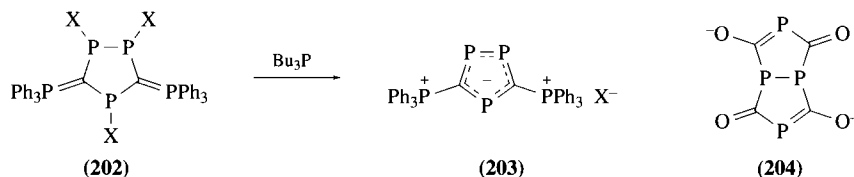
The phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ or its precursor, the phosphalkene $\text{Bu}^t(\text{Me}_3\text{SiO})\text{C}=\text{PSiMe}_3$, reacts in DME with lithium bis(trimethylsilyl)phosphide, $\text{LiP}(\text{SiMe}_3)_2$, to give the 3,5-di-*t*-butyl-1,2-bis(trimethylsilyl)-dihydro-1,2,4-triphospholide (**195**) which spontaneously loses the trimethylsilyl groups. The resulting DME solvated lithium 1,2,4-triphospholide (**196**) is isolated as yellow crystals (molecular structure in Table 6) <85MI 422-01, 87CC1146, B-96MI 422-01>. With phenyl in place of *t*-butyl groups as 3,5-substituents the dihydro-1,2,4-triphospholide is stable and its DME solvated lithium salt can be isolated in dark green crystals <B-96MI 422-01>.



Reduction of the phosphalkyne directly by sodium amalgam <89POL2407> or mediated by a reduced tantalum compound <89POL849> leads to an equimolar mixture of the 1,3-diphospholide and 1,2,4-triphospholide anions ((**197**) and (**109**)). The mixture of $\text{Pr}^t\text{C}\equiv\text{P}$ and $\text{Bu}^t\text{C}\equiv\text{P}$ results in a complex mixture of differently substituted di- and triphospholides <91JOM(415)C15>. The lithium salt of the 1,1,5,5-tetrakis(trimethylsilyl)-2,3,4-triphospha-pentadienide anion (**199**) rearranges in DME above 100°C (presumably via the loss and a $[2 + 3]$ cycloaddition of $\text{Me}_3\text{SiC}\equiv\text{P}$) to form the lithium 1,2,3,5-tetrakis(trimethylsilyl)-dihydro-1,2,4-triphospholide (**200**). In air this is oxidized to give the lithium salt of the 3,5-bis(trimethylsilyl)-1,2,4-triphospholide anion (**201**) which is isolated as yellow microcrystalline lithium salt <96AG354>.

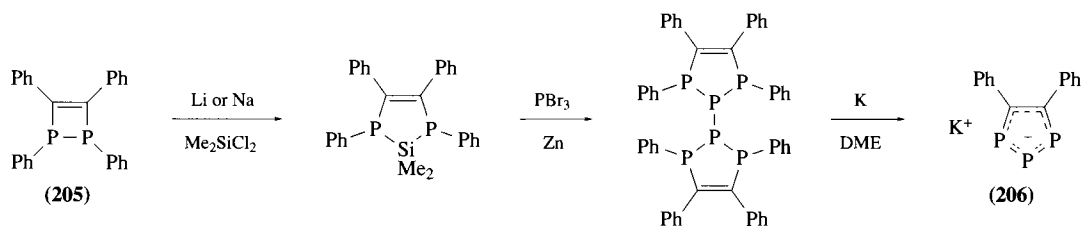


A bis(triphenylphosphonio)-substituted and consequently cationic 1,2,4-triphospholide (**203**) results from the reduction of the respective trihalo-1,2,4-triphospholane (**202**) which in turn is obtained from the condensation of the triphenylphosphonium bis(trimethylsilyl)methylide with phosphorus trichloride or tribromide. The chloride, bromide (molecular structure in Table 6), and triflate of the triphospholide are isolated as yellow crystals <96ZN(B)1>. The phosphorus analogue PCO^- of the cyanate ion on oxidation by SO_2 or I_2 forms a tetrameric dianion (**204**) in which two dihydro-1,2,4-triphospholonolate rings are fused. It is isolated as DME and THF solvated lithium salt. The molecule is folded along the P—P bond <95ZAAC(621)34, B-96MI 422-01>.



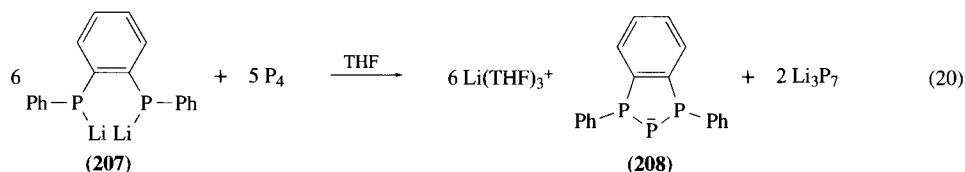
The sodium 1,2,3-triphospholide, tetraphospholide, and pentaphospholide (*Z*, *Æ*, *Ø*) are formed together with polycyclic sodium phosphides as the minor products from elemental white phosphorus with sodium (P/Na ratio = 3) in boiling diglyme; the carbon ring members originate from the solvent <87ZAAC(544)87, 90ZN(B)1139>. The pentaphospholide (but not the tri- or tetraphospholide) is also accessible in tetrahydrofuran from the reaction of white phosphorus with lithium phosphide <87ZAAC(544)87> or with sodium metal or sodium phosphide in the presence of 18-crown-6 <88AG288, 89ZN(B)381> or in boiling dimethyl formamide from red phosphorus with potassium phosphide <91CB1159>.

A specific synthesis of the 4,5-diphenyl 1,2,3-triphospholide ion (**206**) starts from the tetraphenyl dihydro-1,2-diphosphete (**205**) and involves several steps (Scheme 60). In the last step probably at first the central P—P bond of the bis(dihydrotriphospholyl) is cleaved and subsequently the P—Ph bonds. The potassium salt is solvated by DME and isolated as a white powder <93PS(77)254, 94BSF397>.



Scheme 60

Lithium 1,3-diphenyl-dihydro-1,2,3-benzotriphospholide (**208**) results from the action of lithium *o*-phenylenediphosphide (**207**) on white phosphorus <85CB3849>.



4.23

Three or Four Heteroatoms including at least One Arsenic or Antimony

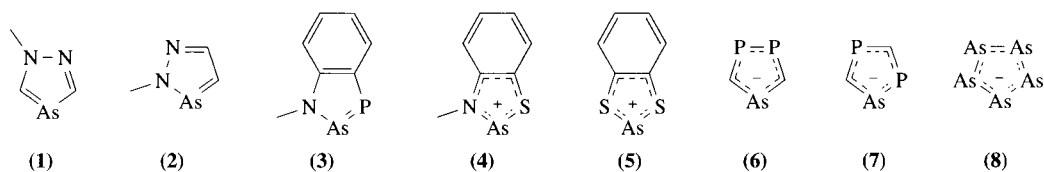
ALFRED SCHMIDPETER

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4.23.1 INTRODUCTION

In accordance with what is reported about heterophospholes in Chapter 3.15, cyclic conjugation in heteroarsoles is restricted to systems with two-coordinate arsenic and only these are covered here. 1,3-Aza-, 1,3-oxa-, and 1,3-phosphaarsoles are mentioned in Chapter 3.16. In addition several types of heteroarsoles with two nitrogen and/or phosphorus atoms (1)–(3) have been reported. As first representatives the 1,2,3-diazaarsoles (2) $\langle ^{73}\text{TL4503} \rangle$ were prepared in a similar way to the 1,2,3-diazaphospholes (see Section 4.22.5) and have been known for consequently almost as long. They have been well investigated mainly for their cycloadditions. Very recent representatives, mostly since 1993, on the other hand are the 1,2,4- and 1,4,2-diphosphaarsolide ions (6) and (7) which are primarily of interest as η^5 -ligands in transition metal complexes and the pentaarsolide ion (8) which is known so far only as η^5 -ligand. Their cationic counterparts are the 1,3,2-benzothiaza- and 1,3,2-benzodithiaarsolium ions (4) and (5). The stibolium cation corresponding to (5) and a 1,4,2-diphosphastibolide anion corresponding to (7) seem to be the only five-membered antimony 6π -heterocycles that have been isolated so far.



No heteroarsoles were mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). A review on arsenic heterocycles exists <B-78M1 423-01> but is somewhat out of date. 1,3,2-Benzothiazaarsolium and 1,3,2-benzodithiaarsolium ions are included in an article on heavier element analogues of carbenes <96AG901>. Two reviews deal with cycloaddition reactions of diazaarsoles <86PS(26)203, 91UK317>.

4.23.2 SPECTRA, STRUCTURE, AND BONDING

4.23.2.1 X-ray Diffraction

The molecular structures of diazaarsoles and thiazaarsoles known from x-ray diffraction are given in Table 1. The five-membered rings are planar and their bond lengths are in accord with a delocalized cyclic π -system. A peculiar feature of the 4-triazenyl-1,2,3-diazaarsole structure is a short intramolecular contact of 250(1) pm between the terminal nitrogen atom of the side chain and the arsenic atom.

Table 1 Bond lengths (pm) and angle at the arsenic atom in 1,2,4- and 1,2,3-diazaarsole rings and in a 1,3,2-benzothiazaarsolium ion from x-ray structure analysis.

Bonds					Angle	Ref.
1,2	2,3	3,4	4,5	1,5		
NN 131(2)	CN 126(2)	AsC 189(1)	AsC 182(1)	CN 138(2)	81.7(7)°	92HAC151
NN 134.7(3)	AsN 184.2(2)	AsC 183.3(3)	CC 141.3(4)	CN 131.6(3)	84.4(1)°	83DOK(268)885
135(2)	193(1)	180(1)	145(2)	130(2)	80.4(7)°	96HAC123
AsN 177.6(4)	AsS 215.4(2)	SC 173.6(5)	CC 138.3(7)	CN 138.2(7)	89.3(1)°	89JA3746, 92CJC703

An x-ray structure analysis has also been performed for a 4,4'-bis(1,2,3-diazaarsole) (<88IZV150>); its molecular dimensions result in an aromaticity index not significantly different from that of a 2*H*-1,2,3-diazaphosphole (<90T5697>).

For the η^5 -CpFe, η^1 -W(CO)₅ complex of 1,2,4-/1,4,2-diphosphaarsolide (<94JOM(480)45>) the bond lengths and angles cannot be assigned accurately due to disorder. The pentaarsolide structure in complexes is discussed in Section 4.23.8.

4.23.2.2 NMR and UV Spectra

The arsenic ring member always causes a downfield shift of the NMR signals of the ring members next to it. Thus the P-1 signal of the 1,4,2-diphosphaarsolide ion ($\delta^{31}\text{P} = 285$) is found at lower field compared to the P-4 signal ($\delta^{31}\text{P} = 249$) or to the P-1,2 signal of the 1,2,4-diphosphaarsolide ion ($\delta^{31}\text{P} = 245$). Furthermore the ¹³C NMR signals of the As—C—P ring fragments are at lower field ($\delta^{13}\text{C} = 220\text{--}223$) than those of the P—C—P fragments ($\delta^{13}\text{C} = 205\text{--}206$) (<89TH 423-01>).

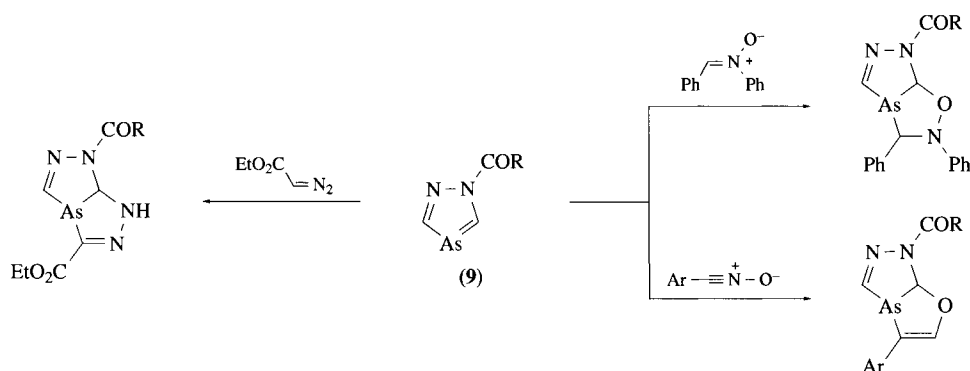
The C-3 and C-5 NMR signals of 1,2,4-diazaarsoles are found by $\Delta\delta^{13}\text{C} = 10$ at lower field than those of 1,2,4-diazaphospholes (<87TL1511>).

In the order 1,2,3-triazole (294 nm), 1,2,3-diazaphosphole (321 nm), 1,2,3-diazaarsole (352 nm) the UV absorption maximum at longest wavelengths experiences a bathochromic shift (<73TL4503>).

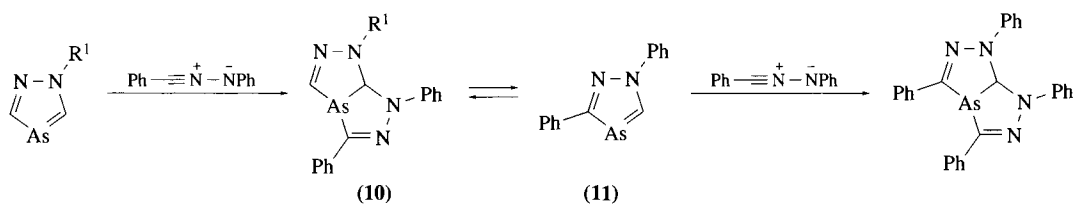
4.23.3 1,2,4-DIAZAARSOLES (1)

4.23.3.1 Reactivity

The 1,2,4-diazaarsoles are colorless oils or crystals. The unsubstituted compound is deprotonated by butyllithium and subsequently alkylated or acylated at N-1 (<86TL2957>). The 1-acyl derivatives (**9**) (R = Me, Ph) readily undergo a regiospecific cycloaddition of nitrones, nitrile oxides and diazoacetic esters (Scheme 1). The cycloaddition of diphenyl nitrile imine is more general in respect to the 1-substituent (R¹ = H, Me, Ph, COMe). The cycloreversion of the adduct (**10**) at higher temperatures provides an *in situ* access to the 1,3-diphenyl diazaarsole (**11**) which immediately enters another cycloaddition (Scheme 2) (<86TL2957>).

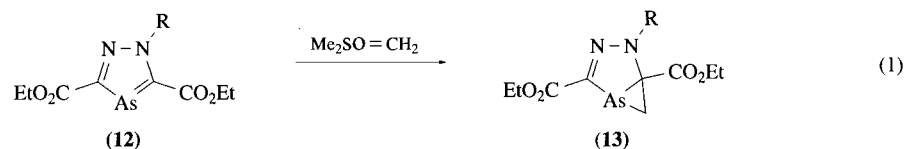


Scheme 1



Scheme 2

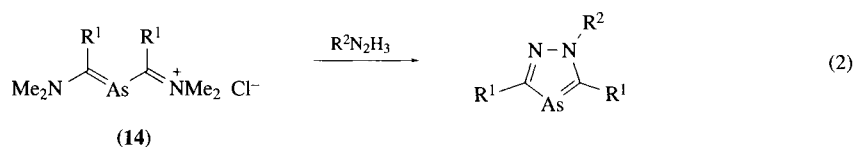
N-Unsubstituted 1,2,4-diazaarsoles are directly alkylated by diphenyl diazomethane, diazo esters, sulfur ylides, and alkyl vinyl ethers <90TL7607, 95HAC403>. 1-Alkyl-1,2,4-diazo-arsoles (**12**) ($R = \text{Me}$, CHPh_2) react with dimethylsulfoxonium ylide to give bicyclic arsiranones (**13**) (Equation (1)) <90TL7607>.



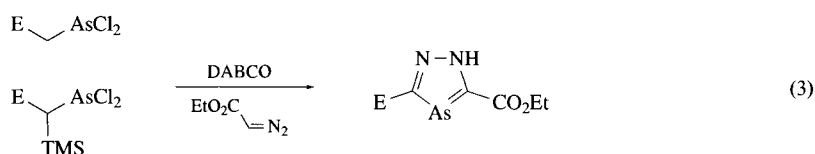
The 1,2,4-diazaarsolo[1,5-*a*]pyridines are *N*-alkylated by methyl iodide <87TL1511>.

4.23.3.2 Synthesis

The first 1,2,4-diazaarsoles were obtained from the condensation of 1,3-bis(dimethylamino) 2-arsaallylic chlorides (**14**) ($R^1 = \text{H}$, Ph) with monosubstituted hydrazines or hydrazine itself ($R^2 = \text{H}$, Me , Ph) (Equation (2)) <86TL2957>.

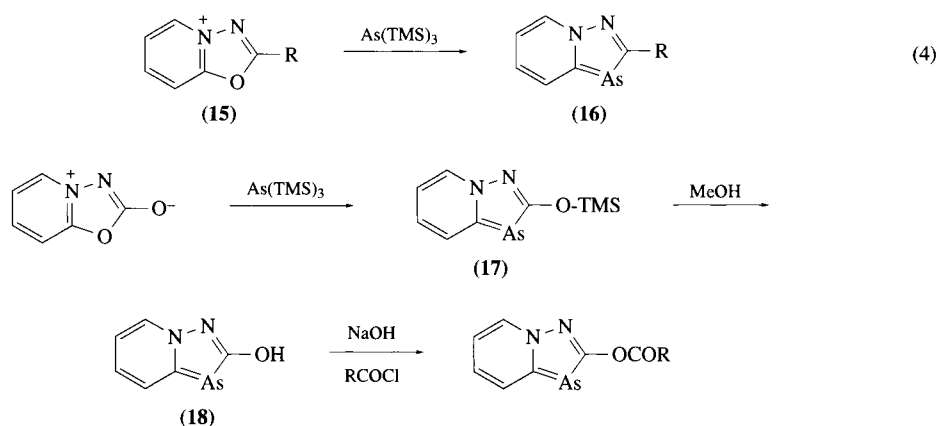


Another route is based on the *in situ* generation of arsaalkenes ($\text{E} = \text{CO}_2\text{Et}$, CONMe_2 , $\text{CMe}=\text{CH}-\text{CO}_2\text{Me}$) and their cycloaddition to ethyl diazoacetate (Equation (3)) <89TL349, 90TL1147, 90TL7607>.



The cycloadduct of 5-methyl-2-phenyl-1,2,3-diazaarsole and ethyl diazoacetate (see Section 4.23.4) opens the As—N bond to yield a 1,2,4-diazaarsole the molecular structure of which is given in Table 1 <92HAC151, 93PS(77)246>.

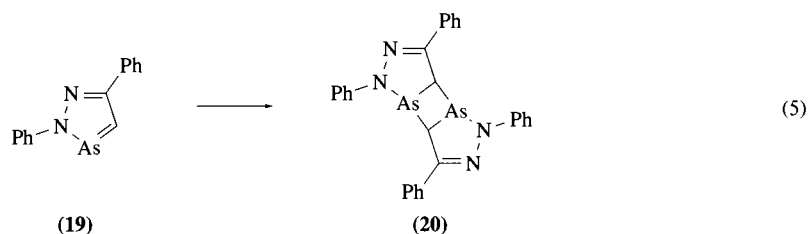
In 1,3,4-oxadiazolo[3,2-*a*]pyridinium salts (**15**) an O/As exchange can be achieved with tris(trimethylsilyl)arsine in boiling acetonitrile to yield 1,2,4-diazaarsolo[1,5-*a*]pyridines (**16**) ($R = \text{Me}$, Pr^i , Bu^i , Ph) (Equation (4)) <87TL1511>. In a corresponding way the compound (**17**) with $R = \text{O}-\text{TMS}$ is obtained. Methanolysis gives the hydroxy derivative (**18**) which exists exclusively in this tautomeric form and which can be *O*-acylated via the sodium salt (Scheme 3) <88TL3387>.



Scheme 3

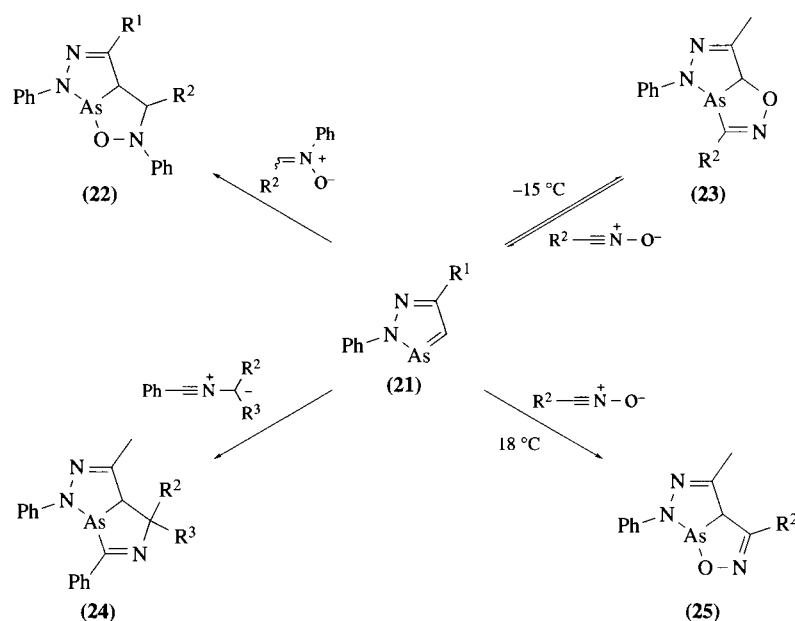
4.23.4 1,2,3-DIAZAARSOLES (2)

2*H*-1,2,3-Diazaphospholes are yellow to orange oils or crystals <73TL4503, 74TL1977>. The mostly used 2,5-diphenyl derivative (**19**) forms a dimer (**20**) when it is kept for a long time (Equation (5)) <83ZOB835>.



4.23.4.1 Reactivity

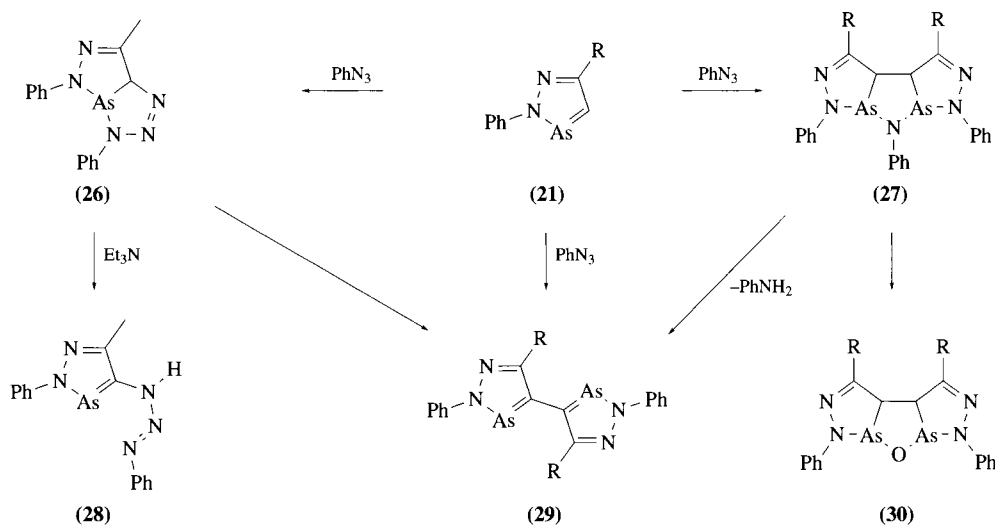
2*H*-1,2,3-Diazaarsoles (**21**) ($R^1 = \text{Me, Ph}$) add nitrones ($R^2 = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4$) regiospecifically to the $\text{As}=\text{C}$ bond to give the $\text{As}-\text{O}$ bonded product (**22**) <79DOK(246)1130, 79DOK(249)120, 87IZV2819>. Nitrile oxides ($R^2 = \text{Me, Bu}^t, \text{Ph, 4-ClC}_6\text{H}_4$) at low temperatures give the $\text{As}-\text{C}$ bonded cycloadduct (**23**) which at room temperature is converted quantitatively into the $\text{As}-\text{O}$ bonded isomer (**25**) via a retrocycloaddition <81CC1131, 83T1507>. The addition of nitrile ylides ($R^2/R^3 = \text{H/H, H/Ph, Me/Me}$) to give (**24**) is also regiospecific (Scheme 4) <83CJC1105>.



Scheme 4

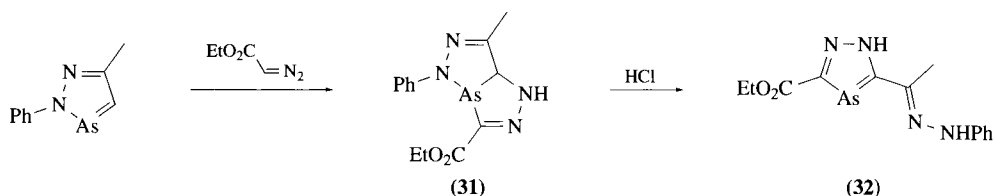
At low temperatures and without solvent the 1,2,3-diazaarsole (**21**) with $R^1 = \text{Me}$ reacts with phenyl azide to give the expected cycloadduct (**26**). It can be isolated but is unstable at room temperature. In triethyl amine or pyridine solution it opens the $\text{As}-\text{N}$ bond of the triazaarsole ring is opened. The molecular structure of the product (**28**) is given in Table 1. From the decomposition of the neat cycloadduct the 4,4'-bis(2*H*-1,2,3-diazaarsole) (**29**) has been isolated. Bis(diazaarsoles), $R = \text{Me, Ph}$, are also obtained from the room temperature reaction of the diazaarsoles (**21**) and phenyl azide. As intermediates tricyclic compounds (**27**) are formed in which two dihydro-diazaarsole rings are anellated to a 1,2,5-azadiarsolidine ring. On heating they are completely converted

to the bis(diazaarsoles) and aniline. Hydrolysis leads to an analogous tricyclic compound (**30**) with a central 1,2,5-oxadiarsolane ring ($R = \text{Ph}$) (Scheme 5) <96HAC123>.

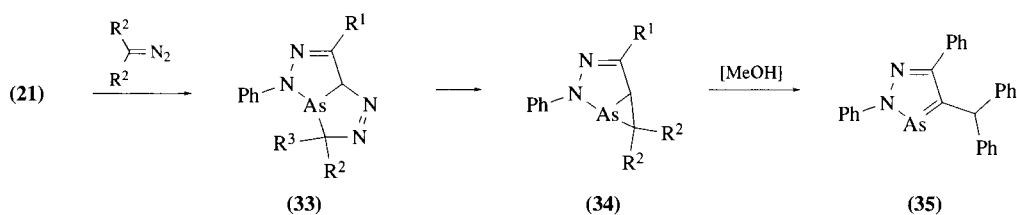


Scheme 5

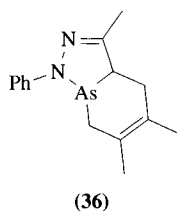
5-Methyl-2-phenyl-1,2,3-diazaarsole adds ethyl diazoacetate to form a bicyclic product (**31**). Hydrogen chloride catalysis opens the 1,2,3-diazaarsole ring and yields a 1,2,4-diazaarsole with a phenyl hydrazone side chain (**32**) (Scheme 6) (molecular structure in Table 1) <92HAC151, 93PS(77)246>. In the reaction with diphenyl and dimethyl diazomethane $\text{R}^2\text{C}=\text{N}$ ($\text{R}^2 = \text{Me}, \text{Ph}$) the 5-methyl-2-phenyl-1,2,3-diazaarsole (**21**) ($\text{R}^1 = \text{Me}$) is more reactive than the 2,5-diphenyl derivative (**21**) ($\text{R}^1 = \text{Ph}$) <91UK317>. The primary cycloadduct (**33**) has been detected in one case at -70°C <86IZV230>. It readily loses nitrogen and yields a bicyclic arsirane (**34**) <82IZV1432, 82IZV2718, 83ZOB835, 84DOK(274)828, 86IZV230, 87IZV2819>. The all-phenyl substituted compound (**34**) ($\text{R}^1, \text{R}^2 = \text{Ph}$) on heating to 250°C with methanol in a sealed tube isomerizes to the 4-diphenylmethyl 1,2,3-diaza-phosphole (**35**) (Scheme 7) (molecular structure in Table 1) <83DOK(268)885, 83ZOB835>. In the reaction with methylphenyl diazomethane 4,4'-bis(2*H*-1,2,3-diazaarsoles) (**29**) are formed <88IZV150> as they are also found as products from the reaction with phenyl azide. 2,3-Dimethylbutadiene and cyclopentadiene give [4 + 2] cycloadducts (**36**) with 5-methyl-2-phenyl-1,2,3-diazaarsole which is more reactive in this respect than the corresponding diazaphosphole <86BSF115>.



Scheme 6

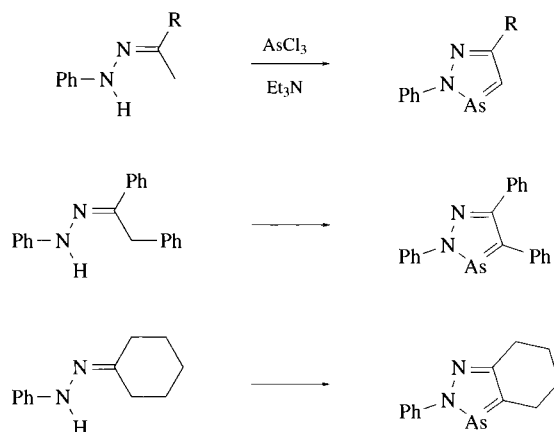


Scheme 7



4.23.4.2 Synthesis

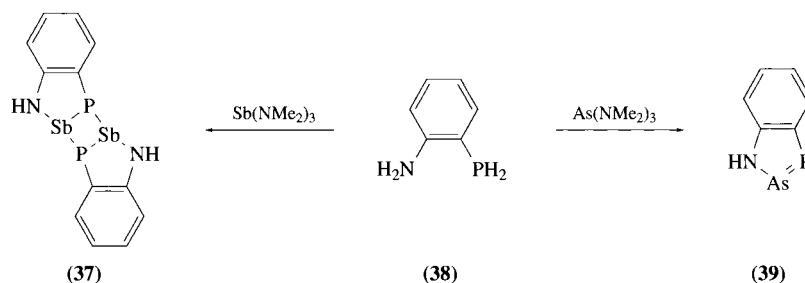
1,2,3-Diazaarsoles ($R = \text{Me, Et, Ph}$) result from the condensation of the phenylhydrazone of a methyl or benzyl ketone with arsenic trichloride in the presence of triethylamine (Scheme 8) $\langle 73\text{TL}4503, 74\text{TL}1977 \rangle$. Phenylhydrazones of cyclopentanone, cyclohexanone, norbornanone, norbornenone, and steroid ketones react as well.



Scheme 8

4.23.5 1,3,2-AZAPHOSPHAARSOLES (3)

Analogous to 1,2,3-benzazadiphospholes (Section 4.22.10) 1,3,2-benzazaphosphaarsole (**39**) and 1,3,2-benzazaphosphastibole (**37**) results from the condensation of 2-aminophenylphosphine (**38**) and tris(dimethylamino)arsine or stibine (Scheme 9) $\langle 93\text{PS}(76)45 \rangle$.

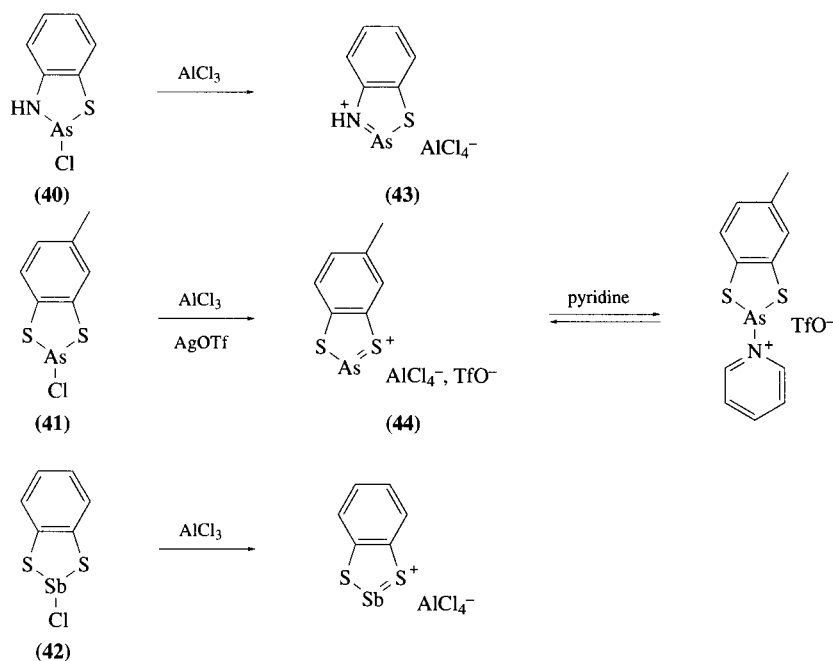


Scheme 9

The phosphorus chemical shift observed for the arsenic derivative $\delta^{31}\text{P} = 315$ is in accordance with the monomeric structure (**39**). This, however, is not the case for that observed for the antimony derivative, $\delta^{31}\text{P} = 44.5$. The mass spectrum of the latter confirms its dimeric structure (**37**).

4.23.6 1,3,2-THIAZAARSOLIUM AND 1,3,2-DITHIAARSOLIUM(STIBOLIUM) SALTS (4) AND (5)

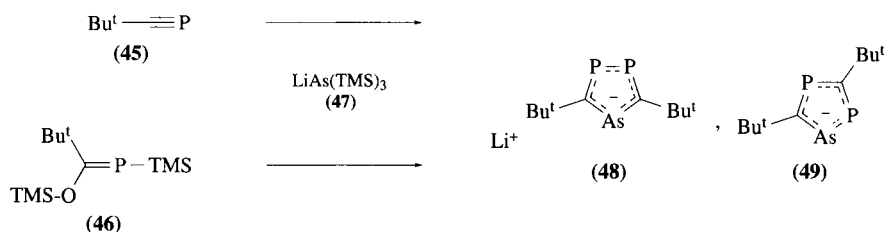
2-Chloro-1,3,2-benzothiazaarsole (**40**), 2-chloro-5-methyl-1,3,2-benzodithiaarsole (**41**) and stibole (**42**) <85JCS(D)69> are converted by reaction with aluminum chloride <89CC19, 92CJC703> and in part with silver triflate <92HAC157> to the corresponding arsolium and stibolium salts (Scheme 9). The molecular structure of the 1,3,2-benzothiazaarsolium tetrachloroaluminate (**43**) is given in Table 1. The dithiaarsolium triflate (**44**) is a strong Lewis acid towards pyridine, however, less acidic than the corresponding dithiaphospholium triflate (Scheme 10) <92HAC157>.



Scheme 10

4.23.7 1,2,4- AND 1,4,2-DIPHOSPHAARSOLIDES (STIBOLIDES) (6) AND (7)

The reaction of the lithium bis(trimethylsilyl)arsenide (**47**) with *t*-butyl phosphaethyne (**45**) <89TH 423-01, 93PS(77)45, 94JOM(480)45> or a phosphalkene precursor thereof (**46**) leads to a mixture of lithium 1,2,4-triphospholide, 1,2,4-diphosphaarsolide (**48**) and 1,4,2-diphosphaarsolide (**49**) (Scheme 11).



Scheme 11

The 1,2,4-diphosphaarsolide ion has been used as η^5 -ligand in Mn-, Fe-, Ru-, and Mo-complexes <93PS(77)45, 93PS(77)275, 94JOM(480)45> and as middle deck of a triple-decker ruthenium complex <95OM4382>. η^5 -Sandwich and triple-decker complexes of the 1,4,2-diazaphospholide ion are also known <94JOM(480)45, 95CCR201, 95OM4382>. Attempts to extend the above reaction to the preparation of a phosphadiarsolide ring system instead led to a tetraarsacubane <93AG86>. A 1,4,2-diphosphastibolide has been prepared analogous to (**49**) and used for the synthesis of ruthenium sandwich complexes <96CC1591>.

4.23.8 PENTAARSOLIDES (8)

The pentaarsolide ring is known as η^5 -ligand $\langle 90AG1137 \rangle$ in the sandwich complexes $C_5Me_5FeAs_5$ and $C_5Me_4EtFeAs_5$ $\langle 90JOM(387)C21 \rangle$ and as the middle deck in the triple-decker complexes $(C_5H_4Me-Cr)_2As_5$ $\langle 89JOM(361)C11, 90CB3 \rangle$ and $(C_5H_5Mo)_2As_5$ $\langle 82JA4727 \rangle$. It forms a planar regular pentagon except in the last mentioned complex. The distortion from idealized 5-fold symmetry observed here (As_3 subunit with 238.9(2) and 239.7(3) pm, As_2 subunit with 257.0(2) pm bond lengths and longer distances in between the two) is traced to the working of Jahn–Teller effects $\langle 89JA2030 \rangle$.

The distortion is even more severe in the triple-decker complex $(CpMo)_2As_4S$ where the planar middle deck is closer to an allylic As_3 group and a separate AsS group rather than an As_4S ring $\langle 90IC798 \rangle$.

4.24

Three or Four Heteroatoms including at least One Other Element

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LEONID I. BELEN'KII
Russian Academy of Sciences, Moscow, Russia

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The explosive increase in the number of methods for synthesis of the heterocycles reviewed in this chapter has resulted in many new and very different five-membered rings brought thus into existence. About 670 references after 1980 were found to cover this field compared with about 30 references in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). Roughly half of the new references are related to rings containing silicon. Accordingly, the chapter is divided into two main sections, the first comprising Si-containing rings, the second dealing with the rest of the material.

The known types of five-membered heterocycles are presented at the beginning of each main section. Possible structural types with all heteroatomic combinations conceivable are almost unbounded, their presentation here would be worthless and is therefore avoided. The nomenclature of these heterocycles is defined by IUPAC rules (both Hantzsch–Widmann and replacement nomenclature are used) which are adhered to throughout the chapter.

Unsaturated and saturated compounds are considered in the same sections since the number of five-membered heterocycles with three and more heteroatoms (and especially their structure types) is limited and their reactivity does not differ fundamentally.

4.24.1 RING SYSTEMS CONTAINING SILICON

4.24.1.1 Introduction

The types of Si-containing five-membered heterocycles synthesized heretofore are shown in Figure 1. Only a few of them were known prior to 1980. Bora rings (**1,m**) deserve mention as the subject of a very broad and comprehensive study which revealed a series of peculiar transformations and structures. Rings with the internal dative bonds (e.g. **k**, **bb** (X = F)) add another dimension to ring

structure. Tetrasilane ring (**z**) is a new member of the polysila rings family. Other rings with four (**p,q,r,v**) heteroatoms and new fused aromatic systems have appeared. Saturated and unsaturated rings occur nearly equally.

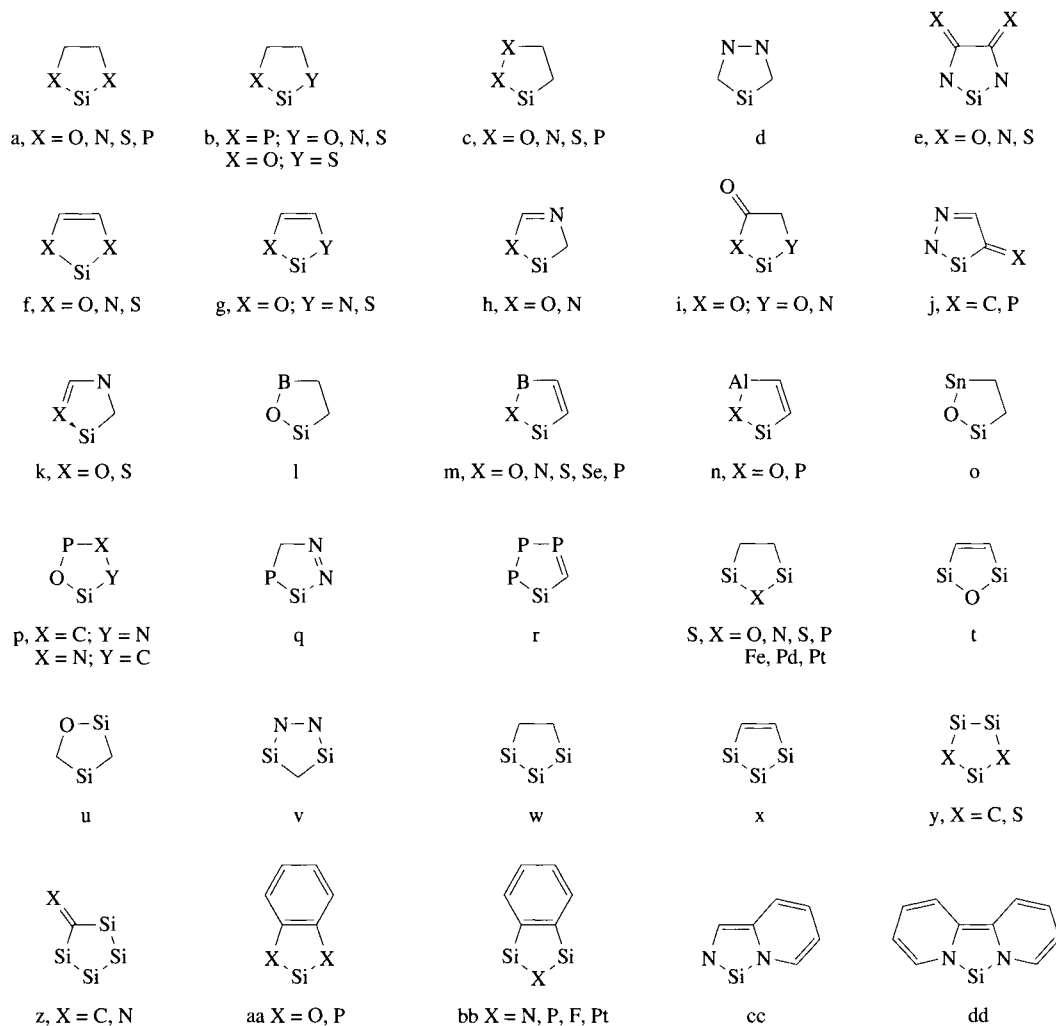


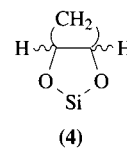
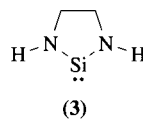
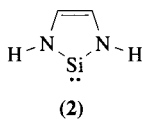
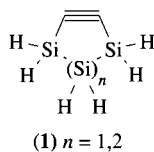
Figure 1 Silicon-containing five-membered heterocycles.

4.24.1.2 Structure of the Ring Systems Containing Silicon

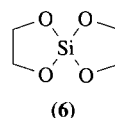
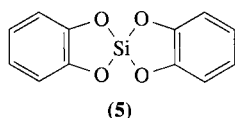
4.24.1.2.1 Theoretical methods

The stability of five- and six-membered polysila rings containing an acetylenic moiety (**1**) according to calculation using second-order perturbation theory (MP2) is lower for the five-membered ring by 21.1 kcal mol⁻¹. The strain imposed by the C≡C moiety on this ring is not offset by some delocalization into the silicon backbone in contrast to the six-membered ring <92JA4920>. By the same method the 6π-electron silylene (**2**) is found to be stabilized relative to the 4π-electron silylene (**3**) by the surprisingly large value of 13.92 kcal mol⁻¹, which may be regarded as an upper limit of aromatic stabilization of (**2**) vs. (**3**) <94JA2691>. The energy difference between *cis*- and *trans*-conformations of dimethylsilyl acetals of cyclic 1,2-diols (**4**) calculated by molecular mechanics is only in very rough agreement with the observed *cis* : *trans* ratio for cyclic 1,2-diols <93TL7891>. 1,2,5-Thiasilaboracyclopent-3-ene sandwich nickel complexes have slightly lower energy and have more favorable charge interaction between two rings in the case of opposite atom sequence in the rings

according to calculations by extended Hückel methods <91JPC9757>. The results are compatible with x-ray data.



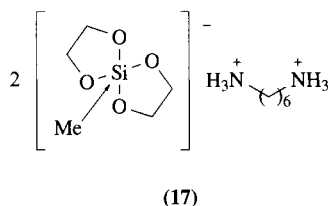
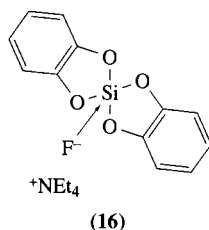
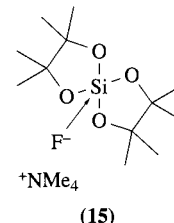
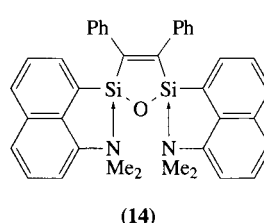
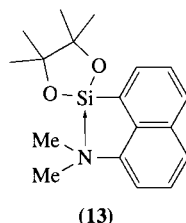
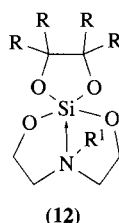
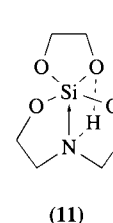
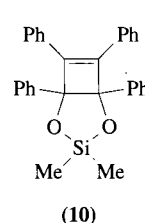
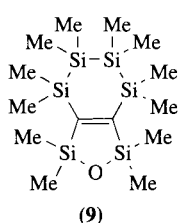
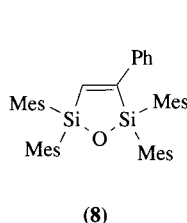
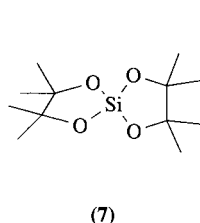
Semi-empirical MO calculations for **(5)** <79AG588> and **(6)** <77JA4899, 77JA4907> showed a tetrahedral configuration at silicon to be preferable to a planar one by 32.9 kcal mol⁻¹ and 34.4 kcal mol⁻¹ (this is much less than for carbon). The planar configuration was predicted to be stabilized by electron donor ligand at the silicon atom which thus becomes pentacoordinated. This prediction was realized with **(16)** (Section 4.24.1.2.2).



MO calculations have been carried out for the reactions of disilacyclopropane (**248**) with oxygen to give dioxadisilacyclopentane (**251**) (Scheme 27) <89TL6705, 93OM1514, 90JA7804> and for the pyrolytic transformation of bisTMS silylene (**236**) to trisilacyclopentane (**238**) <84JOM(272)11>.

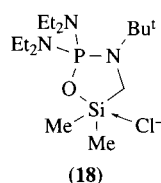
4.24.1.2.2 X-ray diffraction

The Si—O bond lengths (1.626–1.644 Å) in 1,3,2-dioxasila- and 1,2,5-oxadisilacyclopentane rings **(7)** <83AG52>, **(8)** <92T3283> and **(9)** <93OM803> are usually the same as in acyclic structures (1.63–1.64 Å). They increase in a strained fused bicycle **(10)** (1.658 Å) <83CL209> and in the case of pentacoordinated silicon atom with a dative N→Si bond **(11)** (1.683–1.710 Å) <82ZAAC(493)53>, **(12)**; R = H, R' = Me (1.690–1.731 Å) <84MI 424-01>, **(13)** (1.656–1.678 Å) <91OM1236>, **(14)** (1.651 Å) <93OM1113>; an F→Si bond **(15)** (1.683–1.734 Å) <83ZN(B)938>, **(16)** (1.699–1.741 Å) <81JA5269>; a Cl→Si bond **(18)** (1.840 Å) <91MI 424-01>; or a O→Si bond **(17)** (1.711–1.769 Å) <82ZN(B)195>.

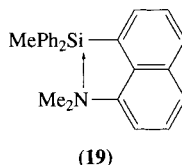


The elongation of Si—O bonds in silicon pentacoordinated compounds relative to the standard length may be taken as a sign of spreading the dative character partly upon these ring Si—O bonds. This is especially apparent in (18), but elongation (by 0.37 Å) of the Si—Cl bond (2.438 Å vs. covalent tetracoordinated 2.401 Å) is much greater than that (0.18 Å) of the Si—O bond implying much more coordinative character in the former. The P—O bond length (1.528 Å) is close to normal for tetracoordinated phosphorus compounds (1.57 Å) and far from that of a double bond (0.86 Å) <91MI 424-01>.

The pentacoordinated hypervalent silicon atom tends markedly from the tetrahedral towards a trigonal-bipyramidal geometry (TBG). TBG is ~100% in (11), (12; R = H, R' = Me), (15), (17) and (18), ~78% in (13) and ~45% in (14), as measured by the sum of their equatorial bond angles (~360°, ~353° and ~343°) compared with the sum in an ideal trigonal bipyramid (360°) and tetrahedron (328.4°). The configuration in (16) is strongly (by ~70%) shifted from TBG towards square-pyramidal, fluorine being apical and the four equatorial oxygen atoms tending to lie in one plane. The nitrogen atom is apical in (11)–(14); fluorine and Me are equatorial in (15) and (17).



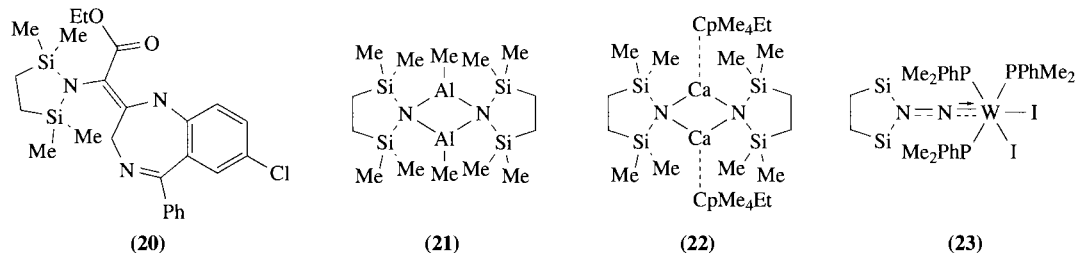
The dative N→Si bond in (14) (2.882 Å) is shorter than in (19) evidently because of the strong electron-withdrawing effect of oxygen bonded to silicon <93OM1113>. It is still shorter in (13) (2.339 Å) where silicon is bonded with two oxygen atoms, and further in (11) (2.004 Å) and (12) (2.032 Å) where silicon is bonded with four oxygen atoms. Apical Si—O bonds (average 1.742 Å) are longer than equatorial (average 1.704 Å) in (11)–(13), (15) and (17). An intramolecular hydrogen bond in (11) is formed with the apical oxygen atom which is normally a better electron donor than equatorial oxygen <82ZAAC(493)53>. The dative F—Si bonds in (15) (1.648 Å) and (16) (1.603 Å) are longer than the covalent bond in SiF₄ (1.56 Å) <83ZN(B)938>. Also the Si—C bond for pentacoordinated silicon (1.876 Å in (17)) is longer than for tetracoordinated (1.851 Å) <82ZN(B)195>.



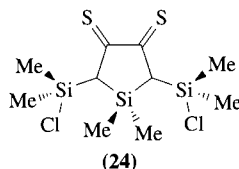
1,3,2-Dioxasilacyclopentane rings in (11)–(13), (15) and (17) have a twist conformation, the carbon atom deviating from the O—Si—O plane on opposite sides. Overcrowding of strongly electronegative CF₃ groups in (12; R = CF₃) elongates C—C bonds (1.627 Å) and shortens C—O bonds (1.390 Å) as compared with (11), (15) and (17) (average 1.503 Å and 1.427 Å respectively). Elongation of the C—C bond (1.60 Å) in the five-membered ring (10) seems to be due to an antibonding interaction between phenyl groups through the C—C bond <83CL209>. In the pentacoordinated counterpart (15) of the tetracoordinated spirobicycle (7) a shortening of C—C (1.496 Å vs. 1.556 Å) and C—O (1.431 Å vs. 1.476 Å) bonds is observed. The 1,2,5-oxadisilacyclopent-3-ene ring in (8), (9) and (14) is almost planar; the C—Si bonds (1.88–1.91 Å) are longer than standard.

Carbon atoms in the nonplanar 1,2,5-azadisilacyclopentane ring (20) are disordered in the crystal lattice to avoid an unfavorable eclipsed conformation and this results in a marked shortening of one Si—C bond (1.844 Å, 1.90 Å vs. 1.87 Å in alkylsilanes) and a slight shortening of the C—C bond (1.51 Å vs. 1.53–1.54 Å in alkanes) <93AX(C)116>; the C—N bonds (1.73–1.74 Å) are normal. Those rings bridged at their tetrabonded nitrogen atoms by aluminum (21) <90POL2205>, calcium (22) <92JA3393> or nitrogen (23) <92OM4116> have the Si—N bond longer (1.78–1.81 Å) than a typical Si—N single bond (1.70–1.76 Å). Here an analogy may be drawn to the general observation that transition from amines to ammonium cations causes C—N bonds to lengthen <66CB1697>. The central four-membered ring in (21) is square planar with equal Al—N bonds (2.005 Å), whereas in (22) one pair of Ca—N bonds is shorter (average 2.409 Å) and the other pair is longer (average

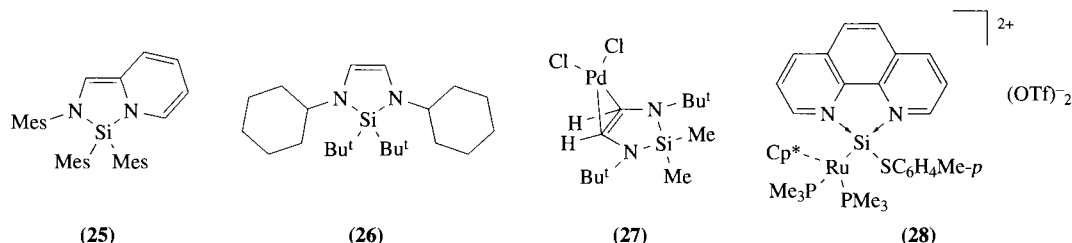
2.482 Å), possibly dative in nature. In (23) the nitrogen atoms are markedly double bonded (1.36 Å).



The 1,3,2-diazasilacyclopentane-3,5-dithione molecule (24) (planar ring) has somewhat extended ring Si—N single bonds (1.784 Å) while the external Si—N bonds (1.770 Å) are close to normal. Bond lengths in the SCN unit are typical for thioamides, the C—C bond (1.535 Å) is markedly longer than a usual C_{sp^2} — C_{sp^2} single bond (1.47–1.49 Å) <82IC3798>.

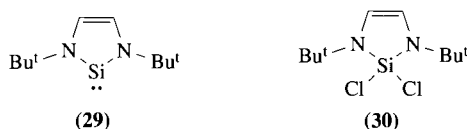


The planar 1,3,2-diazasilacyclopent-4-ene ring in the fused (25) <93OM2881> and nonfused (26) <91JOM(407)31> structures has the Si—N bonds (1.74–1.76 Å) within the range of single bond lengths. They become longer (1.77–1.79 Å) when complexed with $PdCl_2$ at the C=C double bond (27); the complexation is evidenced by the length of Pd—C bonds (2.24–2.29 Å) which are inclined at $\sim 120^\circ$ to the ring plane, the H—C bonds being forced out of the plane ($\sim 140^\circ$) <86ZN(B)1230>. When this ring is formed by donation of free electron pairs from pyridine nitrogen atoms (28), Si—N distances (1.91 Å and 1.95 Å) are indicative of coordinate dative bonds but in a closely related structure one Si—N bond is dative (1.91–1.93 Å) and the other one is extended covalent (1.81–1.82 Å) (Section 4.24.1.3.8) <92JA1518>. Si—Ru and Si—S are the normal covalent single bonds in both structures.

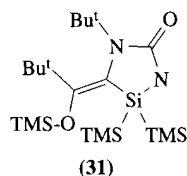


The strongly colored planar fused bicyclic system (25) is quinonoid with distinctly alternating bond lengths 1.33–1.35 Å and 1.42–1.44 Å. A strong π -stacking interaction in the molecule (28) between tolyl and phenanthroline planes is evident (interplane distance is 3.3 Å), as well as between tolyl and cyclopentadienyl planes (the distance is 3.61 Å) which results in columns of stacked molecules.

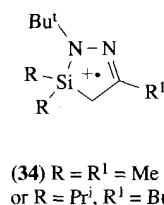
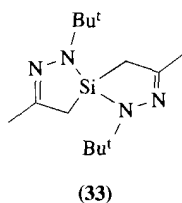
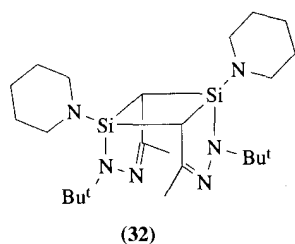
Surprising thermal and chemical stability of the cyclic silylene (29) may be explained by an enhanced aromaticity. This can be seen by comparison with its precursor (30); the difference in length between the single N—C (1.415 Å) and double C=C (1.322 Å) bonds in (30) decreases in (29) (N—C 1.400 Å, C=C 1.347 Å) to imply an increased delocalization. Also the Si—N bond length increases in (29) only by 0.056 Å (from 1.697 Å to 1.753 Å) instead of the 0.080–0.100 Å typical for transition from tetra- to dicoordinate silicon; this may indicate developing partial Si=N double bond character in (29) <94JA2691>.



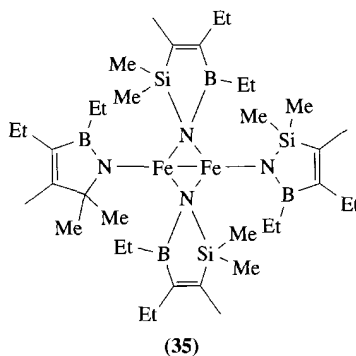
The 1,4,2-diazasilacyclopentane ring in (31) has an envelope conformation, C(5) deviating from the plane by 0.44 Å; Si—N (1.797 Å) and Si—C(5) (~1.9 Å) bonds are longer than the corresponding usual covalent single bonds; Si—Si bonds are normal <93OM529>.



The almost planar 1,2,3-diazasilacyclopent-5-ene rings in the cage-like (32) and spiro (33) structures have normal covalent single and double bonds <84ZAAC(514)49>. In the radical cation of the same ring system (34) the C=N bond (1.245 Å) is shorter and the Si—N (1.781 Å) and C—C_{sp2} (1.523 Å) bonds are longer <83AG630>.



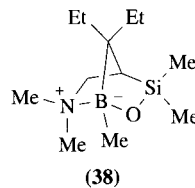
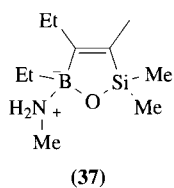
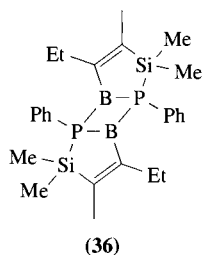
N-Ferrous 1,2,5-azasilaboracyclopent-3-ene derivative exists in the dimeric form (35) in which two single-bonded rings are twisted in opposite directions by 50.6° relative to the central plane square cycle while the other two rings are perpendicular to the central square and bridge both iron atoms. All the rings are nearly planar. The Fe—Fe distance (2.683 Å) when compared with the sum of atomic radii (2.54 Å) and the Fe—Fe bond in iron carbonyls (2.46–2.80 Å) may signify a bonding between iron atoms. Bonds to the tetracoordinated ammonium-like nitrogen atom (N—Fe 2.037 Å, N—Si 1.756 Å, N—B 1.469 Å) are longer than those to the tricoordinated nitrogen atom (N—Fe 1.898 Å, N—Si 1.729 Å, N—B 1.418 Å), but outlying bonds (B—C 1.564 Å, C=C 1.337 Å) are the same length <87CB669>.



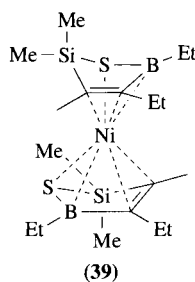
The dimer of 1,2,5-phosphasilaboracyclopent-3-ene derivative (36) is assembled by [2 + 2] cycloaddition of two P—B bonds to form a fused tricyclic system with a central square plane in which interconnecting P—B bonds (2.054 Å) are longer than those in the five-membered nearly planar rings (2.028 Å). The latter are *trans*-inclined to the central square at 112.7° <88CB1381>.

In a complex of 1,2,5-oxasilaboracyclopent-3-ene derivative with MeNH₂ (37) the ring is planar. Intermolecular N—H···O contacts (1.874 Å) are evident <88CB597>. A 3-CH₂NMe₂ group in the 1,2,5-oxasilaboracyclopentane ring makes a bridge to boron resulting in a norbornane-like structure (38) which is represented in the unit cell by two C(3) enantiomers <91CB1017>.

1,2,5-Thiasilaboracyclopent-3-ene derivatives form sandwich-type nickel π -complexes (39) in which nickel is bonded with four atoms (SBCC) of each ring. These atoms (in each set) lie in one



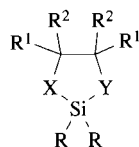
plane with the silicon atoms being bent out of the respective planes by 31.4° $\langle 88\text{CB}709 \rangle$. The molecular structure of the nickel complex of the 1-selena analogue is practically the same; Ni-plane distance is $1.809 \text{ \AA}$ $\langle 88\text{CB}1955 \rangle$.



4.24.1.2.3 NMR spectroscopy

Some chemical shifts for the known silacyclopentane-type structures are shown below as reference points concerning ring atoms and in part (^1H) their immediate vicinity. The values are rounded to the first decimal place.

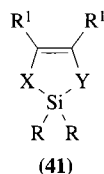
(40a), $\text{X} = \text{Y} = \text{NR}^3$ $\langle 85\text{JOM}(294)7, 86\text{JOM}(304)87, 87\text{ZAAC}(549)149 \rangle$; (40b), $\text{X} = \text{Y} = \text{S}$ $\langle 83\text{ZOB}1572, 84\text{ZAAC}(508)201 \rangle$; (40c), $\text{X} = \text{O}, \text{Y} = \text{S}$ $\langle 84\text{ZAAC}(508)201 \rangle$; (40d), $\text{X} = \text{Y} = \text{PPh}$, 3,4-benzo $\langle 82\text{PS}(12)265 \rangle$; (40e), $\text{X} = \text{NMe}, \text{Y} = \text{PPh}$ $\langle 82\text{PS}(12)279 \rangle$; (40f), $\text{X} = \text{S}, \text{Y} = \text{PPh}$, $\text{R}^2 = \text{H}, \text{Me}$, $\text{R}^2 = \text{Me}_2$ $\langle 82\text{PS}(12)279, 90\text{ZAAC}(588)133 \rangle$; (40g), $\text{X} = \text{Y} = \text{O}$, $\text{R}^1 = \text{Ph}$, $\text{R}^2 + \text{R}^2 = \text{PhC}\equiv\text{CPh}$, $\text{R}^2 = \text{Me}_2$ $\langle 83\text{CL}209 \rangle$.



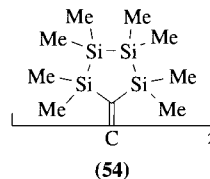
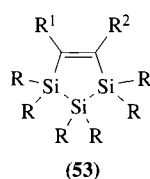
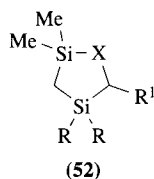
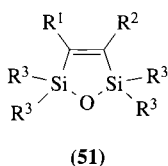
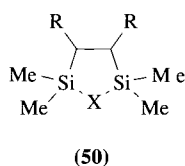
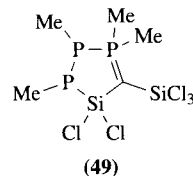
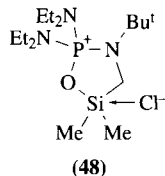
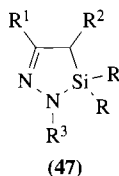
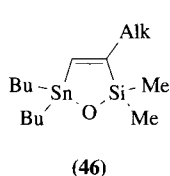
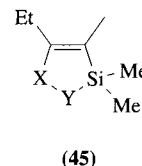
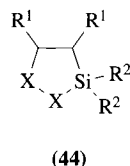
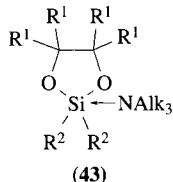
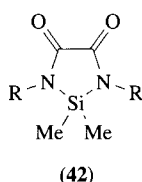
(40) $\text{R}^1 = \text{R}^2 = \text{H}$
in (41a-f)

(41a), $\text{X} = \text{Y} = \text{NR}$, $\text{R}^1 = \text{H}$ $\langle 83\text{CB}136, 86\text{ZN}(B)1230, 91\text{JOM}(407)31, 92\text{JOM}(423)13, 93\text{OM}2881 \rangle$, $\text{R}^2 = \text{Ar}_2$ $\langle 92\text{JOM}(430)\text{C}51 \rangle$, $\text{SiR}_2 = \text{SiCl}_2$, $\text{Si}:(\text{silylene})$ $\langle 94\text{JA}2691 \rangle$; (41b), $\text{X} = \text{Y} = \text{NBu}^1$, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}, \text{Me}$

<83CB136>; **(41c)**, X = Y = O, R¹ = Ph <92JOM(423)13, 92JOM(430)C51>; **(41d)**, X = O, Y = NAlk, R¹ = Ph, R² = Me, OMe <92JOM(423)13>; **(41e)**, X = Y = S, R¹ = H <88RTC440> **(42)**.



(43a), R¹ = H, Me, 4R¹ = benzo, R²₂ = H, Ar, Ar₂ <90JOM(399)11>; **(43b)**, R¹ = Me, Bu^t, CF₃, R²₂ = (OAlk)₂ <83ZOB1076>; **(44a)**, X = S, R¹ = Me, R² = Bu^t <90OM2205>; **(44b)**, X = PPh, R¹ = H, R² = Me <82PS(12)265>; **(45a)**, X = BEt, Y = NR <81AG1009, 88CB597, 88CB709>; **(45b)**, X = BEt, Y = O <88CB709>; **(45c)**, X = BEt, Y = S <88CB709>; **(45d)**, X = BEt₂, Y = NHNa <81AG1009>; **(45e)**, X = BOEt, BO₂Et, Y = NMe <84AG146>; **(46)** <82S218>; **(47a)**, R = Me <81ZAAC(482)65, 83ZN(B)953>; **(47b)**, R² = NR³-N = CR¹-CR² <84ZAAC(514)49>; **(48)** <91MI 424-01>; **(49)** <84ZAAC(518)14>; **(50a)**, X = NR¹, R = H <81JINC2639, 82OM623, 85ACS(B)414, 86SRI991, 86POL643, 87JOM(332)69, 90MM939, 92CB2651, 92JA3393>; **(50b)**, X = O, R = Alk <86T1845>; **(50c)**, X = P Bu^t, PPh, R = H <82PS(12)265>; **(50d)**, X = P ← PPh₂CH₂CH₂PPh₂, R = H <91JOM(418)C6>; **(51)**, R¹ = R² = SiMe₃, R³ = Ar <85JA7706>; **(51b)**, R¹ = SiMe₃, R² = C≡CSiMe₃, R³ = Me <90BCJ3103>; **(52a)**, X = O, R = SiMe₃, R¹ = Ad <94OM1064>; **(52b)**, X = SiH₂, R = Me, R¹ = H <80JOM(195)C1>; **(53a)**, R = Et, R¹ = H, R² = Bu, Ph <83OM1801>; **(53b)**, R = Me, R¹ = Cl, R² = C≡CHet <93JA3111>; **(54)** <93JA1591>.



¹H NMR: **(40a)**, 2.9–3.2 (CH₂CH₂); **(40b)**, 2.7 (CH₂CH₂); **(40f)**, 2.7 (SCH₂), 5.1 (SiH); **(41b)**, 5.9 (SiH); **(41a,b,e)**, 5.5–6.0 (=CH); **(43a)**, 4.5–5.0 (SiH); **(44a)**, 1.3 (SiCH), 3.1 (SCH); **(46)**, 6.8 (=CH); **(47a)**, 1.5–2.2 (CHR²); **(47b)**, 1.7 (CH₂); **(48)**, 3.1 (SiCH₂N); **(50a,c)**, 0.7–1.5 (CH₂CH₂); **(52a)**, 0.0–0.1 (SiCH₂Si), 3.8 (CHAd); **(52b)**, 3.8 (SiH₂); **(53a)**, 6.9 (=CH).

¹³C NMR: **(40a)**, 52.2–53.5 (CH₂CH₂) (44.3 if NR is NSiMe₂X); **(41a,b)**, 110.3–120.0 (=CH); **(41c)**, 137.9 (=CPh); **(41d)**, 131–134 (=CPh); **(42)**, 159–163 (C=O); **(43a)**, 58–65 (CR¹₂); **(44a)**, 13.2 (SiCMe), 54.0 (SCMe); **(45a)**, 149.3–151.6 (CMe), 158.5–159.0 (CEt); **(45b)**, 159.2 (CMe), 158.8 (CEt); **(45c)**, 165.6 (CMe), 161.0 (CEt); **(46)**, 144.4 (=CH), 165.0 (=CR); **(47a)**, 18.6 (CR²), 150.0 (CR¹); **(48)**, 39.2 (SiCH₂N); **(50a)**, 7.1–10.7 (CH₂CH₂); **(50b)**, 17.8 (CHAlk); **(51a)**, 116.6 (=CSiMe₃); **(51b)**, 176.6m (C=C); **(52a)**, –6.8 (SiCH₂Si), 81.6 (CHAd); **(53a)**, 145.6 (=CH); **(53b)**, 120.2, 156.4 (C=C); **(54)**, 62.7 (=C<), 198.0 (=C=).

²⁹Si NMR: **(40a)**, 9.8–10.6 (SiMe₂), –13.1 (SiPh₂); **(40b)**, –6.1 [Si(OPrⁱ)₂], 19.5 (SiMePh), 41.5 (SiMe₂), 57.5 (SiSCH₂CH₂S); **(40c)**, 24.7 (SiMePh); **(40f)**, –8.5 (SiHMe), 7.5 (SiMe₂); **(40g)**, 31.3;

(**41a**), -40.7 (SiCl_2), -19.0 (SiAr_2), 78.3 (Si); (**41c**), -49.8 (SiAr_2); (**41d**), -19.2 ; (**42**), 7.7 – 12.9 ; (**43a**), -38 – -63 ; (**43b**), -70 – -96 ; (**44a**), 48.2 ; (**45a**), 10.0 ($\text{Y} = \text{NH}$), 13.6 ($\text{Y} = \text{NMe}$); (**45b**), 26.8 ; (**45c**), 27.1 ; (**47a**), 19.1 – 21.5 ; (**47b**), 2.2 ; (**48**), -14.8 ; (**50a**), 8.3 – 20.9 ; (**50d**), 34.3 ; (**52a**), -41.8 [$\text{Si}(\text{SiMe}_3)$], 28.2 (SiMe_2); (**53b**), -20.5 , -35.1 , -54.7 .

^{31}P NMR: (**40d**), -48 (*trans*- Ph_2), -51 (*cis*- Ph_2); (**40e**), -93.7 ; (**40f**), -67.8 , -79.1 ; (**44b**), -0.35 (PC), -105.0 (PSi); (**48**), 37.2 ; (**49**), 29 (PMe_2), -49 (PPMe), -120 (SiPMe); (**50c**), -131.2 (PBu^t), -170.5 (PPh); (**50d**), 34.4 .

^{11}B NMR: (**45a**), 44.8 , 46.4 ($\text{Y} = \text{NMe}$), 48.0 ($\text{Y} = \text{NNa}$), 48.5 ($\text{Y} = \text{NH}$); (**45b**), 50.6 ; (**45c**), 73.8 ; (**45d**), -2.3 ; (**45e**), 60.1 ($\text{X} = \text{BOEt}$), 71.5 ($\text{X} = \text{BO}_2\text{Et}$).

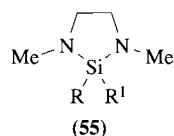
^{14}N NMR: (**42**), $-242/274$; (**45a**), -290 ($\text{Y} = \text{NMe}$); (**45e**), -323 ($\text{X} = \text{BOEt}$), -325 ($\text{X} = \text{BO}_2\text{Et}$).

^{15}N NMR: (**41a**), -282.9 (SiCl_2), -170.3 (Si).

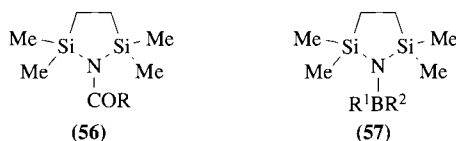
^{17}O NMR: (**45e**), 71 ($\text{X} = \text{BOEt}$), 235.4 (OB; $\text{X} = \text{BO}_2\text{Et}$), 263.3 (OC; $\text{X} = \text{BO}_2\text{Et}$).

Chemical shifts for methyl groups bonded to ring silicon atoms in various structures are in the range ^1H : 0.1 – 0.6 ppm, ^{13}C : -7.5 – $+6.7$ ppm. Substitution of H in (**50a**) ($\text{X} = \text{NH}$) by NbO^{3+} or TaO^{3+} (**87**) induces a high field shift of ^1H and ^{29}Si signals for SiMe_2 groups: $0.07 \rightarrow 0.43$ – 0.44 (^1H), $11.3 \rightarrow 15.9$ – 18.0 (^{29}Si), but almost no changes in ^{13}C spectra and signals for CH_2 groups $\langle 92\text{CB}2651 \rangle$.

Ring NCH_2 entities of 1,3,2-diazasilacyclopentanes (**55**) in ^1H and ^{13}C NMR spectra appear as singlets even with different Si-substituents; $\text{N}-\text{Me}$ signals also merge into a singlet apparently because of rapid inversion of nitrogen atoms $\langle 85\text{JOM}(294)7 \rangle$. Carbon-13 signals of $\text{N}-\text{CH}_2$ and $\text{O}-\text{CH}_2$ entities as well as ^{29}Si signals in five-membered 1,3,2-diazasila- and 1,3,2-dioxasila rings are usually at lower field than for the comparable six-membered rings. This was attributed to a greater strain in the five-membered ring $\langle 85\text{JOM}(294)7$, $86\text{JOM}(304)87 \rangle$ and was used for structural analysis of polymers containing five- and higher membered rings with a SiNSi unit $\langle 93\text{MM}407 \rangle$.

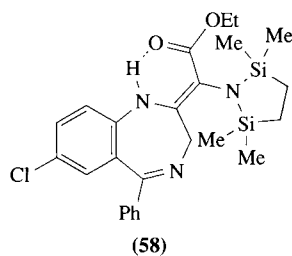


N-Acyl derivatives (**56**) were shown to exist in the amide form by comparison of their ^{13}C , ^{14}N , and ^{17}O NMR spectra with those of the related imidate $\text{RC}(\text{OSiMe}_3)=\text{NSiMe}_3$. In the amide spectra ^{13}C and ^{17}O signals (169 ppm and 403 ppm) were shifted downfield, and ^{14}N signals (-245 ppm) were shifted upfield as compared with the imidate spectrum (161 ppm, 170 ppm, and -120 ppm respectively). The free energy of activation for rotation of the RCO group about the $\text{C}-\text{N}$ bond was determined by coalescence of the ^{29}Si signal to be 10.6 – 12.9 kcal mol $^{-1}$ $\langle 87\text{JOM}(332)69 \rangle$. The same rotational barrier (10.1 – 12.5 kcal mol $^{-1}$) was found for $\text{N}-\text{BR}^1\text{R}^2$ derivatives (**57**) by coalescence of ^1H signals $\langle 81\text{JINC}2639 \rangle$.

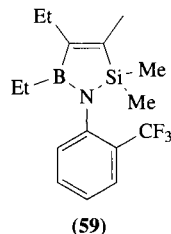


The nuclear Overhauser effect (NOE) in (**58**) between protons of NH , CO_2Et and SiMe_2 groups and nonequivalent ^1H signals of both SiMe_2 groups revealed *cis* orientation of the ester group relative to NH and a restricted rotation of the silaheterocycle about the $\text{C}-\text{N}$ bond $\langle 91\text{JOC}3715 \rangle$.

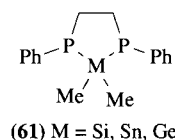
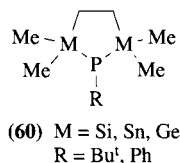
Atropoisomerism of *N*-(*o*- CF_3 -phenyl)substituted derivative (**59**) caused by hindered rotation



about the N—C bond manifests itself in a different chemical shift for the two SiMe groups and, additionally, in “through space” spin–spin coupling with ^{19}F for one signal in each pair ^1H (ppm): 0.25, 0.11 [$^7J(^{19}\text{F}-^1\text{H})$ 1.5 Hz], ^{13}C (ppm): -1.4 , -3.2 [$^6J(^{19}\text{F}-^{13}\text{C})$ 2.6 Hz] <87ZN(B)191>. There is no such effect with an unsubstituted phenyl group.



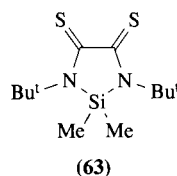
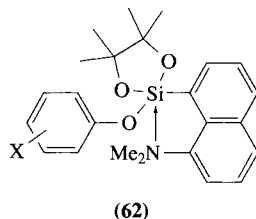
The pyramidal inversion of phosphorus was studied by dynamic NMR spectroscopy using the ^1H signals of N—Me diastereotopic groups in (60) and ^{31}P signals in *Z*- and *E*-diastereomers of (61). Kinetics at coalescence temperature revealed the value of $\Delta G^\ddagger$ to increase in the order of increasing electronegativity $\text{Si} < \text{Sn} < \text{Ge}$ <82JOM(224)247>.



In compounds (12) a dative $\text{N} \rightarrow \text{Si}$ bond is suggested by an upfield shift of ^{13}C (N bonded) and ^{29}Si NMR signals (for 0.8–4.7 ppm and 60–78 ppm, respectively) and by a downfield shift of ^{15}N signals (for 9–15 ppm) compared with analogous compounds in which this bond formation is structurally precluded <83ZOB1076>. A linear relationship was established using coupling constants $^1J(^{15}\text{N}-^{29}\text{Si})$ to determine the free energy of dissociation (60–100 kJ mol^{-1} in the above compounds) for the dative $\text{N} \rightarrow \text{Si}$ bond and to estimate the bond order and length <85JOM(279)343>.

Partial N—Si π -bonding in (29) as compared with (30) is demonstrated by the strong deshielding of the nitrogen atom (^{15}N : -170.3 ppm vs -282.9 ppm in (30)), and also of ring protons (6.75 ppm vs. 5.73 ppm in (30)) <94JA2691>. Intramolecular fluorine exchange in F-bridged pentacoordinated bis(fluorosilyl) benzenes (228) is determined by NMR spectroscopy and rationalized mechanistically <92OM2099>.

Methyl groups of both the dioxasilane and NMe_2 moieties in the coordinative compounds (62) are shown by ^1H NMR spectroscopy to be diastereotopic at 20°C and to coalesce on heating to 55 – 90°C . The free energies of activation of this process were calculated to be 17.2 – 18.3 kcal mol^{-1} and were very little dependent on the nature of X <91OM1236>.



4.24.1.2.4 UV spectroscopy

Some representative UV data are collected in Table 1.

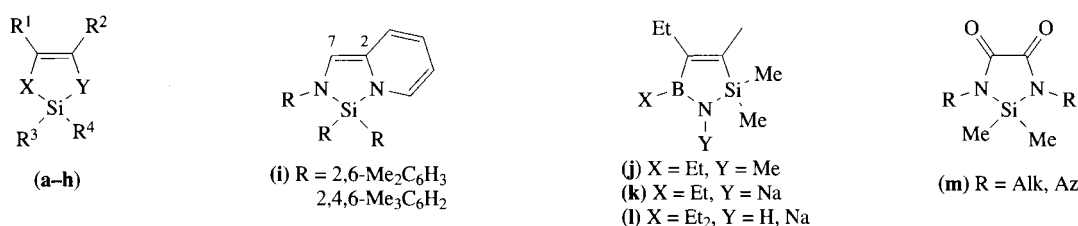
1,3,2-Diazasilacyclopent-4-ene derivatives complexed with palladium and copper halides (Section 4.24.1.3.4.) (cf. (27)) possess UV absorption at 436–655 nm range <86ZN(B)1230>.

Table 1 UV absorption maxima for silacyclopentanes.

Structure	$\lambda_{\max}$ (nm) (log ϵ)	Solvent	Ref.
(10)	225(4.54), 294(4.19)	hexane	83CL209
(188; R ¹ = R ² = Me; R = Bu ^t)	232(4.21), 255(3.98), 322(3.25), 330(2.8)	hexane	83CB136
(63)	320, 355, 465 ($\epsilon = 30 : 10 : 1$)	THF	88ZN(B)1240
(25)	448, 473, 505, 546	hexane	93OM2881
(189)	514 (R = —CH=CH—), 534 (R = H, H)	CH ₂ Cl ₂	92JA1518
(258)	223(4.58)	hexane	84CL393
(234)	218(4.21), 258(4.42), 308(3.92)	c-hexane	93JA3111
(257)	443(2.88)	pentane	93JOM(461)35

4.24.1.2.5 IR spectroscopy

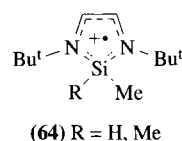
Selected IR frequencies are indicated below (cm⁻¹, bond) for the structures shown in Figure 2. **a**, R¹ = R² = H, R³ = R⁴ = Me, X = Y = NBU^t; **b**, R¹ = R² = H, R³ = R⁴ = Me, X = Y = N-2,6-Me₂C₆H₃; **c**, R¹ = R² = H, R³ = H, R⁴ = Me, X = Y = NBU^t; **d**, R¹ = R² = H, R³ = R⁴ = Bu^t, X = Y = NAlk; **e**, R¹ = R² = H, R³ = R⁴ = Me, X = Y = S; **f**, R¹ = Cl, R² = C≡CHet, R³ = R⁴ = Me, X = Y = SiMe₂; **g**, R¹ = R² = R³ = R⁴ = Me, X = O, Y = S; **h**, R¹ = R² = Ph, R³ = R⁴ = Me, X = Y = O; **i**, R = 2,6-Me₂C₆H₃, 2,4,6-Me₃C₆H₂; **j**, X = Et, Y = Me; **k**, X = Et, Y = Na; **l**, X = Et₂, Y = H, Na; **m**, R = Alk, Ar.

**Figure 2**

C=C: **a**, 1628 <83CB136>; **b**, 1588 <83CB136>; **c**, 1611 <83CB136>; **d**, 1610–1645 <91JOM(407)31>; **e**, 1600 <88RTC440>; **f**, 1545 <93JA3111>; **g**, 1640 <89ZOB1916>; **h**, 1650 <83JCS(P1)875>; **i**, 1588–1591 (C²=C⁷) <93OM2881>; **j**, 1560 <81AG1009>; **k**, 1550 <81AG1009>; **l**, 1535 <81AG1009>; Si—H: **c**, 2065, 735 def. <83CB136>; N—H: **l**, 3300, 3355 <81AG1009>; C=O: **m**, 1680–1720 <85ZN(B)277>; C=C=C: (**54**), 1860 <93JA1591>; C=N: (**257**), 1581 <93JOM(461)35>; Si—O: (**175**), 1050 <94OM1064>.

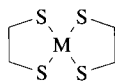
4.24.1.2.6 Photoelectron and ESR spectroscopy

Low values of the first photoelectron potential IE₁ (6.3–6.4 eV) for the alkyl substituted 1,3,2-diazasilacyclopent-4-enes (**188**) demonstrate ready formation of the corresponding stable radical cations (**64**). ESR spectra of the latter have significant spin–spin coupling constants $\alpha_{29\text{Si}}$ (0.76–0.91 mT) and an especially large value for $\alpha_{\text{H-Si}}$ (1.75 mT) which indicates a strong hyperconjugation implicating involvement of the silicon region of the ring in the π -system of the radical cation. The distribution of spin density was calculated to be in accord with this conclusion: 0.2e on each carbon, 0.3e on each N—Si <83CB136>.



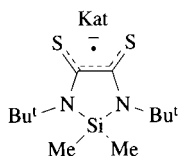
UV photoelectron spectroscopic study of spiranes (**65**) allowed a quantitative estimation of spiroconjugation of the lone pair orbitals of the sulfur atom. This spiroeffect markedly decreases

with increasing size of M. σ -Bonding energy M—S scarcely changes with M, being in the range of 10–11 eV $\langle 83JOM(244)343 \rangle$.



(65) M = C, Si, Ge, Sn

Radical anions of the alkyl substituted 1,3,2-diazasilacyclopentane-4,5-dithione in a contact ion pair with Li^+ or with K^+ -cryptand (66) give low α_N (0.16–0.17 mT) in ESR spectra indicating distribution of spin population over ESR inactive centers, especially on sulfur. A low spin density is revealed even on Li^+ ($\alpha_{7\text{Li}} = 0.0108$ mT) which appears to be out of the ring plane $\langle 88ZN(B)1240 \rangle$. ESR study showed that radical cation (34; $\text{R}, \text{R}^1 = \text{Me}$) gave no signals in solution suggesting dimerization which was confirmed by cryoscopic measurements, whereas radical cation (34; $\text{R} = \text{Pr}^i$, $\text{R}^1 = \text{Bu}^i$) with bulky substituents hindering dimerization had a complex ESR spectrum $\langle 83AG630 \rangle$.



(66) Kat = Li^+ , K^+ -2,2,2-cryptand

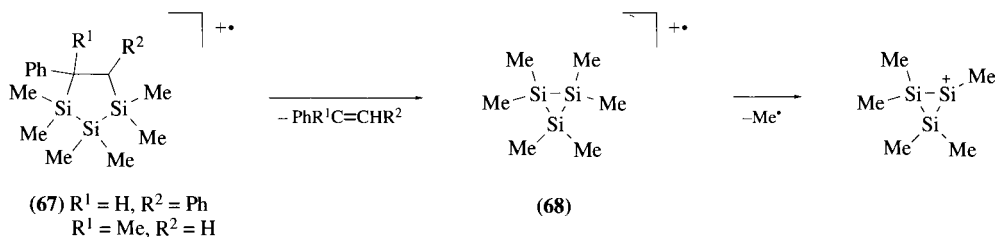
4.24.1.2.7 Mass spectrometry

Molecular ions have been observed for 1,3,2-dioxasila- $\langle 86KGS272, 88JC13 \rangle$, 1,2,4-oxadisila- $\langle 94OM1064 \rangle$, 1,2,3-dithiasila- $\langle 90OM2205 \rangle$, 1,3,2-dithiasila- $\langle 83BSB753 \rangle$, 1,2,5-azadisila- $\langle 81ZAAC(482)65, 85JOM(294)7, 86JOM(304)87, 86T1845, 87JOC678, 92CB2651 \rangle$, 1,2,3-trisila- $\langle 82CC1366 \rangle$ and 1,2,3,4-tetrasilacyclopentanes $\langle 93JA1591 \rangle$, 1,2,5-oxadisila- $\langle 82JOM(236)7, 84CL393, 84JOM(272)123, 85CL643, 85JA7706, 90BCJ3103, 93OM1113 \rangle$, 1,3,2-diazasila- $\langle 82IC3798, 83CB136, 87ZAAC(549)149, 91JOM(407)31, 93OM2881 \rangle$ and 1,2,3-trisilacyclopent-4-enes $\langle 93JA3111 \rangle$. 3,4-Dithione derivatives of 1,2,5-azadisilacyclopentanes split off SiMe_2 fragments extremely easily $\langle 88ZN(B)1240 \rangle$, whereas 3,4-dione derivatives may afford molecular ions $\langle 85ZN(B)277 \rangle$. 1,3,2-Dioxasilacyclopentanes give molecular ions even for their strained fused (10) $\langle 83CL209 \rangle$ and steroid derivatives $\langle 84MI 424-02, 86CPB3298 \rangle$. For the latter the molecular ion observation was recommended as a microanalytical tool.

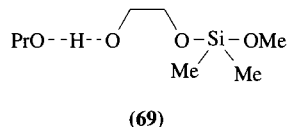
The fragmentation of 1,2,5-azadisilacyclopentanes involves loss of hydrogen or Me from an NMe rather than from a SiMe entity due to the much lower requirements for rehybridization and bond angle in the first case compared with the second case, the strained five-membered ring being especially sensitive to these requirements. Hence, silicon atom is retained in almost all ions of the fragment $\langle 85JOM(294)7 \rangle$.

Detailed investigations of mass spectrometric behavior of 1,3,2-dioxasilacyclopentanes were made $\langle 84MI 424-02, 86CPB3298, 86KGS272 \rangle$, with a special attention to chromass spectrometry $\langle 88JC13 \rangle$. 1,3,2-Dithiasilacyclopentane is characterized by a high abundance of its molecular ion $\text{M}^{+\bullet}$ and prevailing elimination of neutral nonradical fragments CH_4 , C_2H_2 , C_2H_4 , $\text{C}_2\text{H}_4\text{S}$, H_2S , although the base peak ion is formed by $\text{Me}\cdot$ loss from $\text{M}^{+\bullet}$ $\langle 83BSB753 \rangle$.

1,2,3-Trisilacyclopentanes (67) under electron impact appear mostly to lose neutral olefin and form cyclotrisilane radical cation (68) $\langle 82CC1366 \rangle$. However, 1,2,3-trisilacyclopent-4-enes $\langle 93JA3111 \rangle$ and 1,2,3,4-tetrasilacyclopentanes $\langle 93JA1591 \rangle$ produced no (68).



Ion cyclotron resonance was used to show that 2,2-dimethyl-1,3,2-dioxasilacyclopentane in mixture with PrONO and HCO_2Me interacts under electron impact with the intermediate methanol-propoxide anion $[\text{PrO}\cdots\text{H}\cdots\text{OMe}]^-$ to give a mass peak corresponding to (69); analogous products with two OMe or two OPr groups are absent <84JCS(P2)1167>.

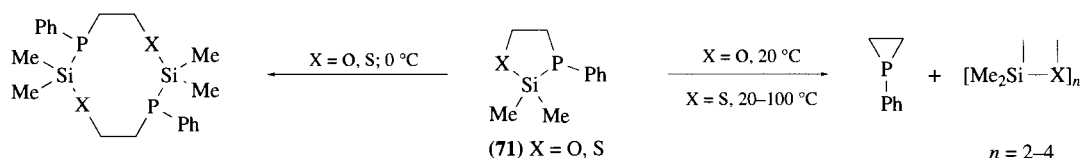
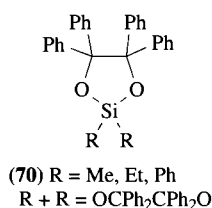


4.24.1.3 Reactivity of the Ring Systems Containing Silicon

All atoms of the heterocycles in Section 4.24.1 are known to react with electrophiles, whereas only silicon and boron atoms have been reported to be susceptible to nucleophilic attack. Both kinds of attack usually lead with the ring opening, which is especially useful for the removal of stabase protection (Section 4.24.1.3.3) from the amino group. Diazasila rings are prone to form radical cations and radical anions and also a remarkably stable cyclic silylene (Section 4.24.1.3.8). The insertion of short-lived species into the 1,2,5-oxadisilacyclopentane ring, the exchange of Pt-link by acetylenes and olefins, and the efficient sulfur transfer (Section 4.24.2.3.11) demonstrate further possibilities of the chemistry reviewed here. Interconversions and many other reactions of novel 1-elementa-2-sila-5-boracyclopent-3-enes are covered in different sections. Reactions with substituents often lead to spiranization or to formation of tricyclic fused systems (Section 4.24.1.3.10). Diverse transformations of stabase protected amines formally belong to this section also; they are too far from the topic to be reviewed, but references are supplied. Reactions with reagents for which the electrophilic or nucleophilic nature and site of attack are not clear are placed in Section 4.24.1.3.11.

4.24.1.3.1 Thermal and photochemical reactions formally involving no other species

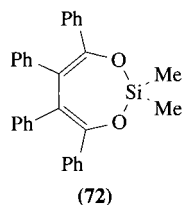
4,4,5,5-Tetraphenyl-1,3,2-dioxasilacyclopentanes (70) at temperatures of at least 120°C undergo ring cleavage of the C—C bond to form biradicals (or polyradicals in the case of spirosiloxane (70; $\text{R} + \text{R} = \text{OCPh}_2\text{CPh}_2\text{O}$)) which are effective initiators of styrene polymerization. Photolytically the compounds are stable <86PB95>. 1-Oxa(thia)-2,3-silaphosphacyclopentanes (71) decompose (oxa easier) at RT to give small and larger rings (Scheme 1) <82PS(12)279>.



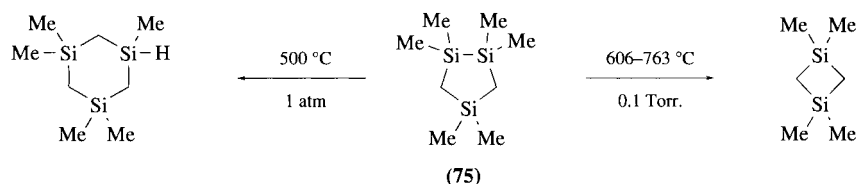
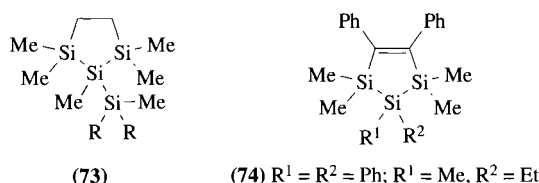
Scheme 1

N,Si-Alkylsubstituted 1,3,2-diazasilacyclopent-4-ene (188; $\text{R} = \text{Bu}^t$, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$) by heating in daylight forms *N,N'*-dialkylsubstituted 1,4-diazabutadiene <86ZN(B)1230>. Thermolysis of

the strained bicycle (**10**) causes ring expansion (**72**). Photolysis of the end product (**72**) through a Pyrex filter reverses the reaction completely, whereas the same irradiation through a quartz wall induces an equilibrium (**10**): (**72**) = 45 : 55 <83CL209>.

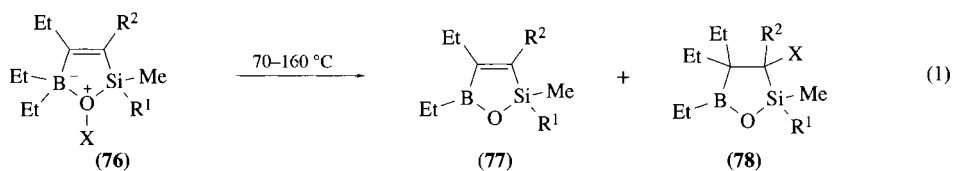


2-Silylated 1,2,3-trisilacyclopentanes (**73**) under photolysis split off their central Si atom as a silylene (trapped by a scavenger) <85JOM(292)167>. 1,2,3-Trisilacyclopent-4-enes (**74**) split off only their central silicon atom as silylene by flash vacuum thermolysis (650–720 °C), whereas by photolysis both central and terminal Si atoms may be extruded depending on the nature of the substituents (Ar better than Alk-stabilized silylene) <84CL393>. Pyrolysis of hexamethyl-1,2,4-trisilacyclopentane (**75**) is unique for Si-compounds since different products arise at normal <76ZAAC(419)249> and low <82OM1453> pressure (Scheme 2).

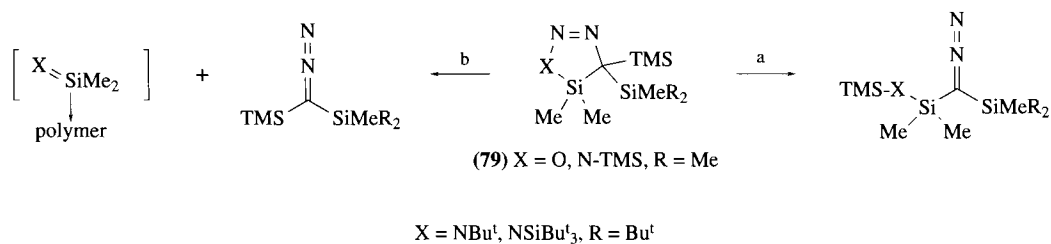


Scheme 2

On heating, substituents on oxygen or boron in (**76**) split off to give (**77**) or migrate to the double bond to give (**78**) (Equation (1)). In the case of X = CH₂NMe₂ bridging of the migrated group to boron forms the norbornane-like heterocycle (cf. (**38**)). Substituents X = Me, SiMe₃ render (**76**) much more resistant to heat <91CB1003>.



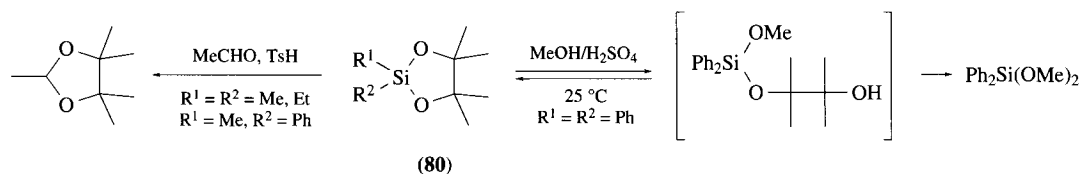
3-TMS-1,2,3,4-triazasilacyclopent-1-ene (**79**; X = NSiMe₃) begins to decompose at –10 °C by (a) 1,3-TMS-shift with ring opening, and (b) [2 + 3] cycloreversion (Scheme 3). The 3-oxa analogue (**79**; X = O) could not be observed in solution even at –65 °C and its formation (Section 4.24.1.4.6) was deduced from decomposition products.



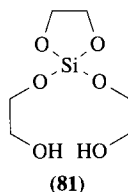
Scheme 3

4.24.1.3.2 Electrophilic attack at ring oxygen

Acid methanolysis cleaves the 1,3,2-dioxasilacyclopentane (**80**) ring at the O atom (Scheme 4); the first step appears to be a fast opening-and-closing process <88CR(307)1445>. Reaction with aldehydes assisted by acid catalysis constitutes a convenient method for preparation of acetals (Scheme 4) <87MI 424-01>. Neutralization of (**182**) with HCl gas gives the diglycolato derivative (**81**) <91NAT642>.

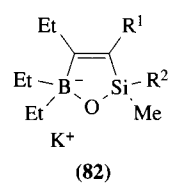
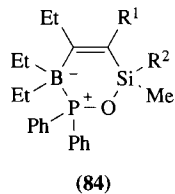
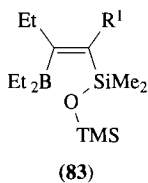
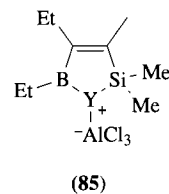


Scheme 4



(81)

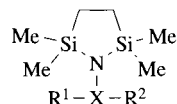
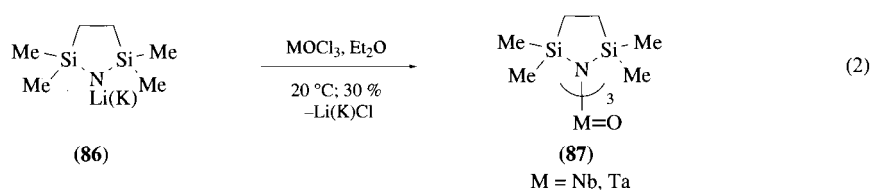
1,2,5-Oxasilaboracyclopent-3-enes (**82**) are *O*-methylated smoothly to give stable internal borato-oxonium compounds (**76**; X = Me) <91CB1003>. By means of XCl reagents other substituents are easily introduced to the ring oxygen atom (X = SiMe₃, GeMe₃, SnMe₃, PbMe₃ and H) of which the last three impart to the substituted derivatives a tendency towards thermal transformations (Section 4.24.1.3.1), while the first two strongly lower the donating ability of the oxygen atom and lead to cleavage of the B—O bond to form an open chain structure (**83**) <91CB1003>. A Ph₂P substituent, introduced by Ph₂PCl, is efficiently inserted into the O—B bond to form (**84**) <91CB1017>. A stable donor-acceptor complex (**85**) is readily formed with AlCl₃ at the ring O <88CB597> or S <88CB709> atom.

R¹, R² = Me, Et, PhR¹, R² = Me, Et, Ph

Y = O, S

4.24.1.3.3 Electrophilic attack at ring nitrogen

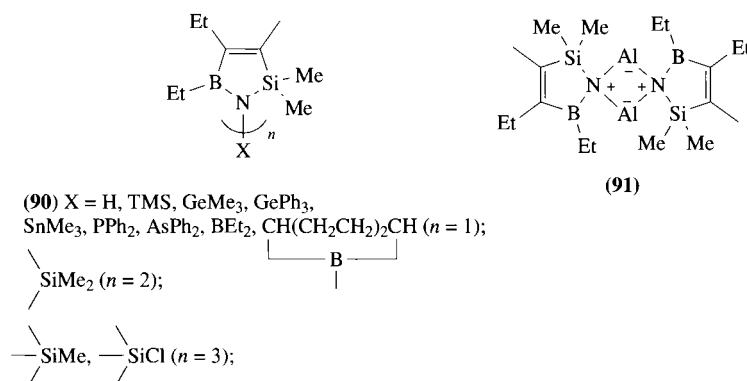
1,2,5-Azadisilacyclopentanes with an unsubstituted ring nitrogen atom are easily *N*-metallated by BuLi in hexane, Et₂O or THF <79IC347, 81JINC2639, 86POL643, 92CB2651>, or KH in THF <88CPB2342, 92JA3393>. In the reaction with AlMe₃ in heptane/PhCl at 120°C methane is evolved and nitrogen atoms are bridged by AlMe₂ groups to form a square ring (**21**) <90POL2205>. Li- or K-derivatives (**86**) are transformed into metal complexes (**87**) (Equation (2)) <92CB2651> and (**22**) <92JA3393> by action of the appropriate metal reagents. Li-derivative (**86**) is *N*-borilated to (**88**) by chloroboranes ClB(Ph)NMe₂, Cl₂BPh and BCl₃ (to give (het)₂BCl) at RT <81JINC2639> and phosphinylated by PCl₃ <79IC347> and (Me₃Si)₂CHPCl₂ <86POL643> to give *N*-phosphinyl derivatives (**89**). K-derivative (**86**) is *N*-alkylated by AlkBr (29–47% yield) in THF at reflux <88CPB2342>.



(**88**) X = B; R¹ = Ph, R² = Cl, NMe₂

(**89**) X = P; R¹ = R² = Cl; R¹ = Cl, R² = CH(TMS)₂

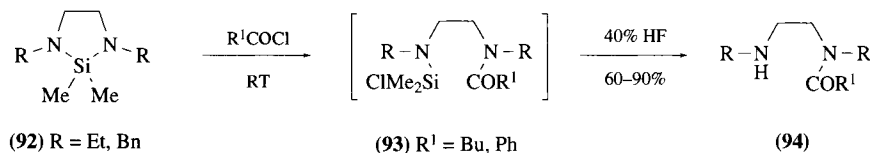
Sodium- and potassium-derivatives of 1,2,5-azasilaboracyclopentenes are *N*-substituted (**90**) with various electrophilic substituents by refluxing with XCl, XCl₂ or XCl₃ in ether or THF (75–94% yield); AlCl₃, AlEt₃, FeCl₂ or CoCl₂ give dimerized substituted products (**91**) and (**35**) <87CB669>.



Susceptibility of the nitrogen atom to proton attack is widely used to remove stabase (SB) protection (Section 4.24.1.4.4) from amino groups. Acid hydrolysis of the 1,2,5-azadisilacyclopentane ring proceeds under very mild conditions at RT and lower, usually with dilute aqueous HCl as such <88CPB2342> or in MeOH <83JOC3318, 90TL6725>, EtOH <84TL5271, 87JOC678, 91JOC3715>, THF <87TL5791> or Et₂O as a two-phase system <85ACS(B)414, 88EUP293351, 90TL6721, 91JOC5147>, with H₃PO₄ <90TL6721>, CF₃CO₂H, AcOH <91JOC1933, 91T9807>, tartaric acid <87MI 424-02>, phosphate buffer <90HCA405>, aqueous NH₄Cl <85JA1698, 92JOC3906, 93JOC3811>, (CF₃CO)₂O or tbaq <87MI 424-02, 90TL6721> may also be used. Sometimes repeated reprecipitations from THF or benzene by MeOH suffice <90MM939>. Benzostabase (BSB) protection (Section 4.24.1.4.4) is somewhat more stable <90TL6721, 90TL6725, 91T9807>, e.g. in phthalate buffer pH 3, BSB disappears in 30 min, and SB

in 6 min at RT <90TL6725>. Specifically BSB is stable to Lewis acids, whereas SB is not <91TL807>. Less popular means of SB deprotection are bases (Section 4.24.1.3.6) and reducing agents (Section 4.24.1.3.8).

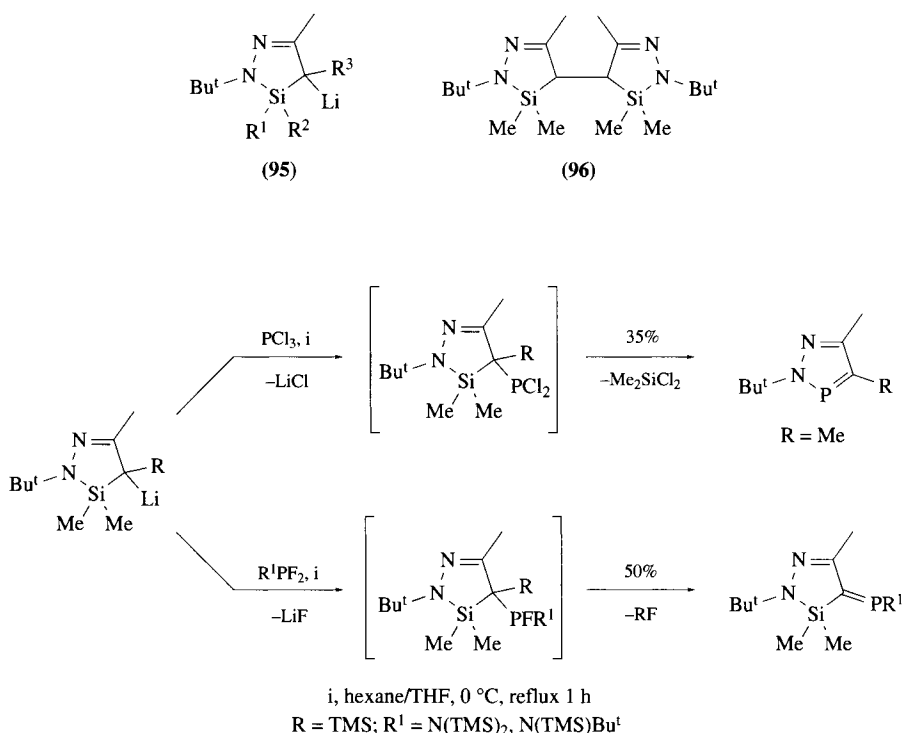
1,3,2-Diazasilacyclopentane fully substituted at nitrogen and silicon atoms (**92**) is ring opened by action of acyl chlorides to give monoacylated diamines (**94**) (Scheme 5). The second amino group is too deactivated by the SiCl substituent for acylation to occur in the ring-opened product (**93**) <82TL979>. Bis-acyl chlorides in xylene at reflux react with (**92**) on both ring nitrogen atoms to give di- and tetraamidomacrocycles in low yield <88T5845>.



Scheme 5

4.24.1.3.4 Electrophilic attack at ring carbon

C-Lithiated (by BuLi) 1,2,3-diazasilacyclopent-4-enes (**95**) are C-silylated by various chloro and fluoro silanes <81ZAAC(482)65, 84ZAAC(514)49>; C-stannylated by Me₃SnCl; C-methylated by MeI; C-borilated by BF₃·Et₂O (bridging two rings) <81ZAAC(482)65>; C-phosphinylated by Cl₂PPh, F₂PN(SiMe₃)₂, F₂PN(SiMe₃)Bu^t <83ZAAC(501)57> and Cl₂PBu^t <82AG461>; and C-arsinylated by Cl₂AsBu^t <83ZAAC(501)57>, all near RT. The unlithiated form (**95**) may be C-monobrominated by reflux with NBS in CCl₄ (20% yield) <81ZAAC(482)65>. The C-lithiated form is oxidatively coupled by heating with chlorides of bivalent transition metals to give products of the type (**96**) presumably via neutral radicals according to cyclovoltammetry which showed the oxidation potential of **95**; R¹ = R² = Me, R³ = H to be E_p = 1.24 V <83ZN(B)953>. Substitution with phosphorous halides may lead to further transformations (Scheme 6) <83ZAAC(501)57>.

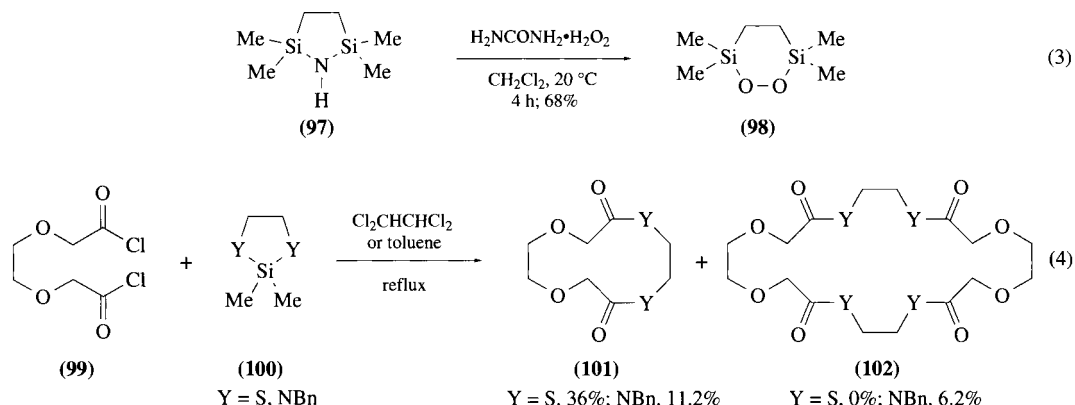


Scheme 6

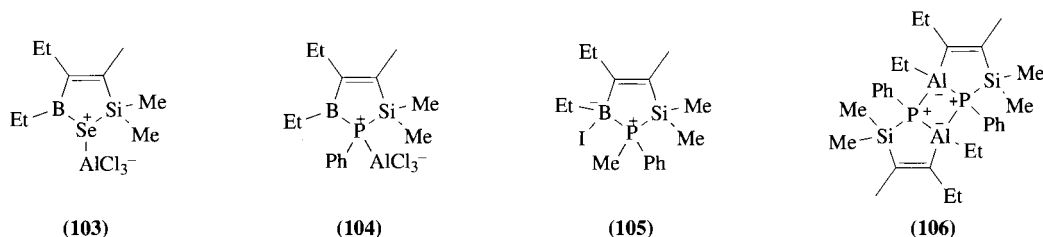
1,3,2-Diazasilacyclopent-4-enes (**188**; $R = \text{Bu}^t, \text{CHPr}^i$; $R^1, R^2 = \text{Me, Ph, Cl}$) readily form complexes with PdCl_2 , PdBr_2 , CuCl , and CuBr at the ring $\text{C}=\text{C}$ bond (cf. (**27**)) $\langle 86\text{ZN(B)1230} \rangle$. The $\text{C}=\text{C}$ double bond also adds *o*-quinones to give (2 + 4) cycloadducts $\langle 86\text{ZN(B)1230} \rangle$.

4.24.1.3.5 Electrophilic attack at ring silicon, sulfur, selenium, and phosphorus

2,2,5,5-Tetramethyl-1,2,5-azadisilacyclopentane (**97**) silylates diazoquinone entities at O atoms in novolak resin $\langle 89\text{MI 424-01, 90MI 424-01} \rangle$. It is converted to cyclic silyl peroxide (**98**) by treatment with the urea complex of H_2O_2 (Equation (3)) $\langle 92\text{TL8015} \rangle$. 1,3-Dithia(diaza)-2-silacyclopentanes (**100**) are ring opened by diacid dichlorides (**99**) to give macrocycles of monomeric (**101**) and dimeric (**102**) types (Equation (4)) $\langle 88\text{T5845} \rangle$.

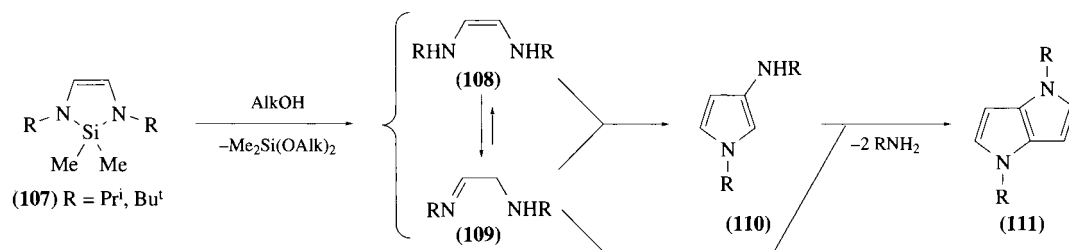


AlCl_3 adds to the Se atom of the 1,2,5-selenasilaboracyclopent-3-ene ring to form adduct (**103**) $\langle 88\text{CB1955} \rangle$. The 1,2,5-phosphasilaboracyclopent-3-ene ring reacts at its P atom with AlCl_3 , MeI and AlEt_3 at 20–50 °C to give (**104**), (**105**) and (**106**) respectively, the last being a result of replacement of boron for aluminum $\langle 88\text{CB1381} \rangle$.



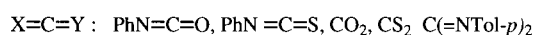
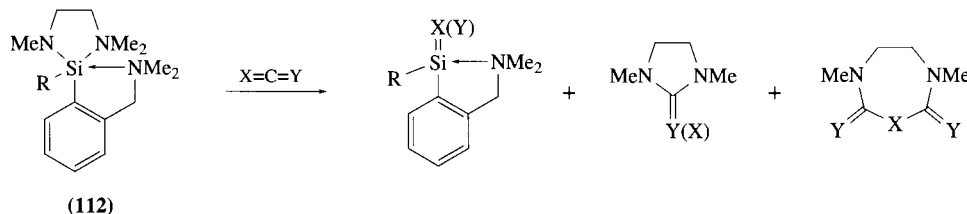
4.24.1.3.6 Nucleophilic attack at ring silicon

1,3,2-Diazasilacyclopent-4-enes (**107**) in MeOH undergo alcoholysis to give 3-aminopyrroles (**110**) presumably via diamino ethene (**108**) and its tautomer (**109**) (Scheme 7). With a limited amount of alcohol the process slows down and the major part of (**110**) succeeds in interacting with (**109**) to give fused pyrroles (**111**) $\langle 89\text{CB129} \rangle$.



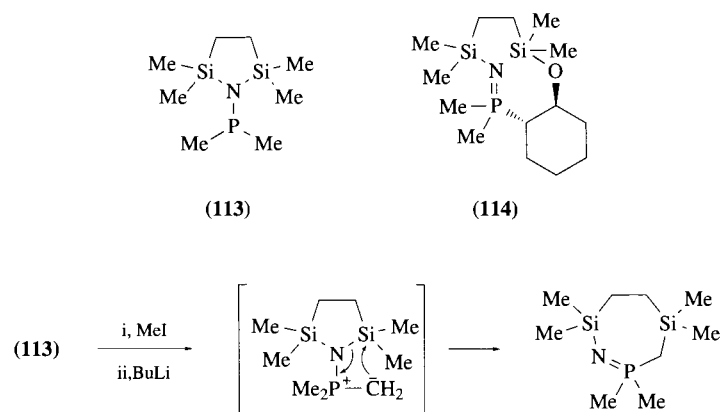
Scheme 7

Heterocumulenes $X=C=Y$ insert themselves into one and (to a lesser degree) both Si—N bonds of 1,3,2-diazasilacyclopentanes (**112**) with expansion of the ring, usually at -50°C to RT. This is followed by transformation to other products generally in fair to high yields (Scheme 8). Carbonyl compounds and a diphosphetane derivative react similarly [91JOM(419)9].



Scheme 8

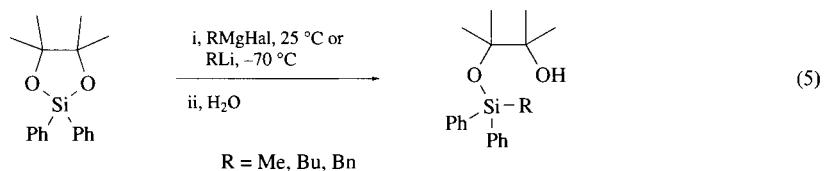
N-Phosphinyl derivative (**113**) reacts with cyclohexane epoxide in the presence of ZnBr_2 catalyst to give a cyclic phosphinimide (**114**). This result implies an intramolecular silicon 1,5-transfer despite unfavorable geometry which appears to require chair-chair inversion after the initial *trans*-diaxial epoxy ring opening [84JOC1828]. Intramolecular 1,3-silyl shifts from N to C occur when negative charge is developed on the carbon adjacent to the P atom, e.g. Scheme 9 [79IC347, 84IC2063].



Scheme 9

SB protection of amino groups has been removed by a catalytic amount of NaOMe in MeOH at 50°C [86SC809], KOH in MeOH at reflux [88TL6537] and BSB protection has been removed by inorganic alkalis in MeOH at RT [91T9807], but as a rule deprotection by acid hydrolysis proceeds more readily (cf. Section 4.24.1.3.3).

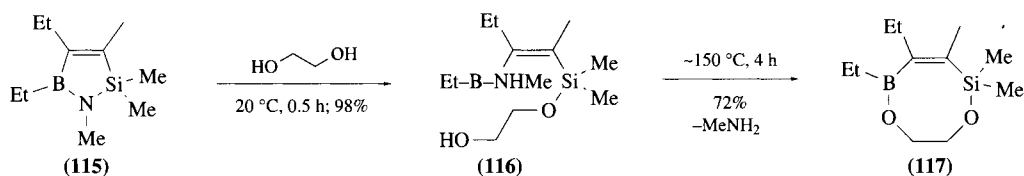
1,3,2-Dioxasilacyclopentanes are readily hydrolyzed in neutral media at RT to $\text{HO}-\text{C}-\text{C}-\text{OSiR}_2\text{OH}$; with bulky substituents at the silicon atom ($\text{R} = \text{Bu}^t$) an alkaline medium (pH 10) is required [82TL4871]. In MeOH with K_2CO_3 1,2-diols are obtained in 75–90% yield at RT [92TL2099]. Organo Li and Mg compounds react very rapidly at low and ambient temperatures with these cyclic disiloxanes (Equation (5)) [88CR(307)1351].



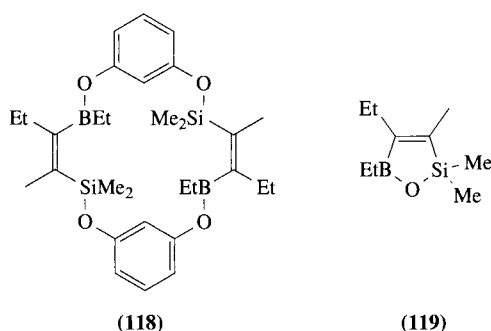
Pentacoordinated silicon compounds with a dative $\text{F} \rightarrow \text{Si}$ bond ((**15**) and (**16**)) are obtained from the corresponding spirosiloxanes and R_4NF at RT [81JA5269, 83ZN(B)938]. The trigonal-bipyramidal geometry of Si atom bonds in the pentacoordinated complex (**13**) is in line with its electrophilic character which favors ready substitution of hydrogen at silicon by AlkOH , ArOH , AlkCO_2H , ArCO_2H or by chlorine atom of PCl_5 (reflux in CCl_4) [91OM1236]. The pentacoordinated complex

with dative $O \rightarrow Si$ bond (**182**) enters the related nucleophilic exchange equilibrium reactions on heating with alcohols and 1,2-diols, including polyglycols, to give other spirocompounds and also oligomers and polymers in high yields <91NAT642>.

1,2- and 1,3-Diols attack the Si atom in 1,2,5-azasilaboracyclopent-3-enes (**115**) to give at RT an open-chain structure (**116**) which is closed to an expanded heterocycle (**117**) at 110–160 °C (Scheme 10); dioxybenzenes and -naphthalene react similarly, 1,3-dioxybenzene affording a macrocycle (**118**) <90CB1013>. Monohydroxy alcohols (at 20–70 °C) and phenols (at 130–150 °C) give *B,Si*-dialkoxy (diphenoxy) analogues of (**117**) <88CB597, 90CB1013>. Water replaces the nitrogen in (**115**) for oxygen atom at RT to form (**119**) as a complex with $MeNH_2$ which is removed by heating with $Et_2O \cdot BF_3$ in ether <88CB597>. Aliphatic and aromatic mono- and diamines at 120–150 °C react by their primary amino groups to exchange the N in (**115**) ($NMe \rightarrow NR$). Monosubstituted hydrazines in this transamination (70–150 °C) give the *N*-aminoazasilaboracyclopentene or the diazasilaboracyclohexene isomer <87CB669>



Scheme 10

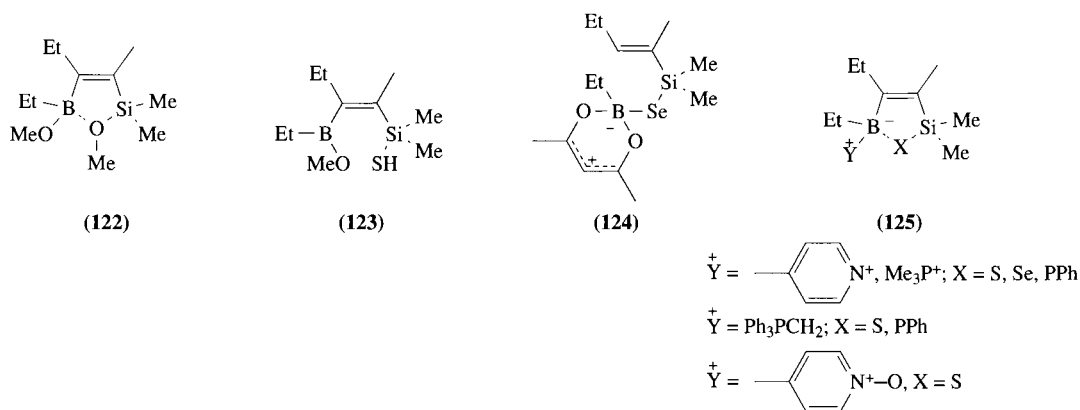


4.24.1.3.7 Nucleophilic attack at ring boron

The 1,2,5-azasilaboracyclopent-3-ene ring (**115**) is opened and recyclized by AcOH to the oxa analogue (**119**) apparently through initial attack by carbonyl oxygen at ring boron assisted by coordination of the ring N to the carbonyl C <88CB597>. Acetic acid cleaves the 1,2,5-oxa(thia)silaboracyclopent-3-ene ring (**120**) by nucleophilic attack at boron; PCl_5 attacks both boron and silicon atoms <88CB597, 88CB709>.

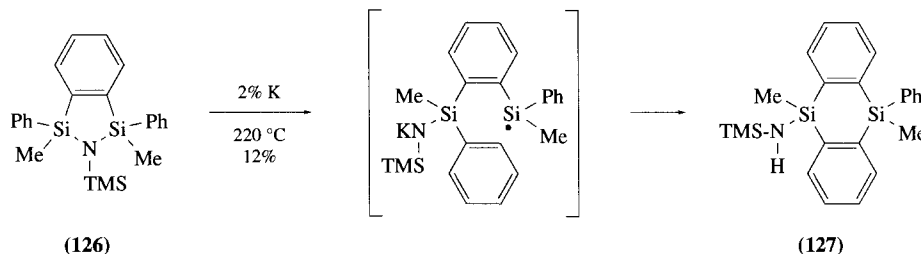
Methanol opens these rings at 20–60 °C to produce dimethoxy compounds (**122**) <88CB709, 88CB1381, 88CB1955>; in the case of the thia ring (**120**; $X = S$) an intermediate (**123**) was isolated indicating that initial attack is at boron <88CB709>. The oxa ring (**120**; $X = O$) is opened by heating with alcohols at over 100 °C at which temperature the $B-C$ bond undergoes protolysis <88CB597>. Nucleophilic attack of acetylacetone (**121**) at the boron atom of (**120**; $X = S, Se, NMe, PhP$) results in recyclization to the oxa ring (**120**; $X = O$); in the case of (**120**; $X = Se$) cleavage of the $B-C$ bond predominates (~60%) to give (**124**) <88CB597, 88CB709, 88CB1381, 88CB1955>.

Oxidation of (**120**; $X = O$) and (**120**; $X = NMe$) by amine *N*-oxide leads to insertion of an oxygen atom into the $B-C$ bond (Scheme 11) <84AG146, 88CB597>. The phosphorus analogue (**120**; $X = PPh$), which exists as a dimer, also exchanges PPh for oxygen on reaction with amine *N*-oxides <88CB1381>. Nucleophiles ($Y:$) add to boron in 1,2,5-thia(selena, phospho)silaboracyclopent-3-enes at RT to give dipolar adducts (**125**).



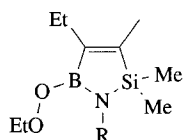
Benzo-1,2,5-azadisilacyclopentane (**126**) ring opens on heating with potassium to give radical species which recyclize to a new condensed system (**127**) (Scheme 12) <88MI 424-01>. Alkyl substituted 1,2,3-diazasilacyclopent-5-enes have a very low gas-phase oxidation potential (6.2 eV) and are oxidized at RT to radical cation (**34**) by $\text{AlCl}_3/\text{CH}_2\text{Cl}_2$ system with retention of the conformation of the ring and substituents <83AG630>. 1,3-Di-*i*-butyl-2,2-dimethyl-1,3,2-diazasilacyclopentane-3,4-dithione is reduced to radical anion (**66**) by K in the presence of 2,2,2-cryptand or $\text{LiB}(\text{Ph})_4$ in THF

at -73°C <88ZN(B)1240>. On treatment with Na/Hg at 20°C for 9 days phenanthroline Si-complex (**28**) with two dative $\text{N} \rightarrow \text{Si}$ bonds undergoes a reductive coupling via single C—C bond formation to give a dimer in both halves of which one dative $\text{N} \rightarrow \text{Si}$ bond transforms into a normal covalent one <92JA1518>.



Scheme 12

Nontypically (cf. Section 4.24.1.3.3), NaBH_4 in EtOH at reflux was used to remove BSB protection (Section 4.24.1.4.4) from an amino group <90JMC2569>. Hexamethyl-1,2,3-dioxasilacyclopentane (**254**; $\text{X} = \text{O}$) oxidizes I^- in acid medium to I_2 and Ph_3P to Ph_3PO by heating <82JOM(225)177>. Tetramesityl-1,2,3,5-dioxadisilacyclopentane (**251**) is reduced by LiAlH_4 to tetramesityl-1,3-disilapropane-1,3-diol and by Ph_3P to tetramesityl-1,2,4-oxadisilacyclobutane <89TL6705>. Molecular O_2 is inserted at RT into the B—C bond of 1,2,5-azasilaboracyclopent-3-ene (**90**; $\text{X} = \text{Alk}$, Ph ; $n = 1$) to give in high yield peroxide (**128**) which is stable below -20°C <84AG146, 88CB597>. The O-analogue (**120**; $\text{X} = \text{O}$) of (**90**) reacts faster but gives no stable insertion product <88CB597>. Stable silylene (**29**) was obtained by reduction of dichloro derivative (**29**) by K <94JA2691>. No change of (**29**) was noticed after heating its solution in toluene at 150°C for 4 months. It is distilled at $85^{\circ}\text{C}/0.1$ torr undecomposed, and does not react with typical trapping reagents, or with Lewis bases. It gives a stable sandwich π -complex (**30**) $_2\text{Ni}(\text{CO})_2$ thus manifesting its aromatic nature.

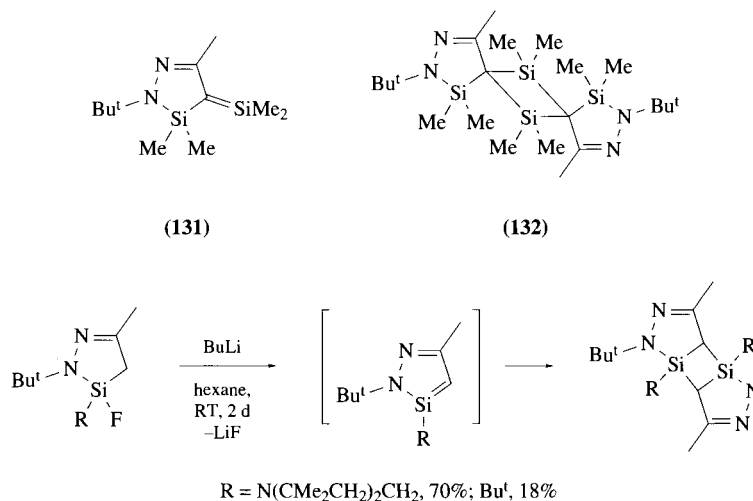
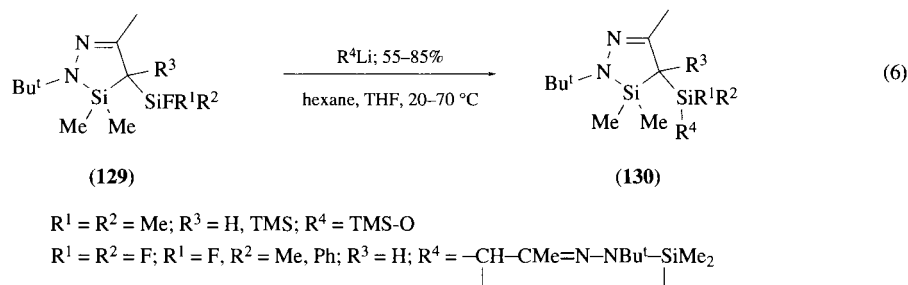
(128) $\text{R} = \text{Me}$, Ph , Bn

4.24.1.3.9 Reactions with cyclic transition states

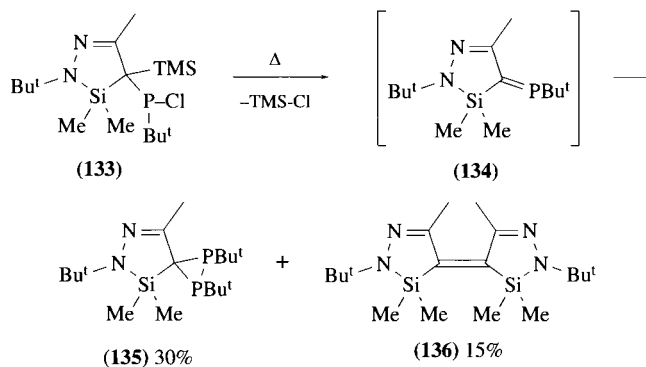
The products from 1,3,2-diazasilacyclopent-4-enes (**107**; $\text{R} = \text{Bu}^t$, $2,6\text{-Me}_2\text{C}_6\text{H}_4$) and TCNE or acetylene dicarboxylic esters result from cleavage of initial (2 + 2) cycloadducts which are isolable in the case of (**107**; $\text{R} = \text{Bu}^t$) and the acetylenic ester <87CB795>.

4.24.1.3.10 Reactions of substituents

Fluorine attached to the external Si atom in silylated 1,2,3-diazasilacyclopent-5-enes (**129**) undergoes nucleophilic displacement by R^4Li to give (**130**) (Equation (6)) <84ZAAC(514)49>. Lithiated compounds (**129**; $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Li}$) lose LiF to give silaethenes (**131**) which (2 + 2)-cyclo-dimerize to give a dispirosystem (**132**) <81ZAAC(482)65, 84ZAAC(514)49>. With bulky substituents on the external Si (**130**; $\text{R}^1 = \text{R}^2 = \text{F}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{N}(\text{SiMe}_2\text{Bu}^t)_2$, $\text{N}(\text{Bu}^t)\text{SiMe}_2\text{Bu}^t$) no spirocyclic have been obtained <84ZAAC(514)49>. Under mass spectrometry the dimer (**132**) dissociates to monomer molecules as evidenced by a strong molecular ion peak corresponding to (**131**) <81ZAAC(482)65>. If a ring $\text{Si}=\text{C}$ bond is generated (2 + 2)-dimerization proceeds even with bulky substituents (Scheme 13) <84ZAAC(514)49>. The 4-chlorophosphine derivative of 1,2,3-diazasilacyclopent-5-ene (**133**) is transformed during distillation to a spirocyclic diphosphirane (**135**) along with a double-bonded bicycle (**136**) apparently via intermediate phosphene (**134**) (Scheme 14) <82AG461>.

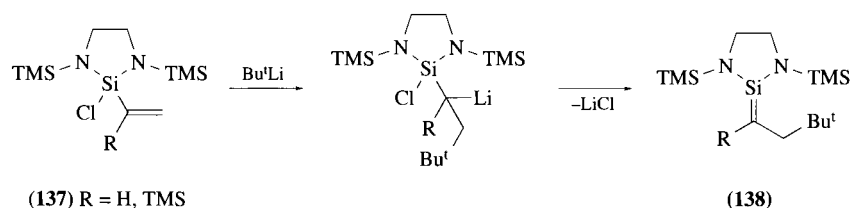


Scheme 13

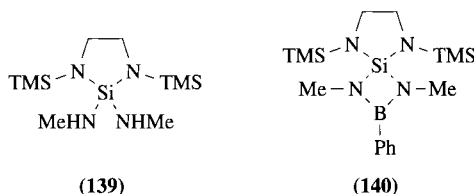


Scheme 14

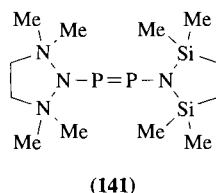
Exocyclic Si=C bonded 1,3,2-diazasilacyclopentanes (**138**) are generated by a sequence of addition-elimination reactions from the *Si*-chloro-*Si*-vinyl derivatives (**137**) (Scheme 15). They undergo trimerization to a trisilacyclohexane, add polar reagents and give the (2 + 2) or (4 + 2) cycloadducts with dienes depending on structure <92ZN(B)795, 92ZN(B)804>. *Si*,*Si*-Diamino derivative (**139**) in the form of its di-Li-salt reacts with Cl₂BPh to give the spiro system (**140**) <87ZAAC(549)149>.



Scheme 15



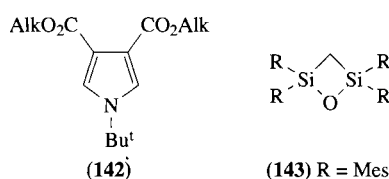
N-Dichlorophosphinyl 1,2,5-azadisilacyclopentane (**89**) is coupled at P to give (**141**) by the action of $\text{Hg}(\text{SiMe}_3)_2$ <83PS(18)31> and exchanges its chlorine atoms for Me groups by treatment with MeMgBr (68% yield) <79IC347>. The *N*-alkylchlorophosphinyl derivative is smoothly *P*-alkylated by Bu^tLi <84IC2063>. The *N*-dimethylphosphinyl derivative is quaternized by aliphatic bromides to give phosphonium salts and on treatment with methyl chloroformate the PMe_2 group is replaced by a COOMe group (15% yield) <82OM623>. *N*-Chloroboryl derivative (**88**; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Cl}$) is *B*-methylated or *B*-aminated by MeLi or NH_3 <81JINC2639>. In the W-complex (**23**) one PMe_2Ph ligand is readily exchanged by CO , $\text{CH}_2=\text{CH}_2$, AlkCN , ArCN or $\text{Bu}^t\text{N}=\text{C}$ <92OM4116>. Ca-complex (**22**) is not hydrogenolized by H_2 in accord with difficult hydrogenolysis of $\text{Mg}-\text{N}$ bonds in organo Mg amides <92JA3393>. Peroxides (**128**) show a capacity for oxidizing, e.g. Et_3B to Et_2BOEt <84AG146>.



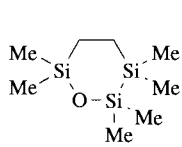
SB protection of amines (cf. Section 4.24.1.4.4) allows various transformations involving deprotonation elsewhere in the molecule to be carried out. For example, the lithium enolate of SB-protected aminoacetic ester has been used in the stereoselective synthesis of 3-aminoazetidin-2-ones by reaction with imines <84TL3849, 85JA1698, 86JOC1929, 86TL1695, 87RTC516, 87TL4347, 87TL5369, 88JCS(P1)945, 88TL2467, 90TL4989, 91JA5147, 91JA5742, 91JOC1933, 91JOC5868, 91OM2467, 91T9061, 92JOC3906> (for an example using the Zn enolate, see <90CC503>). It has also been subjected to *O*-silylation <85CPB2228>, *C*-alkylation <83HCA960, 83JOC3318> (including SB-protected α -aminopropionic ester <85ACS(B)414, 93MI 424-01>, *C*-hydroxyalkylation by aldehydes <89AG491, 90HCA405>, and *C*-heteroarylation <91JOC3715> followed by other transformation. The Na-derivative of SB-protected β -aminopropionic ester was α -fluorinated by *N*-fluoropyridinium salt <88MI 424-02>. Other SB-protected amines lithiated in their (hetero)aromatic nucleus were used to provide substitution reactions <86SC809, 87MI 424-02, 87TL5791, 88TL6537>. Reactions involving lithiated reagents <89TL3393, 93JOC3811, 93TL4693, 93TL7057> and, more commonly, organomagnesium halides <87JOC678, 88JAP88275590, 88JAP88275612, 90JMC2569> with molecules having an SB-protected amino group have been carried out. SB-protected amines bearing halomagnesium entity have also been employed <84TL5271, 93EUP540356>.

4.24.1.3.11 Other reactions

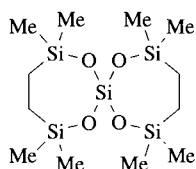
N,N'-Di-*t*-butyl substituted 1,3,2-diazasilacyclopent-4-ene (**188**; $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R} = \text{Bu}^t$) is cleaved oxidatively by $\text{CF}_3\text{SO}_3\text{Ag}$ in reflux in hexane in the dark to form *N,N'*-di-*t*-butyl 1,4-diazabutadiene and Ag (84% yield) <86ZN(B)1230>. Cyclobuteno-1,3,2-dioxasilacyclopentane (**10**) on TLC alumina undergoes opening of both rings to give 1,2-dibenzoyl-1,2-diphenylethane in 54% yield <83CL209>. The cyclobuteno-1,3,2-diazasilacyclopentane [2 + 2] adduct of (**107**) with acetylene dicarboxylic ester transforms into pyrrole derivative (**142**) in $\text{MeOH}/\text{H}_2\text{SO}_4$ at 20°C (87% yield) <87CB795>. Peroxide ring derivative (**251**) rearranges on a SiO_2 column to (**143**) in 90% yield <89TL6705>.



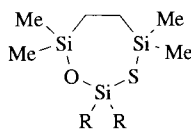
Typical of the 1,2,5-oxadisilacyclopentane ring is insertion of active short-lived species into its Si—O bond: $\text{Me}_2\text{Si}\cdot$, $\text{O}=\text{Si}=\text{O}$, $\text{R}_2\text{Si}=\text{S}$, $\text{RMeSi}=\text{O}$, $\text{Me}_2\text{C}=\text{O}$, $\text{RB}=\text{O}$ to give (144)–(149) respectively. The reaction is conducted with the source of the active species under normal heating <82OM1288, 83JA1263, 83OM1798, 87CL237>, flash vacuum copyrolysis <84JOM(271)191, 84OM1340, 86CL1685> or irradiation <85JA2987, 87CL1075>.



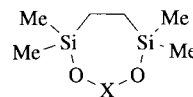
(144)



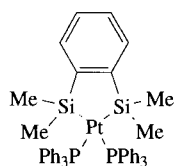
(145)



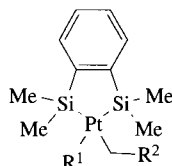
(146) R = Me, Et

(147) X = Me_2Si
X = $\text{Me}(\text{TMS})\text{Si}$ (148) X = Me_2Ge (149) X = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2\text{B}$

The PPh moiety in the 1,2,5-phosphasilaboracyclopent-3-ene ring (120; X = PPh) (Section 4.24.1.3.7) is replaced by sulfur or selenium by the action of the element <88CB1955>. The Pt-moiety in (150) is exchanged by alkynes <91OM16> and olefins <91OM16, 92JOM(428)1> to give a variety of products. Alkynes give the 1,4-dihydro-1,4-disilanthalene six-membered Si-ring almost exclusively, while olefins $\text{R}^1\text{CH}=\text{CHR}^2$ afford predominantly the five-membered Si-ring (151). The crucial step in the proposed mechanism is insertion of a $\text{C}\equiv\text{C}$ or $\text{C}=\text{C}$ unit into the Si—Pt bond followed by removal of the Pt-moiety. The last process and regrouping to the five-membered Si-ring is assisted in the case of olefins by 1,2- $(\text{HMe}_2\text{Si})_2\text{C}_6\text{H}_4$ <92JOM(428)1>. The Pd analogue of (150) reacts with alkynes similarly <84JOM(271)337>.

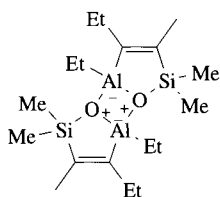


(150)

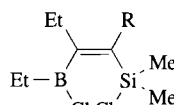


(151)

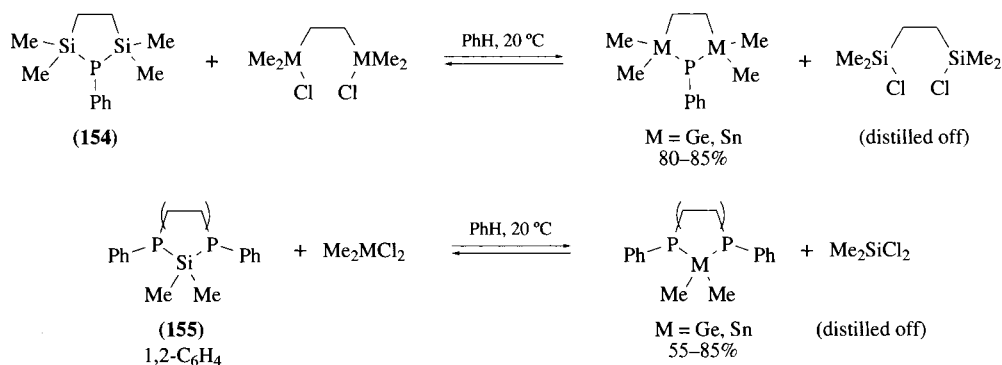
1,2,5-Oxasilaboracyclopent-3-ene derivative (119) exchanges its B for Al with AlEt_3 at 120°C , or is ring opened with BCl_3 at -10°C to 20°C to give (152) and (153), respectively <88CB597>. *N*-Methyl aza analogue (115) exchanges an Et group (at boron) for chlorine with Cl_2BEt at 70°C <88CB597>. Exchange reactions are used for (154) and (155) to replace silicon by germanium and tin atoms in the ring (Scheme 16) <82PS(12)265>. In this way a stable diphospha germilene (156) is obtained (64% yield) from (155) and dioxane complex $\text{GeCl}_2 \cdot \text{C}_4\text{H}_8\text{O}_2$ <82PS(12)265>. 1,3,2-Oxazaphosphacyclopent-4-ene derivative (157) is produced (70% yield) by treatment of its 2-sila(2,2- Me_2) analogue with PCl_3 <90ZOB1431>. 1,2,5-Thiadisilacyclopentane (225) is an efficient sulfur transfer reagent <87TL6139>. π -Complexation of 1,2,5-oxa(thia, seleno, phospho)silaboracyclopent-3-enes <88CB597, 88CB709, 88CB1941, 88CB1955> by heating with transition metal reagents affords carbonyl and sandwich complexes.



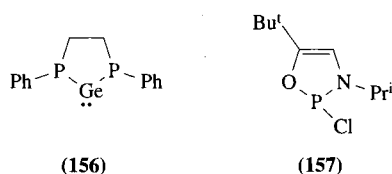
(152)



(153)



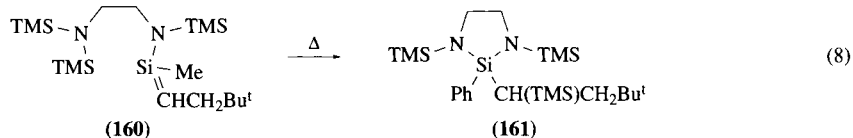
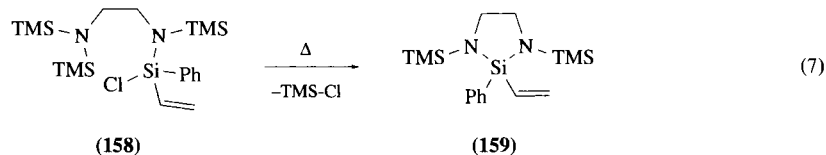
Scheme 16



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

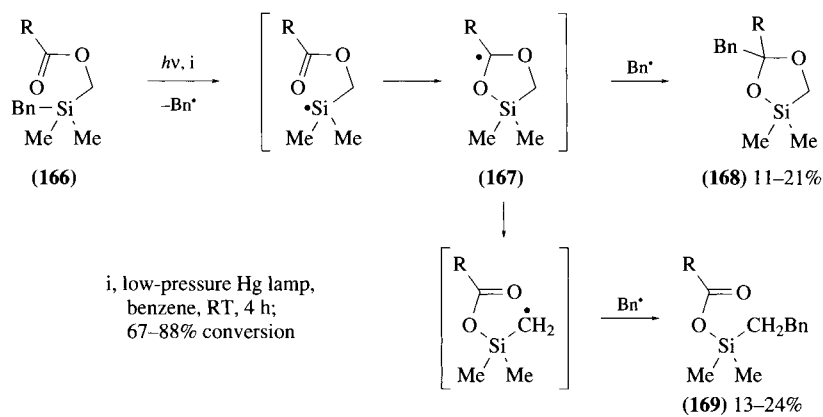
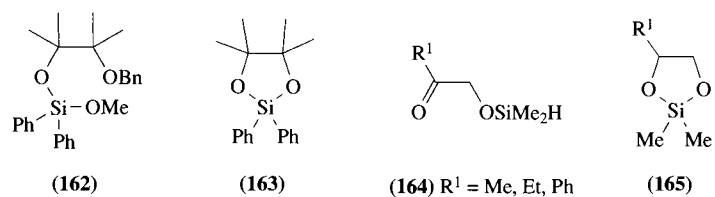
4.24.1.4.1 Formation of one bond between two heteroatoms

The *N*-TMS-*N'*-chlorosilylethylenediamine (**158**) when heated cyclizes to 1,3,2-diazasilacyclopentane derivative (**159**) with elimination of Me_3SiCl (Equation (7)) [92ZN(B)1377]. When the Si atom in the initial ethylenediamine is double bonded (**160**) the cyclization is accompanied by migration of Me_3Si from nitrogen to the double-bonded carbon atom (**161**) (Equation (8)) [92ZN(B)1377].

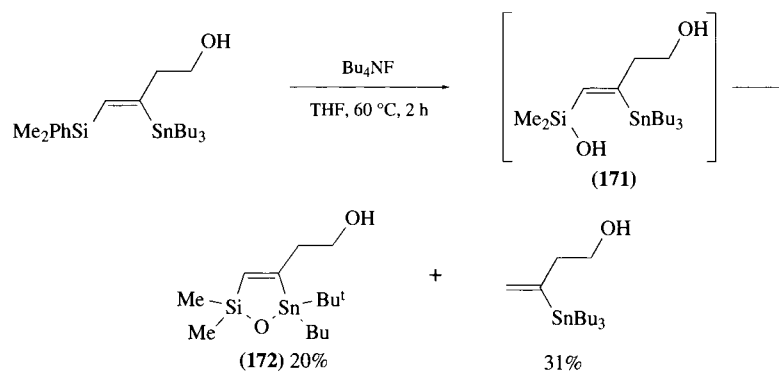
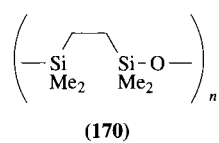
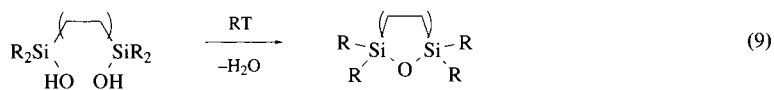


Silyl benzyl diether of 2,3-dimethylbutanediol-2,3 (**162**) under hydrogenolysis gives the corresponding 1,3,2-dioxasilacyclopentane (**163**) supposedly through the intermediate alcohol which appears to be strongly inclined to a spontaneous rapid ring closure [88CR(307)1445]. Dimethylsilyl ethers of hydroxyketones (**164**) can be cyclized to 1,3,2-dioxasilacyclopentanes (**165**) quantitatively and highly stereoselectively by intramolecular hydrosilylation with an appropriate chiral transition metal catalyst [92TL2099]. (Acyloxymethyl)benzylsilanes (**166**) under UV irradiation cyclize to 1,3,4-dioxasilacyclopentanes (**168**) evidently via initial homolysis to Bn radical and intermediate formation of cyclic radical (**167**) which also leads to a ring-opened product (**169**) (Scheme 17); by means of a D-labeling technique the formation of (**168**) was shown to proceed in the solvent cage [85JA7767].

vic-Disilanol are prone to lose a molecule of water to close to 1,2,5-oxadisilacyclopentane or -pentene rings by heating or even at RT (Equation (9)) [83BCJ175, 86T1845, 90BCJ3103]. Closure of the former ring starting with polysiloxane (**170**) requires a drastic alkali hydrolysis (KOH, 250 °C; 57% yield) [92TL8015]. The analogous Sn ring (**172**) is closed via a presumed intermediate silanol (**171**) produced in a desilylation process (Scheme 18) [89S218].

R = Me, Bu^t

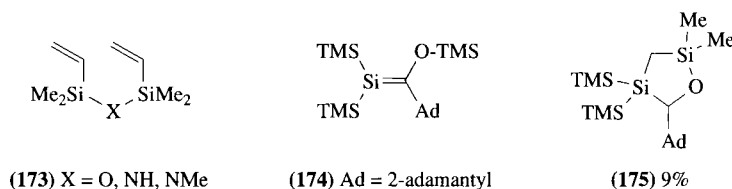
Scheme 17



Scheme 18

4.24.1.4.2 Formation of one bond adjacent to heteroatom

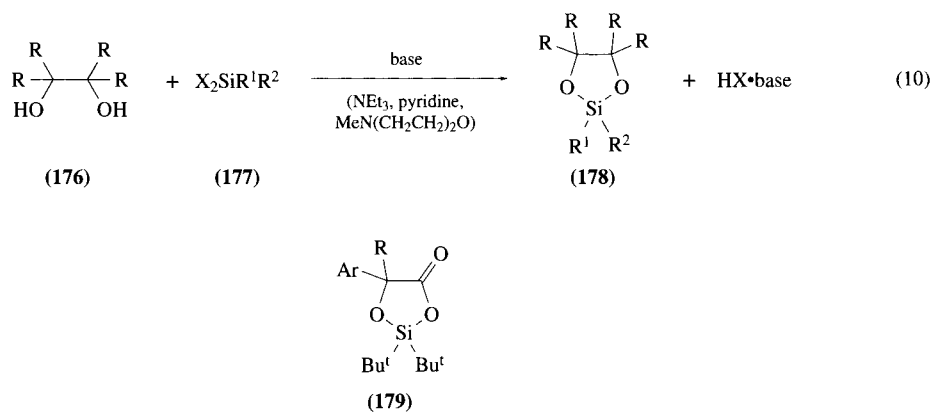
Silicon vinyl derivatives of disiloxanes and disilazanes (**173**) under conditions of radical polymerization cyclize to form 1,2,5-oxadisila- and -azadisilacyclopentane rings containing polymers <93MM407>. Heating of silene (**174**) with $\text{Ni}(\text{PEt}_3)_4$ produces among other products 1,2,4-oxadisilacyclopentane (**175**) <94OM1064>.



4.24.1.4.3 Formation of two bonds: Four-atom fragments and silicon

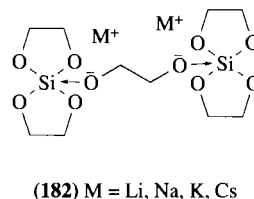
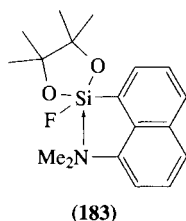
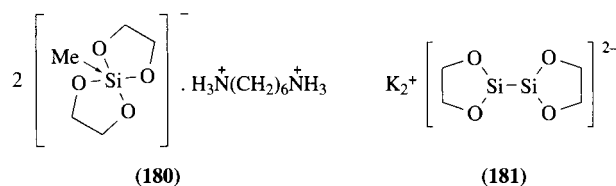
(i) 1,4-O,O-Fragments

One of the important routes to 1,2,5-dioxadisilacyclopentanes (**178**) involves treatment of *vic* diols (**176**) with various Si-difunctional reagents (**177**) usually in the presence of a base (Equation (10)). Pinacol (**176**; R = Me) boiled with ^{14}C -labeled Me_2SiCl_2 (and Et_3N) in benzene gives the corresponding labeled (**178**) in 74% yield <90MI 424-02>; when heated at 190°C with $\text{Si}(\text{OEt})_4$ in the presence of $\text{Ti}(\text{OPr}^i)_4$ catalyst it affords a spirosiloxane (**7**) <69JOC2496>. Diol (**176**; R = Ph) reacts with (**177**; $\text{R}^1, \text{R}^2 = \text{Me}, \text{Et}, \text{Bu}^t, \text{Ph}, \text{vinyl}$) at RT in THF (Et_3N as a base) to give (**178**) (11–54% yield); with SiCl_4 a spirosiloxane is obtained (24% yield) <86PB95>. Diol (**176**; 4R: 1,2- H_2 , 1,2- $(\text{CO}_2\text{Et})_2$) is converted into (**178**) by $\text{Si}(\text{OEt})_4$ or Me_2SiCl_2 <88MI 424-03>. Treatment with Bu^tSiCl_2 may be applied to aliphatic diols analogously, but in the case of aromatic diols 1-hydroxybenzotriazole is required as catalyst, the latter also being needed with α -aryl- α -hydroxycarboxylic acids to obtain carbonyl derivatives (**179**) <88JC13>.



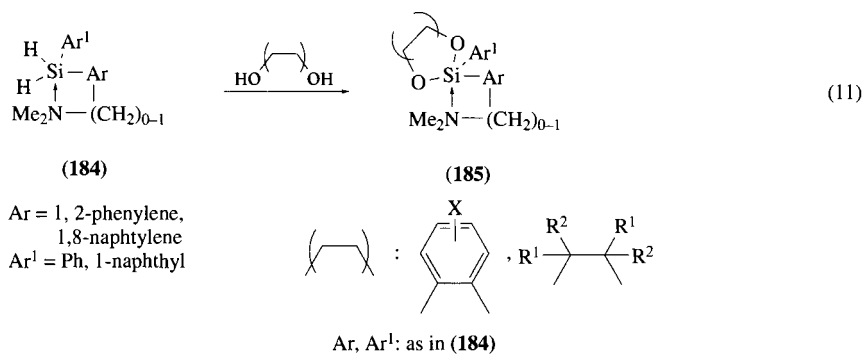
Ethylene glycol (**176**; R = H) with (**177**; $\text{R}^1 = \text{Me}, \text{R}^2 = \text{X} = \text{OMe}$) and hexamethylene diamine as base gives the spiro siloxane anion (**180**) containing a pentacoordinated silicon atom <82ZN(B)195>, whereas with SiO_2 and KOH in EtOH it affords bis-anion (**181**) <91MIP9116328>. Heating with silica gel in the presence of an alkali metal hydroxide gives a Si-pentacoordinated complex with a dative $\text{O} \rightarrow \text{Si}$ bond (**182**) <91NAT642>. When bis(ethanol)amine is added to the reacting (**176**) and (**177**; $\text{X} = \text{R}^1 = \text{R}^2 = \text{OMe}$) chelates with a pentacoordinated Si atom (**12**) are obtained in 46–60% yield <82ZAAC(493)53, 84MI 424-01, 85JOM(279)343>. The chelate (**183**) is obtained in 41% yield from the di-

Li salt of pinacol and the corresponding chelated F_3Si -naphthalene derivative at 20°C in THF <91OM1236>.



Other very effective cyclizing agents (177) have been devised, e.g. $R_2Si(OTf)_2$ ($R = Pr^i, Bu^i$) <82TL4871> and $CF_3C(OSiEt_2H)=NSiEt_2H$ <84MI 424-02, 86CPB3298>, and used at RT with pyridine bases very conveniently for protection of *vic* diols, the latter agent was applied specifically for steroids with a hydroxylated 17-side chain. Both aliphatic and aromatic *vic* diols react at 80°C with $Ph_2Si(CN)_2$ neat without any additives to give (178) in 5 min in 90% yield <86JOC3545>.

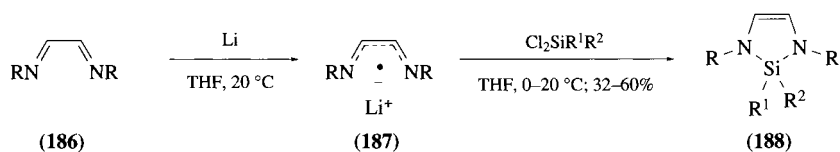
Hydrosilanes have been invoked as cyclizing agents. When Me_2SiHCl or $MePhSiHCl$ is added to diol (176; $R = Ph$) in $CHCl_3$ a vigorous exothermic H_2 evolution ensues to give (178; $R^1, R^2 = Me, Me$ or Me, Ph) <86PB95>. In aminoaryldihydrosilanes (184) Si—H bonds are activated by nucleophilic ligands allowing dehydrocondensation with aliphatic and aromatic *vic* diols to produce chelates (185) in 60–95% yields by gently heating (25–70°C) in CCl_4 or neat (Equation (11)) <90JOM(399)11>. A Ti-catalyst, Cp_2TiX_2 ($X = Cl, Ph$), is found to bring about this reaction with simple dihydrosilanes, PhR^2SiH_2 ; glycerine failed to form a bicyclic siloxane <90CE21, 92JOM(428)315>. Na as a catalyst and $H_2SiBu^i_2$ as a silylating agent are also used in this ring closure <84JAP8455889>.



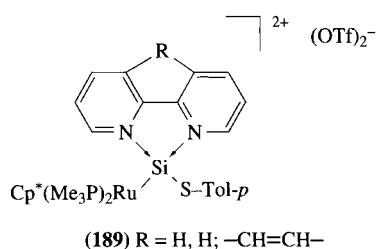
(ii) 1,4-*N,N*-Fragments (also some *O,O* and *O,N*)

N,N'-Disubstituted 1,4-diazabutadienes (186) with lithium (or BuLi, RMgHal) give radical anions (187) which react with dichlorosilanes to form 1,3,2-diazasilacyclopent-4-enes (188) (Scheme 19) <83CB136, 87CB795, 91JOM(407)31>. The complex triflate $C_p^*(Me_3P)_2Ru-Si(OTf)_2-STol-p$ transforms 2,2'-bipyridyl and phenanthroline to chelated cations (189) at RT in 95% yield <92JA1518>.

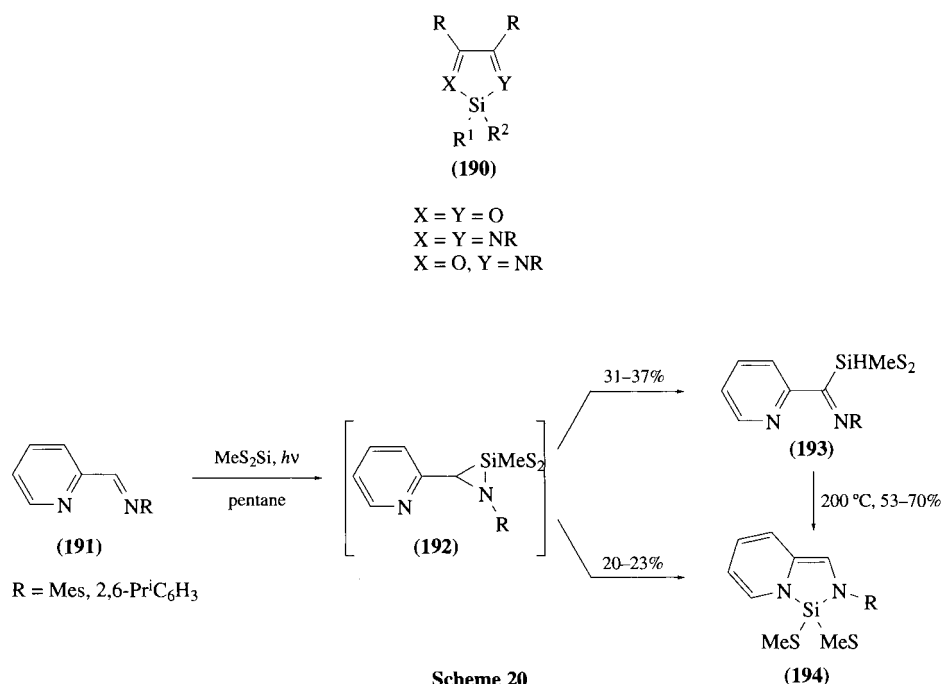
Silylene, SiR^1R^2 , adds across 1,4-heterodienes to give 1,3-dihetera-2-silacyclopent-3-enes (190). The dienes and silylene sources are subjected to gentle heating <92JOM(430)C51>, high temperature pyrolysis <92JOM(423)13> or photolysis at RT <91JOM(407)31, 93JOM(454)35, 93OM2881> or at high temperature <84OM1123>. The presence of Buⁱ groups in silylene is claimed to be imperative because less bulky groups would favor formation of other rings <91JOM(407)31>. Pyridine-2-alimine (191) appears to add silylene under photochemical conditions first across the exocyclic C=N bond to



Scheme 19



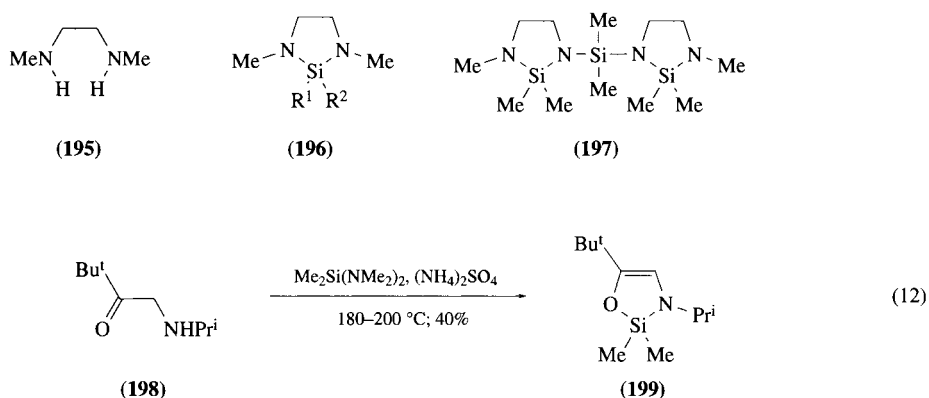
give **(192)** with subsequent rearrangement both to the insertion (31–37% yield) **(193)** and the formal (4 + 1)-cycloaddition products **(194)** (Scheme 20). Product **(193)** rearranges thermally (200 °C) to **(194)** <93OM2881>.



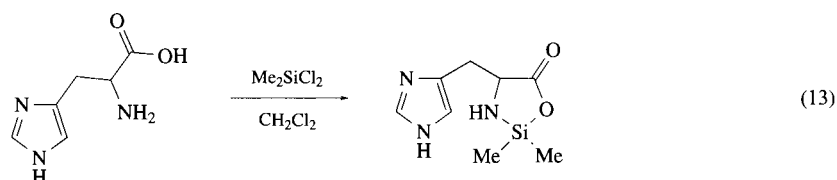
Scheme 20

The 1,3,2-diazasilacyclopentane ring **(196)** is formed in high yield from the di-*N*-Li derivative of the ethylene diamine **(195)** and fluoromethoxysilanes $\text{R}^1\text{R}^2\text{SiF}(\text{OMe})$. Products with penta-coordinated Si atom **(112)** are so obtained when the reacting silanes contain *o*-(dimethylaminomethyl)phenyl or -naphthyl substituents <91JOM(419)9>. The ring closure by SiBr_4 affords only a poor yield of **(196; R¹ = R² = Br)** <84ZAAC(511)185>. The cyclization proceeds more efficiently when *N,N'*-dimethyl ethylenediamine **(195)** is heated alone with bis(dialkylamino)silane $\text{R}^1\text{R}^2\text{Si}(\text{Nalk}_2)_2$ in the presence of a catalytic amount of $(\text{NH}_4)_2\text{SO}_4$: 30–45% yield <85JOM(294)7>, 82–92% yield <65JOM(3)245>, ~100% yield <65IC116>. Tetrakis(dimethylamino)silane affords a spirocompound in 65% yield <65JOM(3)245>. *N*-Monomethyl ethylenediamine gives a bridged bicycle **(197)** with $\text{Me}_2\text{Si}(\text{NR}_2)_2$ evidently via the expected cyclization product <86JOM(304)87>. β -Aminoketone **(198)** gives 1,3,2-oxazasilacyclopent-4-ene **(199)** in this reaction via its enol form (Equation (12))

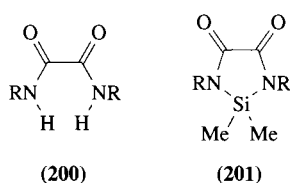
<90ZOB1431>. A disiloxane may serve as cyclizing agent for *N,N'*-disilylsubstituted ethylenediamines in the presence of a K catalyst <90MI 424-03>.



The 1,3,2-oxaazasilacyclopentane ring can be used to protect the amino acid grouping (Equation (13)) <91TL475>.

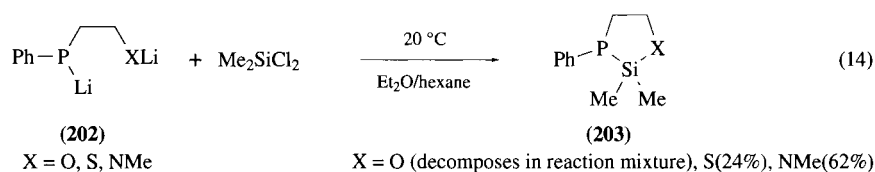


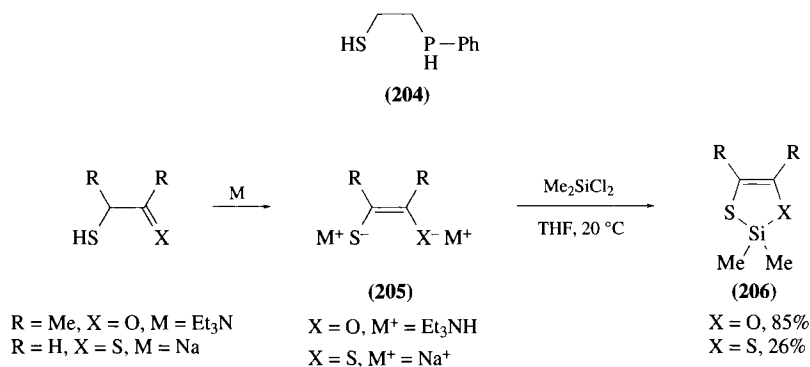
N,N'-Disubstituted oxamide (**200**) with Me_2SiCl_2 cyclizes to (**201**) through its Li derivative or better in the presence of Et_3N , but still better when $\text{Me}_2\text{Si}(\text{NEt}_2)_2$ is employed instead of Me_2SiCl_2 <85ZN(B)277>. Dithiooxamide with Me_2SiCl_2 in the presence of Et_3N at 20°C gives the *N,N'*-disilylated cyclic product (**24**) (11% yield); similar products are obtained (12% or 42% yield) when *N,N'*-bis(TMS) dithiooxamide is *N,N'*-metallated with BuLi followed by treatment with Me_2SiCl_2 at RT <82IC3798, 88ZN(B)1240>. Bis TMS oxamidines have also been cyclized in the same way <93ZN(B)1386>.



(iii) 1,4-*O,S*; *O,P*; *S,S*; *S,P*; *P,P*-Fragments

Lithium-derivatives of *vic* phosphino hetero difunctional ethanes (**202**) rapidly form 1-oxa(thia, aza)-2-sila-3-phosphacyclopentanes (**203**) with Me_2SiCl_2 (Equation (14)) <82PS(12)279>. Li-derivatives (**202**; $\text{X} = \text{PPh}$) of *vic* diphosphino compounds are cyclized by Me_2SiCl_2 in high dilution <82PS(12)265>. A bis-triflate $\text{R}^1\text{R}^2\text{Si}(\text{OTf})_2$ has been used to cyclize *vic* thiol phosphino substrates (**204**) <90ZAAC(588)133> and a bis ester enolate to cyclize a *vic* dithiol <83TL1373>. 1,3,2-Oxathiasila- and 1,3,2-dithiasilacyclopentenes (**206**; $\text{X} = \text{O}, \text{S}$) are formed from the appropriate difunctional ethylenes (**205**) (Scheme 21) <89ZOB1916, 88RTC440>.

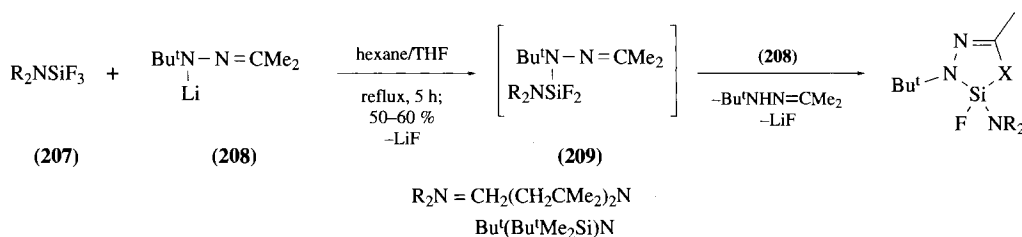




Scheme 21

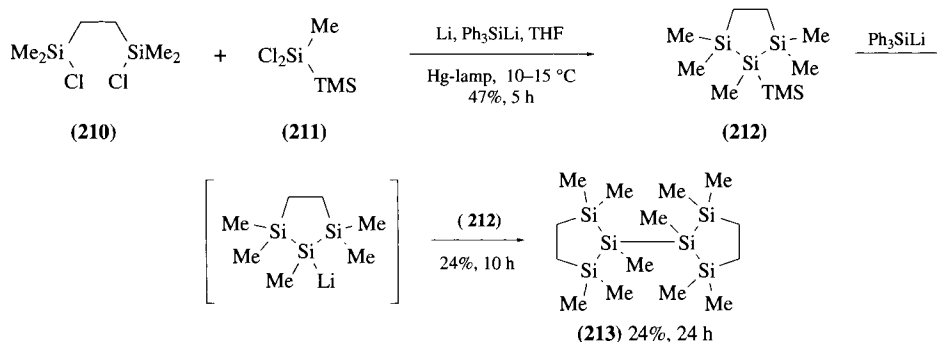
(iv) 1,4-C,N; Si,Si-Fragments

The 1,3,2-diazasilacyclopent-5-ene ring is formed by the action of bulky substituted amino-trifluorosilanes (**207**) on *N*-lithiated acetone *t*-butylhydrazone (**208**). The intermediate (**209**) is cyclized by lithiation of a terminal Me group by (**208**) (Scheme 22) <84ZAAC(514)49>. Fluoro-silylhydrazone (**209**) (made also with R¹R²SiF₂) may be prepared at a low temperature and cyclized by Bu^tLi at reflux; bulky substituents at nitrogen and silicon atoms in (**209**) are essential to ensure fair yields <79JOM(178)409>.



Scheme 22

Reaction of *vic* bis(chlorosilyl)alkanes (**210**) with 1,1-dichlorotetramethyldisilane (**211**) in the presence of lithium and a catalytic amount of Ph₃SiLi under UV irradiation affords *inter alia* 1,2,3-trisilacyclopentane (**212**) and (**213**) (Scheme 23) <85JOM(292)167>.

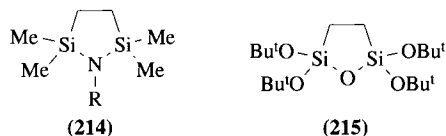


Scheme 23

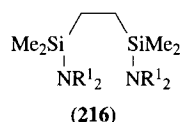
4.24.1.4.4 Formation of two bonds: Four-atom fragments and nitrogen

1,2-Bis(chlorodimethylsilyl)ethane (**210**) readily reacts with amines (RNH₂, R = H, alk, Ar) in the presence of a base to afford 1,2,5-azadisilacyclopentanes (**214**) in fair to high yields <81MI 424-

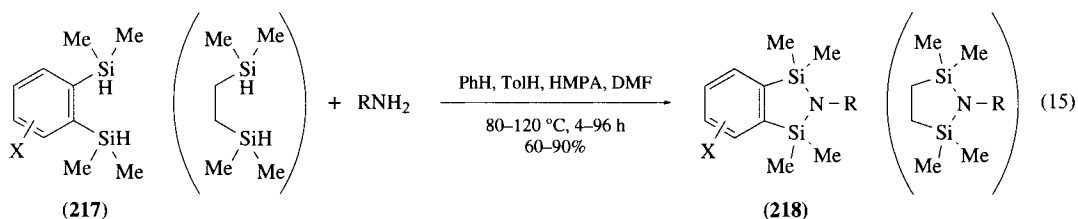
01, 81TL1787, 83EUP96496, 84TL5271, 85ACS(B)414, 85EUP133407, 86SC809, 87JOC678, 87MI 424-02, 87TL5791, 88EUP293351, 88MI 424-01, 88TL3865, 88TL6537, 90JMC2569, 90MM939). It was noted (84TL1253) that amines with pK_a 10–11 require the presence of Et_3N as a base, but those with pK_a 4–5 require $BuLi$. This reaction is the basis of SB protection of amines and is reversed readily, usually by mild acid hydrolysis or by other means (e.g. $NaBH_4$) (Section 4.24.1.3.8). The cyclization of (210) is also brought about using $MeNLi_2$ at RT (60% yield) (86SRI991) or with $RCON(TMS)_2$ by heat (70–83% yield) while distilling off $ClSiMe_3$ (87JOM(332)69). Dichloride analogous with (210) (Bu^tO for Me) is cyclized to (215) by treatment with Bu^tOH and Et_3N neat at $20^\circ C$ for 19 days, Bu^tCl and $Et_3N \cdot HCl$ being coproducts (91ZOB1184).



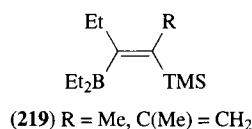
Instead of dichloro derivative (210) a bis(dialkylamino) derivative (216) may be used in the reaction with aryl- (84TL1253) or hetarylamines (91JOC6787) to give (251; $R = \text{Ar}$, hetaryl) by heating in the presence of a catalytic amount of ZnI_2 . This reaction also works well when (216) is replaced by (214; $R = \text{Me}$) (84TL1253). When ethylenediamine is used instead of $ArNH_2$ with $(NH_4)_2SO_4$ as a catalyst, both amino groups are involved in the reaction (62–71% yield) (87MI 424-03).



Dehydrogenative silylation of aromatic (90TL6721) or aliphatic (90TL6725, 91T9807) amines with 1,2-bis(dimethylsilyl)arenes (217) (90TL6721, 90TL6725, 91T9807) or -ethane (90TL6721) leading to cyclization occurs on heating in the presence of catalysts $PdCl_2$ (most efficient), Pd/C , $(PhP)_3RhCl$, CsF or $TBAF$ (Equation (15)). BSB protection of amino groups with a benzodisilyl entity is carried out effectively even with sterically hindered amino groups where attempts at SB protection failed (91T9807). Fluorination of the benzene ring increases the reactivity of (217) (91T9807). The cyclization of (217) may also be brought about by $NaNH_2$ in refluxing benzene, the resulting azadisilaheterocycle as a $N-Na$ derivative affords (218) when treated with an alkyl bromide (90TL6725). A saturated (propellane type) analogue of (217) cyclized by sodium in liquid NH_3 but in poor yield (86T1845). An alternative effective way for BSB protection of amino groups is offered by use of 1,2-bis(dimethylbromosilyl)arenes in the presence of Et_3N (91T9807).



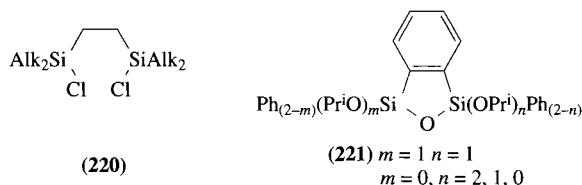
Interestingly, formation of (23) was accomplished by cyclization of (210) on a catalytically fixed N_2 complex (92OM4116). An unconventional cyclization to the azasilacyclopentene system was achieved in high yields by amination of *cis* 1-boryl-2-silylethylenes (219) with sodamide (81AG1009, 87CB669, 88CB597).



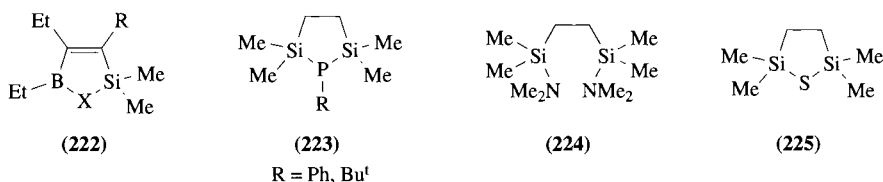
4.24.1.4.5 Formation of two bonds: Four-atom fragments and C, O, S, Se, P, or Pt

The allene (**54**) is produced in the reaction of lithiated allene with tetrasilane dichloride, $\text{Cl}(\text{SiMe}_2)_4\text{Cl}$ <93JA1591>.

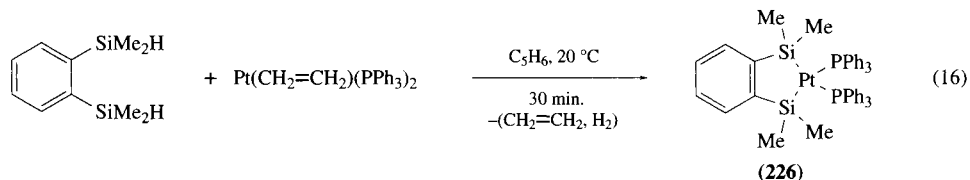
Oxadisilacyclopentane ring closure is effected by strong heating of 1,2-bis(chlorosilyl)ethane (**220**) with KOH <93JAP9325182>. *cis*-1-Boryl-2-silylethylenes, e.g. (**219**), on treatment with KOH give the oxasilaboracyclopentene system (**82**) (>90% yield) through an isolatable intermediate adduct <90CB1253>. Alcoholysis of *o*-aminosilyl-chlorosilyl benzenes leads to benzo-1,2,5-oxadisilacyclopentane ring closure (**221**) <92OM2099>.



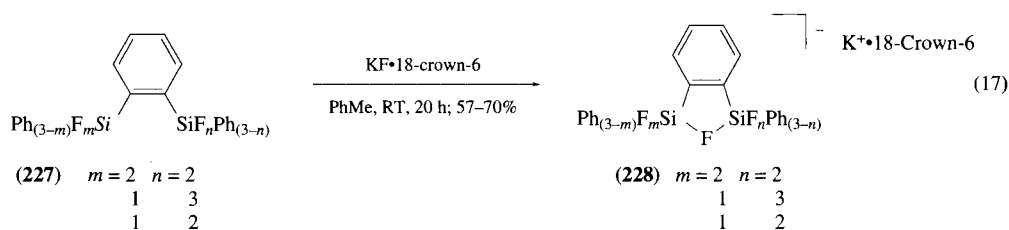
Heterocycles (**222**; X = S, Se, PhP) are obtained in high yields by treatment of (**153**; R = Me, $\text{C}(\text{Me})=\text{CH}_2$) with Na_2S , Li_2S <88CB709>, Na_2Se <88CB1955> and PhPLi_2 <88CB1381>. Bis-silyl chloride (**210**) was also cyclized by PhPLi_2 to give (**223**; R = Ph), or by $\text{Bu}^t\text{P}(\text{SiMe}_3)_2$ in an exchange equilibrium reaction to give (**223**; R = Bu^t) in high yield after removal of ClSiMe_3 by distillation <82PS(12)265>. *vic* Bis(aminosilyl) derivative (**224**) with H_2S and a ZnI catalyst gives 1,2,5-thiadisilacyclopentane (**225**) <87TL6139>.



The 1,3,2-disilaplatinacyclopentane ring (**226**) is formed from 1,2-bis(dimethylsilyl)benzene on reaction with a Pt complex (Equation (16)) <91OM16, 92JOM(428)1>. An analogous reaction occurs with 1,2-bisdimethylsilylethane <91JOM(418)C6>.



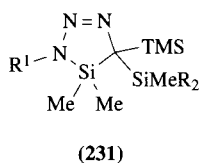
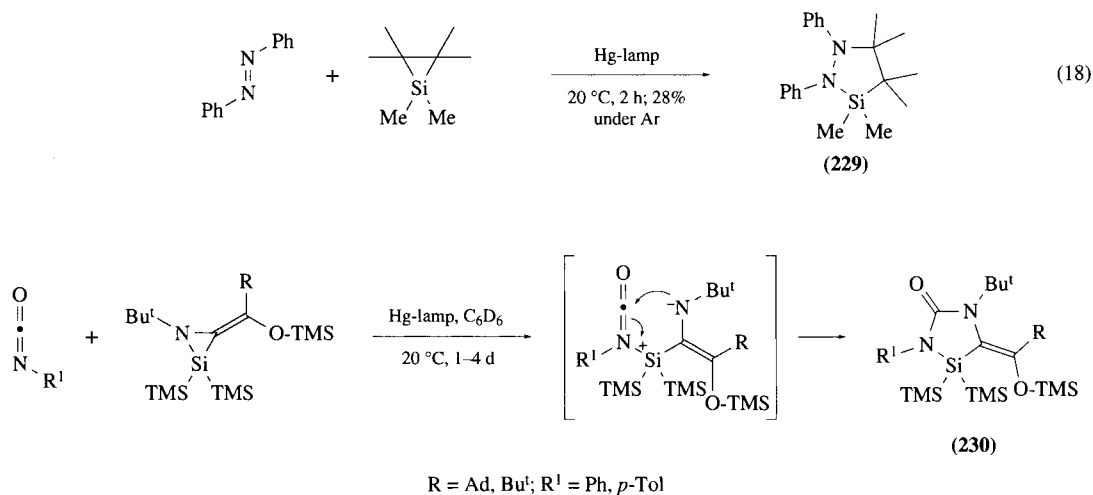
The F-bridge between two pentacoordinate Si atoms in (**228**) is introduced into (**227**) using “crowned” KF (Equation (17)) <90JA2422, 92OM2099>.



4.24.1.4.6 Formation of two bonds: [3 + 2] Atom fragments by cycloaddition

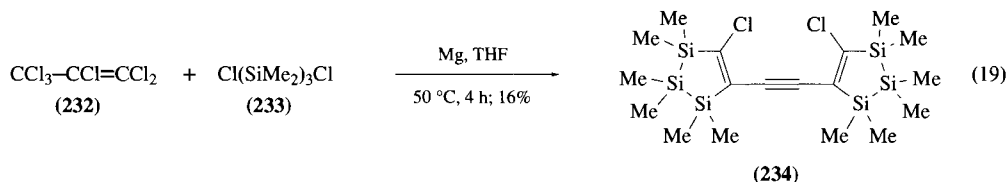
The 1,2,3-diazasilacyclopentane (**229**) is formed in a photochemical reaction between *trans* azobenzene and hexamethylsilacyclop propane (Equation (18)) <84OM579>. 1,3,4-Diazasilacyclopentane (**230**) is formed in a formally analogous manner (Scheme 24) in high yields <93OM529>. The much

less stable 1,2,3,4-triazasilacyclopentane ring (**231**) is assembled by addition of azide, R^1N_3 , to a silaalkene $Si=C$ bond (81CB3518, 86CB1467). These compounds usually decompose below $0^\circ C$ (Section 4.24.1.3.1) and are detected in solution by ^1H NMR spectroscopy. Only (**231**; $R = Me$, $R' = p\text{-Tol}$) was isolated (m.p. $67^\circ C$ decomp.). When N_2O was used in place of R^1N_3 a 3-oxa analogue of (**231**) was probably formed as judged by the decomposition products (Scheme 3).

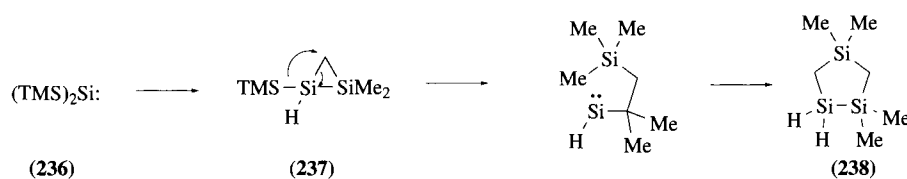
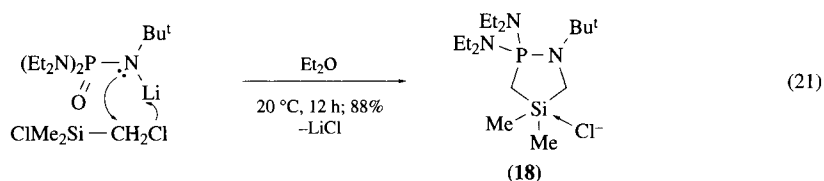
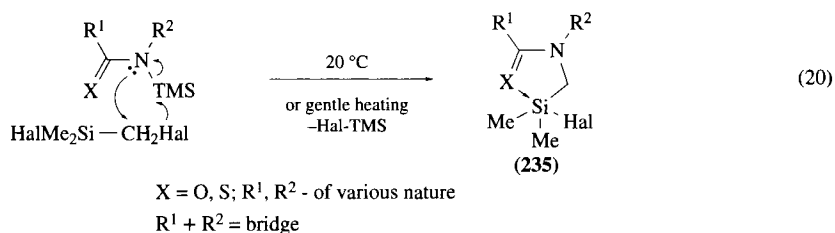


4.24.1.4.7 Formation of two bonds: [3 + 2] Atom fragments by other processes

The Mg promoted reaction between perchloropropene (**232**) and permethyl-1,3-dichlorotrisilane (**233**) produces an acetylenic structure with two 1,2,3-trisilacyclopent-4-ene rings (**234**) (Equation (19)) (93JA3111).



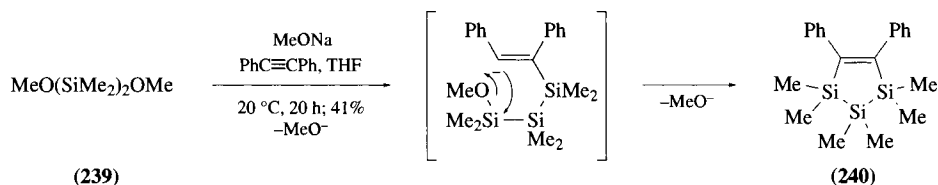
1-Oxa(thia)-3,5-azasilacyclopentane rings with a dative $O(S) \rightarrow Si$ bond (**235**) are made by a general method (Equation (20)) reviewed in (91MI 424-02). An analogous ring with an exocyclic dative $Cl \rightarrow Si$ bond (**18**) is obtained by a similar reaction (Equation (21)) (91MI 424-01). Bis(TMS)-silylene (**236**) generated by flash vacuum pyrolysis of tris(TMS)chloro(or methoxy)silane is transformed into 1,2,4-trisilacyclopentane derivative (**238**) (80JOM(195)C1) evidently via disilacyclopropane (**237**) followed by TMS shift and ring closure by $C-H$ insertion (Scheme 25) (84JOM(272)11).



Scheme 25

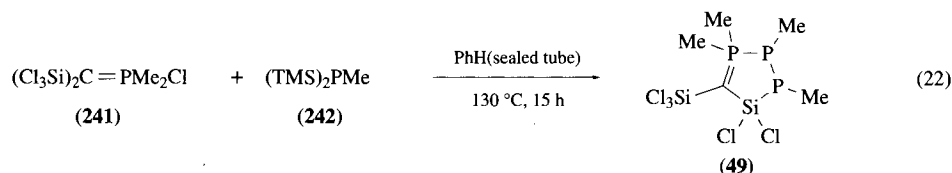
4.24.1.4.8 Formation of three bonds

Formation of the 1,2,3-trisilacyclopent-4-ene (**240**) takes place in a MeONa catalyzed reaction between alkynes and 1,2-dimethoxysilane (**239**) (Scheme 26) [81JOM(218)27]. Under similar conditions stilbene produces a saturated analogue [82CC1366]; reaction with unsymmetrically 1,1-disubstituted ethylenes is much less satisfactory [83JOM(244)329].



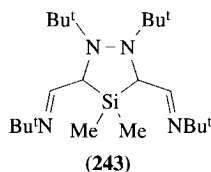
Scheme 26

Chlorinated disilylmethylenephosphorane (**241**) on heating with disilylphosphane (**242**) gives 1,2,3,4-triphosphacyclopentane (**49**) (Equation (22)) [84ZAAC(518)14]. 1,4-Diazabutadiene (**186**; R = Bu^t) on reaction with Li and Me₂SiCl₂ (Scheme 19) gives (**243**) as a side product [83CB136]. 1,2,5-Dioxasilacyclopentanes are formed from aromatic ketones.

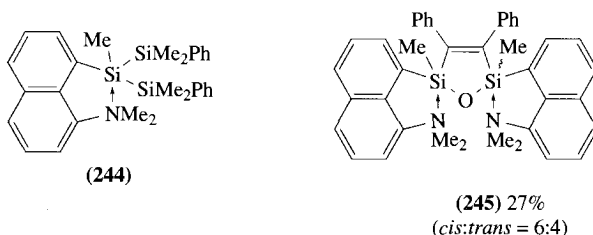


4.24.1.4.9 Formation of four bonds

Heating the trisilane internal amino complex (**244**) with a Ni or Pd catalyst results in splitting off the disilane, PhMe₂SiSiMe₂Ph, to leave a silylene which was captured by a trapping agent PhC≡CPh



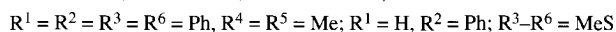
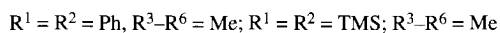
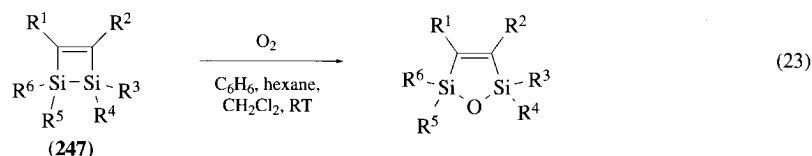
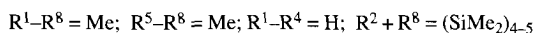
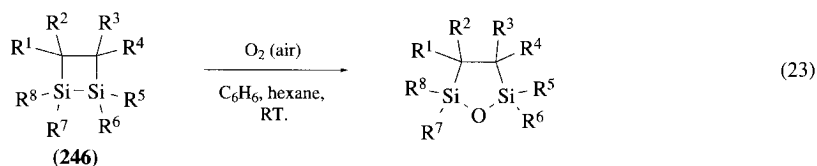
to form the 1,2,5-oxadisilacyclopent-3-ene complex (245), most likely via oxidation of a 1,2-disilacyclobutene intermediate <93OM1113>.



4.24.1.5 Ring Synthesis by Transformation of Other Heterocycles

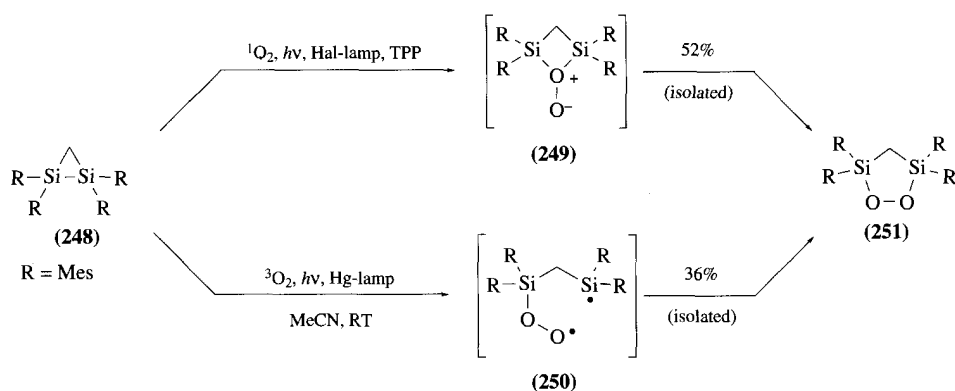
4.24.1.5.1 Insertion

1,2-Disilacyclobutanes (246) and -butenes-3 (247) are readily oxidized in air, the oxygen being inserted into the Si—Si bond to give 1,2,5-oxadisilacyclopentanes and -pentenes in varying yields (Equation (23)) <80JOM(187)297, 80JOM(201)179, 84JOM(271)337, 84JOM(272)123, 93OM803>; (Equation (24)) <84CT393, 84JOM(272)123, 85CL643, 91TL6605, 92T3283>. Very high yields of oxadisilacyclopentane (87–96%) are attained when MCPBA is used at 0°C to oxidize (246; R¹ + R² = R³ + R⁴ = (Me₃Si)₂C=, R⁵–R⁸ = Me; R¹ = R² = SiMe₃, R³ + R⁴ = (Me₃Si)₂C=, R⁵–R⁸ = Me) <82JOM(236)7> or when it is hydrolyzed with deoxygenated water at RT (246; R¹–R⁸ = Me) <84JOM(271)337>. Lower yields result when (247; R¹ = R² = Me₃Si, R³–R⁶ = Mes) is treated by Me₃N → O or water at RT <85JA7706>.

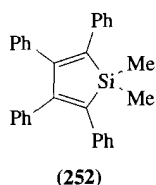


Insertion of two oxygen atoms into the Si—Si bond of disilirane (248) to give (257) can be effected with ¹O₂, (generated by sensitized halogen lamp irradiation) via a peroxonium intermediate (249) <89TL6705, 93OM1514> or with ³O₂ (generated by Hg lamp irradiation) via a triplet open-ring adduct (250) <90JA7804>. 1,4-Dimethylnaphthalene 1,4-peroxide or (PhO)₃P·O₃ as a source of ¹O₂ yields 5–11% (251) (Scheme 27) <89TL6705>. The intermediate (250) was observed by IR spectroscopy at 16 K in solid O₂ matrix from which (251) appeared at 20°C in 75% yield <90JA7804>. Photooxygenation

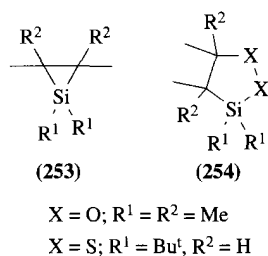
or ozonation (by triphenyl phosphite ozonide) of silacyclopentadiene derivative **(252)** affords a strained fused bicycle **(10)** <83CL209>.



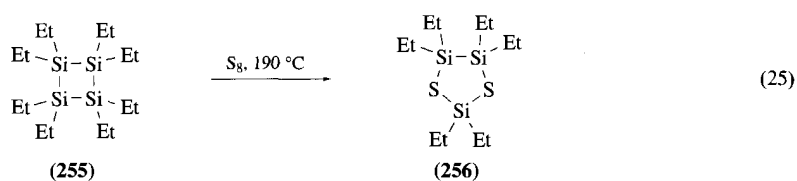
Scheme 27

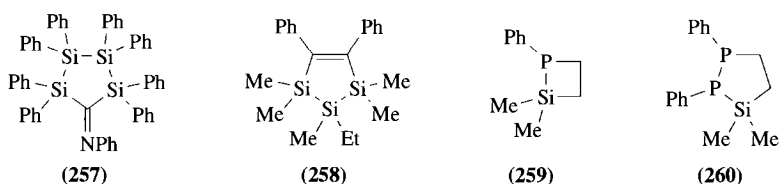


Facile insertion of O_2 <82JOM(225)177> and S_2 (from S_8) <90OM2205> into the Si—C bond of the silirane ring **(253)** occurs to give **(254; X = O, S)**. The stereochemistry of the latter reaction suggests a radical mechanism.

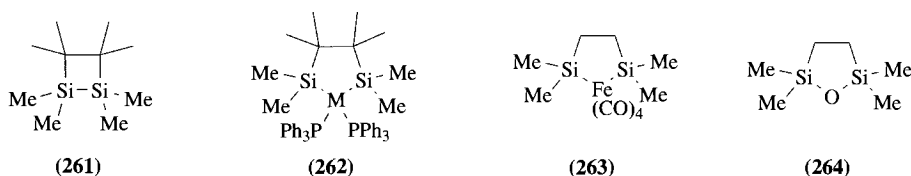


Insertion of a S atom into the Si—Si bond of **(246; $\text{R}^1\text{—R}^8 = \text{Me}$)** is also effected by elemental sulfur at 60°C in benzene to give the corresponding 1,2,5-thiadisilacyclopentane in 88% yield <84JOM(271)337>. Two sulfur atoms may be inserted into a cyclotetrasilane **(255)** by strong heating with S_8 to obtain a 1,3-dithia-2,4,5-trisilacyclopentane **(256)** (Equation (25)) <83OM1798>. With $\text{Pd}(\text{OAc})_2$ catalyst insertion of $\text{PhN}=\text{C}$ into the octaphenyl analogue of **(255)** occurs to afford **(257)** in 11% yield <93JOM(461)35>. Silylene, MeEtSi: , is inserted into the Si—Si bond of **(247; $\text{R}^1 = \text{R}^2 = \text{Ph}$; $\text{R}^3\text{—R}^6 = \text{Me}$)** at 390°C to give 1,2,3-trisilacyclopent-4-ene **(258)** in 42% yield <84CL393>. Phenylphosphinidene, PhP: , is inserted into the Si—P bond of 2-silaphosphetanes **(259)** to form 1,2,3-diphosphacyclopentanes **(260)** <82PS(12)265>.

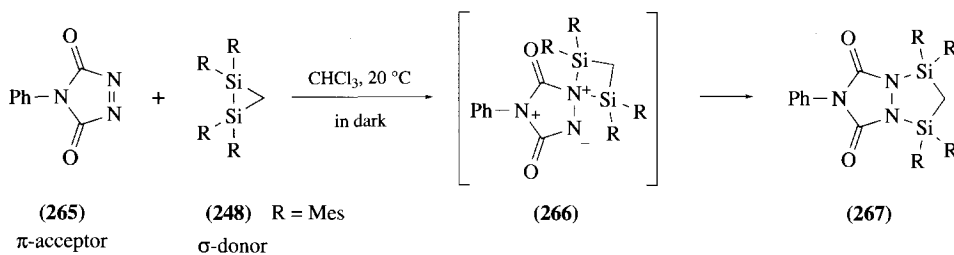




Pd and Pt atoms derived from $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ and $(\text{Ph}_3\text{P})_2\text{Pt}(\text{CH}_2=\text{CH}_2)$ are smoothly inserted into 1,2-disilacyclobutane (**261**) to give the corresponding five-membered heterocycles (**262**; $\text{M} = \text{Pd}$, Pt) $\langle 84\text{JOM}(271)337 \rangle$. Reaction of the heterocycle (**263**) with aldehydes in the presence of Ph_3P leads ultimately to the 1,2,5-oxadisilacyclopentane (**264**) $\langle 83\text{OM}1846 \rangle$.



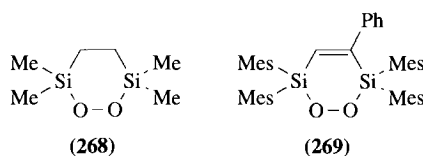
A N atom of the triazolinedione (**265**) is readily inserted into the Si—Si bond of disilirane (**248**) to form the 1,2,3,5-diazadisilacyclopentane (**267**) via the spectroscopically observed $[\pi^2 + \sigma^2]$ -addition intermediate (**266**) (Scheme 28) $\langle 91\text{JA}6286 \rangle$.

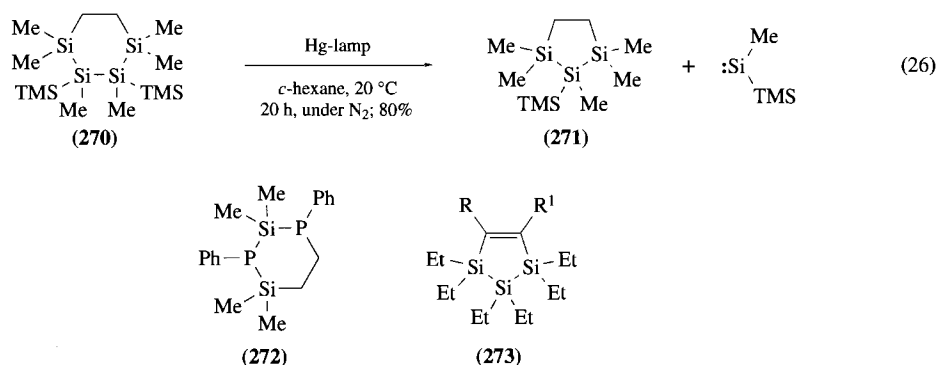


Scheme 28

4.24.1.5.2 Elimination and extrusion

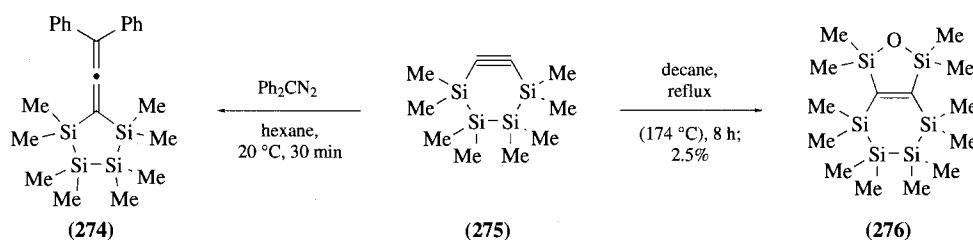
Six-membered 1,2-dioxaheterocycles (**268**) and (**269**) are readily deoxygenated by Ph_3P $\langle 92\text{TL}8015 \rangle$ or transfer their oxygen atom to a substituent $\langle 91\text{TL}6605, 92\text{T}3283 \rangle$ to form 1,2,5-oxadisilacyclopentane (**264**) or -pent-3-ene rings (**8**). On photolysis 2,3-disilylated 1,2,3,4-tetrasilacyclohexane (**270**) expels one of the ring silicon atoms as a silylene (trapped by added Et_2MeSiH) to form 1,2,3-trisilacyclopentane (**271**) (Equation (26)) $\langle 85\text{JOM}(292)167 \rangle$. Extrusion of Me_2Si from the six-membered phosphora ring (**272**) to give (**260**) was also observed $\langle 82\text{PS}(12)265 \rangle$. A catalyzed insertion of an acetylenic $\text{RC}\equiv\text{CR}'$ unit into cyclotetrasilane (**255**) gives mainly the tetrasilacyclohexene with minute amounts of 1,2,3-trisilacyclopentene (**273**) presumably resulting from extrusion of Et_2Si from the former $\langle 83\text{OM}1801 \rangle$.



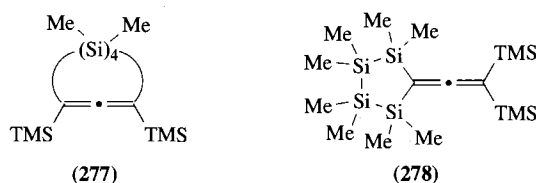


4.24.1.5.3 Rearrangements and other transformations

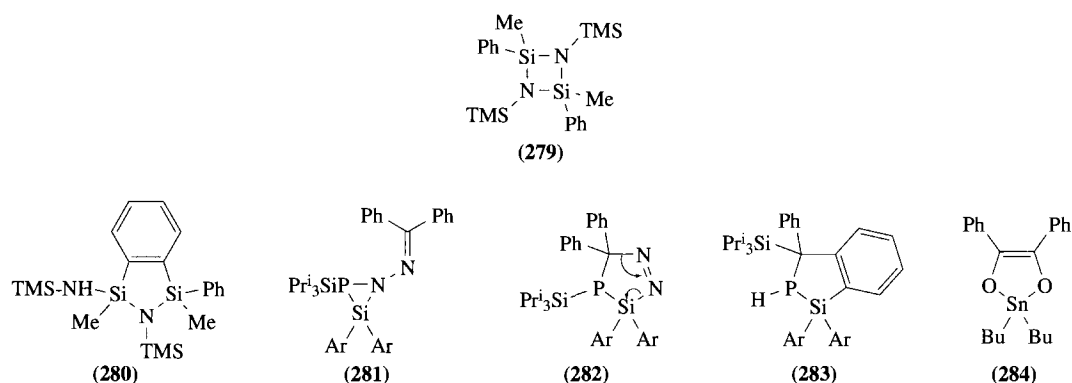
Thermolysis of permethyltetrasilacyclohexyne (275) gives a negligible amount of bicycle (276) and in the reaction with phenyldiazomethane the tetrasilacyclopentane derivative (274) is produced (Scheme 29) <93OM803>. Thermolysis of other six-membered polysila rings also affords five-membered polysila rings e.g. (54) <93JA1591>. Permethyl-1,3-disilyltetrasilacyclohepta-1,2-diene (277) isomerizes at 530 °C into the five-membered polysila ring structure (278) <93JA2534>.



Scheme 29



Cyclodisilazane (279) rearranges to a benzo-1,2,5-azadisilacyclopentane derivative (280) on heating with a catalytic amount of potassium <88MI 424-01>. A complicated transformation to heterocyclopentanes (282) and (283) occurs on heating azaphosphasiliridine (281) <92AG(E)751>. Exchange of SnBu₂ for SiMe₂ proceeds readily when 1,3,2-dioxastannacyclopent-4-ene (284) is treated with Me₂SiCl₂ <83JCS(P)1875>.



4.24.1.6 Survey of Ring Synthesis

The rapidly growing interest in these kinds of Si heterocycles has given rise to many and various methods for their synthesis. Most involve the combination of four-atom fragments with the Si atom. Not only simple 1,2-diols and -diamines, but also other *vic* difunctional structures have been used successfully for this purpose. To increase their reactivity anion or even radical anion, e.g. (187), derivatives and special leaving groups have been employed. The range and diversity of the Si-containing cyclizing agents has been a major factor in the success of the approach. The most common and accessible agent is dichloro dialkyl(aryl) silane. More effective agents of this type were devised, such as silyl bis(triflate), -biscyanide, -bis(dialkylamine), -bis(enolate), -methoxyfluoride, and -bulky substituted disiloxane to cyclize most different nonionized substrates. Silylene generated by a wide variety of methods adds across 1,4-heterodienes to give the heterocyclopentene systems. Dihydrosilanes activated by amino ligands (184) or a special catalyst (Section 4.24.1.4.2) can also play the role of cyclizing agents. Reaction of Li-salt of acetone *t*-butylhydrazone with amino-trifluorosilanes (Scheme 22) should be mentioned as an important transformation leading to a less accessible 1,2,3-diazasilacyclopent-5-ene ring.

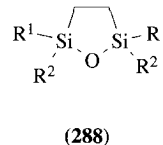
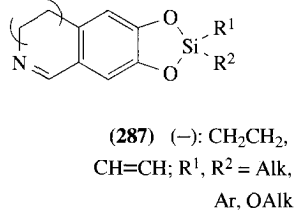
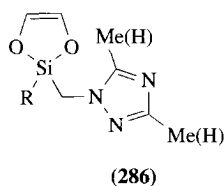
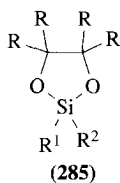
Another major group of methods is based on employment of various other heterocycles. Insertion of oxygen, sulfur, and other atoms and groups into Si—Si, Si—C and Si—Fe bonds of small heterocycles have been developed in continuation of efforts prior to 1980. Elimination or extrusion of structural units from larger heterocycles and rearrangement of various heterocycles are novel lines of development in the 1980s and 1990s.

Amongst the great variety of other methods covered in the preceding synthesis sections, the following are worthy of mention: the disilylation of a primary amino group by a *vic* disilyl entity as in the very useful SB and BSB protection procedure; the use of transition metal catalysis, e.g. (174) → (175) and (164) → (165); formation of N- and S-containing disila rings by cyclization of *vic* bis aminosilylethanes, e.g. (216) and (224); cyclization involving catalytically fixed N₂ and the use of "crown KF" to introduce F bridging of two Si atoms (228).

4.24.1.7 Important Compounds and Applications

1,3,2-Dioxasilacyclopentane derivatives (285, R = H, R¹, R² = Alk, OAlk, OSiAlk₃, SiAlk₃) are used in the preparation of catalysts necessary for manufacture of polypropene with good processability and rigidity <92JAP92372609, 92JAP92372610, 93JAP9309241, 93JAP9325230, 93JAP9325231> or stereoregular α -olefin polymers <92JAP9280207, 92JAP9280208, 92JAP9280209, 92JPP9280210>. Derivatives (285, R¹, R² = Alk, Ar) are used as initiators for selective degradation of polymers (made from propene and benzopinacol) to produce polymers of narrow molecular weight distribution <89EUP326166>, as free radical initiators in curable compositions <87USP4675426>, or (in the form of Si-vinyl derivatives) for vinyl polymerization <87USP4535174>, as a frothing agent (R = R¹ = Me, R² = Ph) for conditioning of coal slurry with kerosine <88URP1384340> and as a silica gel modifier (4R: 1,2-H₂, 1,2-(COOEt)₂, R¹ = R² = OEt) <88MI 424-03>.

Derivatives (286) demonstrate broad-spectrum fungicidal activity <85USP4510136>, (287) are useful as intermediates for agrochemicals and pharmaceuticals <89MIP8909774>. Chloromethyl derivative (285; 3R = 3H, R = CH₂Cl, R¹ = R² = Me) impairs kidney function in rats <88MI 424-05>. 1,2,5-Oxadisilacyclopentane derivatives (288) variously substituted undergo ring-opening polymerization to polysiloxane polymers <92EUP465262, 92EUP465263>.



4.24.2 FIVE-MEMBERED RINGS WITH THREE OR FOUR HETEROATOMS INCLUDING AT LEAST ONE GROUP IV HETEROELEMENT OTHER THAN SILICON

4.24.2.1 Introduction

In Section 4.24.2 the literature from 1982 to the beginning of 1994 (according to *Chemical Abstracts*) is considered. Earlier data concerning five-membered rings with three or more heteroatoms including at least one Ge, Sn or Pb atom are scarce and there is no information in CHEC-I on these heterocycles. Valuable data on germanium heterocycles can be found in the monograph by Lesbire *et al.* <B-71MI 424-01> and some of these data have been included in this section. Tin and lead heterocycles of the type mentioned above were poorly investigated up to 1982 <75HOU(8/7)1, 78HOU(8/6)1, 78HOU(8/6)181, 82COC(2)399, 82COC(2)629, 82COC(2)519> and this is true for lead heterocycles until now.

Available information on five-membered rings with 3–5 heteroatoms including at least one Ge, Sn or Pb atom is distributed quite unevenly depending on the metal nature and structure pattern. Germanium and tin heterocycles are much better studied than their lead analogues, the most extensive investigations being devoted to 1,3-hetero-2-metallacyclopentanes for all three metals. As for silicon-containing five-membered heterocycles, the number of compounds with double bonds in the cycle (as well as their structure types) is limited and their chemistry is very narrow compared with that of saturated analogues. Therefore, unsaturated and saturated compounds are discussed in the same sections. Hantzsch–Widmann names are preferred for derivatives of tetravalent metals while replacement nomenclature is simpler for compounds of Ge(II), Sn(II) and Pb(II).

4.24.2.2 General Problems

Heterocycles treated in this section belong to several structure types. The metal atoms in compounds under discussion can exist not only in the tetravalent but also in the “carbenoid” divalent state and the heterocycles differ not only in the nature and number of metal atoms but also in the nature of ring bonds of the latter. Thus, besides conventional organometallic compounds having only M—C bonds there are heterocycles with M—M bonds and those with C—M—X or X—M—Y fragments (X and Y—common heteroatoms like O, S, N). The last type is the most numerous and important group of five-membered Ge-, Sn- and Pb-heterocycles in which the metals are involved in M—X and M—Y bonds similar to those in respective metal alkoxides, thiolates and amides. This feature not only affects the structural parameters of these compounds but determines their chemical properties, synthetic routes and applications.

Theoretical calculations (both quantum-chemical and molecular mechanics) concerning five-membered Ge-, Sn- and Pb-heterocycles under discussion are not available, probably owing to computational difficulties. Meanwhile, there are some specific “heterocyclic” problems which are awaiting solution.

One such problem is the possibility of the existence and aromatic character of analogues of five-membered heteroaromatics with one heteroatom and those of azoles in which one or several ring C atoms are substituted by a metal atom, e.g. structures (289)–(305) (M = Ge, Sn, Pb; X = O, S, NR). The other specific problems involve antiaromaticity of 8π -electron carbenoids (306) and homoaromaticity of 6π -electron systems with a tetravalent metal (307).

4.24.2.3 Experimental Structural Methods

4.24.2.3.1 X-ray diffraction

(i) Germanium heterocycles

For several 1,3,2-diazagermole, 1,3,2-diazagermolane and tetraazagermole derivatives x-ray structural data are published <89CB245, 92AG(E)1485>. Table 2 presents characteristic bond lengths and angles in “saturated” 1,3-di-*t*-butyl-1,3-diaza-2-germa(II)-cyclopentane and unsaturated 1,3-di-*t*-butyl-1,3-diaza-2-germa(II)-cyclopent-4-ene <92AG(E)1485>.

In 1,3-bis-(trimethylsilyl)-1,3-diaza-2-germa(II)-indane (308) Ge—N bond lengths are ca. 1.86 Å, and the N—Ge—N angle is ca. 87°. The five-membered rings of hexaazadigermadispirododecane (309) are characterized by Ge—N bond lengths ca. 1.81 Å and N—Ge—N angles ca. 92.3°. In

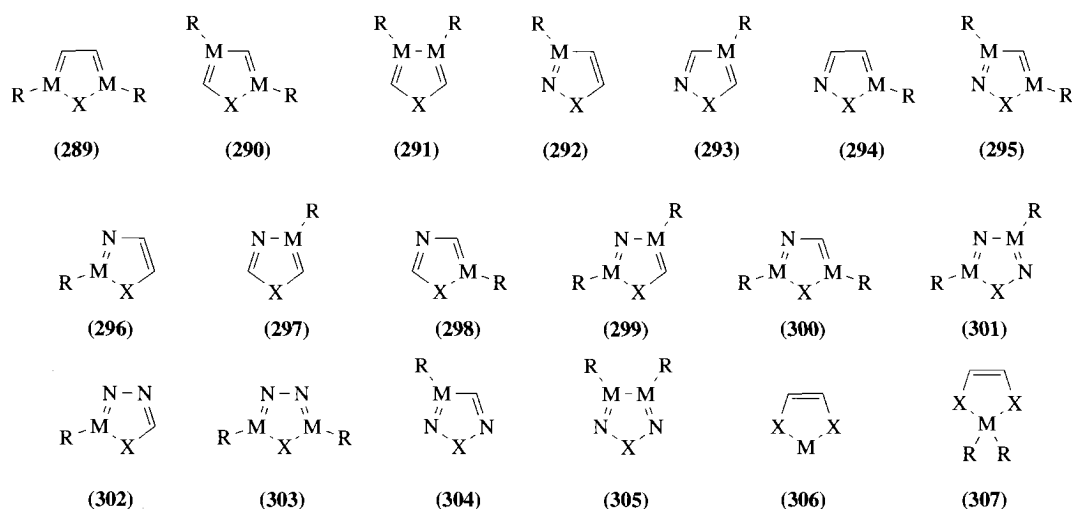
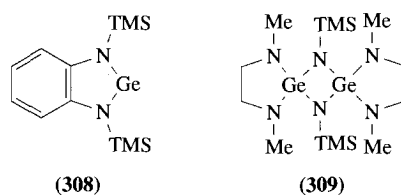


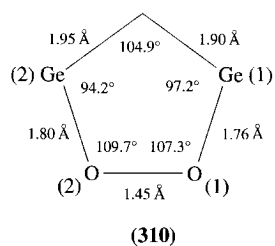
Table 2 Bond lengths and angles in 1,3-di-*t*-butyl-1,3-diaza-2-germa (II)-cyclopentane and 1,3-diaza-2-germa (II)-cyclopent-4-ene molecules.

Molecule	Bond lengths (Å)			Bond angles (°)		
	Ge—N	C—N	C—C	N(1)GeN(2)	NCC	GeNC
1,3-Diaza-2-germa(II)-cyclopentane	1.833	1.459	1.571	88.0	105.7	113.1
1,3-Diaza-2-germa(II)-cyclopent-4-ene	1.856	1.384	1.364	84.8	144.3	113.3

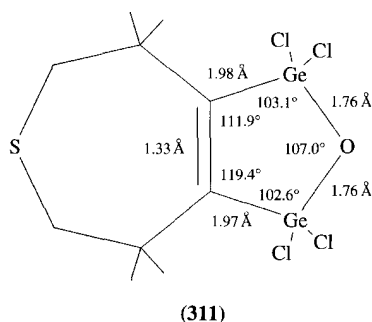
tetraazagermole Ge—N bonds have a medium length (ca. 1.82 Å) and the endocyclic N—Ge—N angle (82.2°) is smaller than in the two preceding compounds <89CB245>.



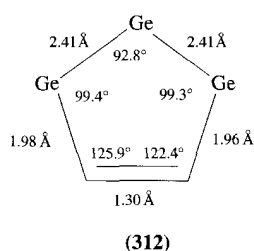
The formally symmetrical molecule of 1,2,3,5-dioxadigermolane (**310**) has, according to an x-ray analysis, a noncoplanar structure (dihedral angle Ge(1)-O(1)-O(2)-Ge(2) ca. 57°) with different bond lengths and angles <92CC457>.



Fused $\Delta^{1,7}$ -2,2,6,6,8,8-hexamethyl-8-germa-4-thiabicyclo-[5.1.0]octene was investigated by x-ray analysis <89MI 424-02>; its 1,2,5-oxadigermole fragment is apparent in structure (**311**).



X-ray investigation of 1,1,2,2,3,3-hexamethyl-4-(2-ethynylphenyl)-1,2,3-trigermacyclopent-4-ene was accomplished $\langle 93\text{AX}(\text{C})182 \rangle$ and the bond lengths and angles in the ring are presented on structure (312).



(ii) Tin heterocycles

X-ray investigation of the Sn(II)-heterocycle, 1,3-dioxa-2-stanna(II)-cyclopentane, showed it to consist of a three-dimensional network of linked dioxastanna(II)-cyclopentane units in the solid $\langle 82\text{ZN}(\text{B})1144 \rangle$.

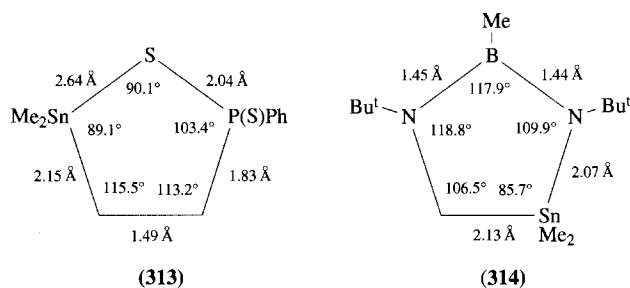
The crystal structures of 1,3,2-dioxastannolanes, 1,3,2-oxathiastannolanes and 1,3,2-dithiastannolanes depend strongly on the nature and steric requirements of substituents at the tin atom. As shown by x-ray analysis $\langle 84\text{JOM}(270)\text{Cl}$, $86\text{JCS}(\text{D})297 \rangle$, the crystal 2,2-dibutyl-1,3,2-dioxastannolane exists as an infinite ribbon coordination polymer with hexa-coordinate Sn atoms surrounded by two carbon and four oxygen atoms in a highly distorted octahedron. The average Sn—O bond length within the unit is 2.04(1) Å and that between the unit 2.51(1) Å; the endocyclic O—Sn—O angle is 79.0(5)°, and the exocyclic C—Sn—C angle is 138.6(6)°. 2,2-Dibutyl-1,3,2-oxathiastannolane is shown to give a linear polymer with penta-coordinate Sn atoms in a distorted trigonal bipyramidal configuration $\langle 87\text{JOM}(325)129 \rangle$. Individual molecules of 2,2-dibutyl-1,3,2-dithiastannolane in the solid state interact weakly with two neighboring molecules to form two long Sn—S coordinate bonds (ca. 3.7 Å), i.e. tin atoms can be regarded as being weakly six-coordinate; each 2,2-dimethyl-1,3,2-dithiastannolane molecule in the solid forms one short coordinate bond (3.18 Å) to a neighboring molecule, and the tin atoms can be regarded as being strongly penta-coordinate $\langle 88\text{JOM}(352)283 \rangle$. In contrast, both 2,2-di-*tert*-butyl-1,3,2-dioxastannolane and 2,2-di-*tert*-butyl-1,3,2-oxathiastannolane exist as dimers in the crystal, while 2,2-di-*tert*-butyl-1,3,2-dithiastannolane is a simple monomer $\langle 89\text{JOM}(363)45 \rangle$.

The crystal structures of 2,2-dialkyl-1,3,2-dithiastannolanes depend on the alkyl group $\langle 88\text{JOM}(352)283 \rangle$. Thus, individual molecules of 2,2-dibutyl-1,3,2-dithiastannolane in the crystal interact weakly with two neighboring molecules to form two long coordination Sn—S bonds (3.69 Å), and therefore the tin atoms can be regarded as being weakly hexa-coordinate. In contrast, 2,2-dimethyl-1,3,2-dithiastannolane forms one short coordination Sn—S bond (3.18 Å), and the tin atom can be regarded as being strongly penta-coordinate. 2,2-Diethyl- and 2,2-diisopropyl-1,3,2-dithiastannolanes have structures similar to that of the 2,2-dibutyl derivative $\langle 88\text{JOM}(352)283 \rangle$; typical bond lengths and bond angles for the latter are: Sn—S 2.414 Å, Sn—C(Bu) 2.115 Å, S—C 1.796 Å, C—C 1.444 Å, C(Bu)—Sn—S 112.7°, C(Bu)—Sn—C(Bu) 122.6°, Sn—S—C 97.5°, S—Sn—S 90.5°, S—C(4)—C(5) 117.0°. The data cited are in rather good agreement with those for 2,2-dimethyl-1,3,2-dithiastannolane $\langle 83\text{AX}(\text{C})451 \rangle$, the only discrepancy being a much longer C—C bond (1.509 Å) for the

latter. X-ray structural data for the complex of 2-butyl-2-chloro-1,3,2-dithiastannolane with 1,10-phenanthroline <91JOM(411)99> as well as for spiro-bis-1,3,2-dithiastannolane and its complexes with pyridine and 2-(2-aminoethyl)pyridine <92ICA185> are also available. Di-*t*-butyl-(glycylglycinato)tin(IV) monohydrate has an interesting structure in the solid <89AX(C)728>. In this compound having fused 1,3-diazastannolane and 1,3,2-oxazastannolidine fragments with a common Sn—N bond the polyhedron around the tin atom is a distorted trigonal bipyramid formed by two equatorial *t*-butyl groups and the tridentate, nearly planar, glycylglycinate ligand, the equatorial Sn—N bond being short (2.085 Å). The molecules are connected through a hydrogen bond network, involving H-bonds formed by the water molecule with NH₂ and CO groups of both peptide and carboxylate fragments and those between NH₂ and carboxylate CO groups of neighboring molecules.

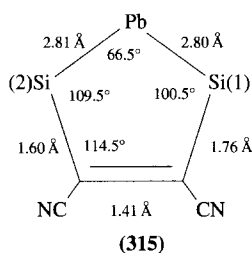
X-ray diffraction study of the HMPT adduct of a cyclic organotin dithiophosphinate, 5,5-dimethyl-2-phenyl-1,5,2-thiastannaphospholane-2-thione (**313**) has shown that the tin atom has a trigonal bipyramidal environment with a HMPT molecule and sulfur atom in axial positions <86JOM(309)273>. The structure of 1,3-di-*tert*-butyl-2,4,4-trimethyl-1,3,4,2-diazastannaborolidine (**314**) was studied by x-ray diffraction <87JOM(326)307>.

An inorganic heterocycle, 3,3,5,5-tetrakis[di(trimethylsilylmethyl)]-1,2,4,3,5-trioxadistannolane was studied by x-ray diffraction and bond lengths and main bond angles are published <90CC1461>.



(iii) Lead heterocycles

The molecular structure of lead(II) derivative, 4,5-dicyano-1,3,2-dithiaplumbol (**315**), has been determined by x-ray diffraction <89ZN(B)1531>.



4.24.2.3.2 NMR spectroscopy

(i) Germanium heterocycles

Proton, ¹³C, ¹⁴N, ¹⁵N and ²⁹Si NMR spectra for several 1,3,2-diazagermoles, 1,3,2-diazagermolanes and tetraazagermoles have been investigated <89CB245, 92AG(E)1485>. ¹H and ¹⁹C NMR data are available for 1,3-diazagermoles <89TL6669> and 1,3-diazagermolanes <85CB2020>, as well as for 2,4,5-thiadiazagermoles, one 2,4,5-oxadiazagermole <82AG455> and a unique 2,3,5-trithiagermolane derivative <91TL6143>. Unsaturated 1,3-dithiagermoles with both divalent and trivalent germanium are characterized by ¹H NMR spectra <88TC440> and so too are Δ³-2,3,4-triazagermoles <86CB2980>.

Inversion at phosphorus in 2,3-diphenyl-2,1,3-germa(II)- and 2,3-diphenyl-2,1,3-germa(IV)-diphospholanes as well as in 1-*tert*-butyl and 1-phenyl-substituted 2,5,1-digerma(IV)-phospholanes was studied by ^1H and ^{31}P dynamic NMR spectroscopy <82JOM(224)247>.

(ii) Tin heterocycles

Numerous NMR data for various 1,3,2-dioxastannolanes in solutions are available. In particular, the stereodynamics of 1,3,2-dioxastannolanes was investigated by ^1H , ^{13}C and ^{119}Sn NMR at variable temperature <85JCS(P2)799, 86ICAL15, 86JA4873, 86JOM(315)277, 87JOC4444, 90CJC2102>. These studies allowed not only activation parameters for the five-membered ring-puckering process to be obtained but also gave evidence for both association equilibria involving dimers and higher oligomers and an intramolecular exchange of diol moieties between tin atoms within the dimer. In contrast to some earlier results, no evidence for the presence of monomers in solutions of 1,3,2-dioxastannolanes was obtained <90JA1364>. NMR study of C-ring-substituted 1,3,2-dioxastannolanes including those formed from carbohydrate-derived 1,2-diols <90CJC1007> gave results of general stereochemical interest and, in particular, made it possible to determine the enantiomeric purity of 1,2-diols without chiral auxiliaries <86JA4873>.

Conformational study by dynamic ^1H NMR spectroscopy was also performed for some 1,3,2-dithiastannolanes differing by substituents at Sn and C atoms <82JCS(D)2073>. Vibrational, ^1H NMR and Mössbauer spectra indicate that fused 2,2-disubstituted benzo-1,3,2-dithiastannolanes (1,3-dithia-2-stannaindanes) are associated in the solid (penta-coordination of tin) and monomeric in solution <85JOM(290)41>.

X-ray crystal structural data for 1,3,2-dioxastannolanes were complemented by data from ^{119}Sn NMR studies in the solid state <92CJC205>, and this allowed the states of oligomerization for solid compounds which had not been previously studied by x-ray crystallography to be determined. A similar study was performed for 2,2-dialkyl-1,3,2-oxathia- and -dithiastannolanes using ^{13}C and $^{117/119}\text{Sn}$ NMR spectroscopy both in solution and in the solid state <87JOM(325)129, 88JOM(352)283>. It is of interest that 2,2-di-*tert*-butyl-1,3,2-dioxastannolane exists as a penta-coordinate dimer both in the crystal (x-ray, $^{117/119}\text{Sn}$ NMR) and solution ($^{117/119}\text{Sn}$ NMR), while the corresponding oxathia-stannolane which is dimeric in the crystal (see Section 4.24.1.3.1) is in equilibrium with the monomer in solution; 2,2-di-*tert*-butyl-1,3,2-dithiastannolane is a simple monomer both in the crystal and in solution <89JOM(363)45>.

Study of IR, ^1H and ^{119}Sn NMR and Mössbauer spectra as well as molecular weights of complexes formed by 2,2-dibutyl-1,3,2-dioxastannolane and its methyl-substituted derivatives with pyridine, DMSO, DMF, sulfolane and THF <83JOM(258)7> gave evidence that these complexes, being equimolar, have a trigonal bipyramidal configuration with an apical ligand, equatorial butyl groups, and the dioxastannolane ring bridging apical and equatorial positions.

Fused benzo-1,3,2-dithiastannolanes are characterized by ^1H NMR spectral data including ^{119}Sn - ^1H spin-spin coupling constants <85JOM(290)41>.

2,2-Dimethyl-1,3-bis(trimethylsilyl)-1,3-diazastannolidine was investigated using ^{15}N and ^{119}Sn NMR spectroscopy <85JMR(61)536>. Derivatives of divalent tin, 5,5-dimethyl-1-trimethylsilyl-3-R-1,3,2 λ^2 -diazastannolidines (R = Me₃Si, Pr) were shown by a multinuclear NMR study to be dimers while monomer-dimer equilibria at room temperature and above exist in cases of related inorganic heterocycles, 1,3-di-R-4,4,5,5-tetramethyl-1,3,4,5,2 λ^2 -diazadisilastannolidines (R = Et, Pr) <90ICA205>.

^1H , ^{31}P and ^{119}Sn NMR spectra have been obtained for the cyclic triorganotin dithiophosphate (313), its 2,2-di-*tert*-butyl-substituted homologue and their complexes with HMPT <86JOM(309)273>.

The study of ^1H , ^{11}B , ^{13}C and ^{119}Sn NMR spectra (which included through-space ^{19}F - ^1H and ^{19}F - ^{13}C spin-spin couplings) of 4,5-diethyl-2,2,3-trimethyl-1-(*o*-trifluoromethylphenyl)-2,5-dihydro-1*H*-1,2,5-azastannaborole, the first representative of the series, allowed atropisomerism owing to hindered rotation around the *N*-aryl bond to be observed <87ZN(B)191>.

(iii) Lead heterocycles

For fused 2,2-disubstituted benzo- and quinazolino[2,3-*c*]-1,3,2-dithiaplumbolanes ^1H NMR spectra including ^{207}Pb - ^1H spin-spin splittings are available <85JOM(290)41>.

Cyclic plumbylanes, 5,5-dimethyl-1-trimethylsilyl-3-R-1,3,2 λ^2 -diazaplumbolidines (R = Me₃Si,

Prⁱ), like their tin congeners (see above), were shown by ¹H, ¹³C, ¹⁵N, ²⁹Si and ²⁰⁷Pb NMR spectra <90ICA205> to be dimers while monomer–dimer equilibria at room temperature and above exist in the cases of 1,3-di-R-4,4,5,5-tetramethyl-1,3,4,5,2λ²-diazadisilaplumbolidines (R = Et, Prⁱ).

4.24.2.3.3 IR and Raman spectroscopy

Vibrational (IR and Raman) spectra of 2-germazolidines and 2,5-digermazolidines were investigated and a careful analysis of $\nu(\text{GeN})$, $\nu_s(\text{GeNGe})$ and $\nu_a(\text{GeNGe})$ modes was carried out <85SA(A)1081>.

Cyclic triorganotin dithiophosphinates like (313) and their HMPT adducts are characterized by IR spectra <86JOM(309)273>.

Vibrational spectra (both IR and Raman) of several fused benzo- and quinazolino[2,3-*c*]-1,3,2-dithiaplumb(IV)-olene were investigated <85JOM(290)41>. Raman and IR bands of 1,3,2-dithiaplumb(II)-olane have been interpreted <89JST(197)171>.

4.24.2.3.4 Mössbauer spectroscopy

Many of the tin heterocycles have been characterized by Mössbauer spectra. Among these the complexes formed by 2,2-dibutyl-1,3,2-dioxastannolane and its methyl-substituted derivatives with pyridine, DMSO, DMF, sulfolane and THF <83JOM(258)7> and fused benzo-1,3,2-dithiastannolanes <85JOM(290)41> should be mentioned.

4.24.2.4 Thermodynamic Aspects

Dynamic NMR measurements gave estimates of enthalpies and free energies for equilibria of 1,3,2-dioxastannolane oligomers in solution <86JOM(315)277, 92CJC197> as well as for activation parameters of ring puckering in 1,3,2-dioxas- <85JCS(P2)799> and 1,3,2-dithiastannolanes <82JCS(D)2073>.

Electronic structure and bonding in 2,2-diphenyl-1,3,2-dithiastannolane and -plumbolane were studied by UV photoelectron spectroscopy and ionization energies based on their He(I) and He(II) UV photoelectron spectra have been measured <83ICAL35>.

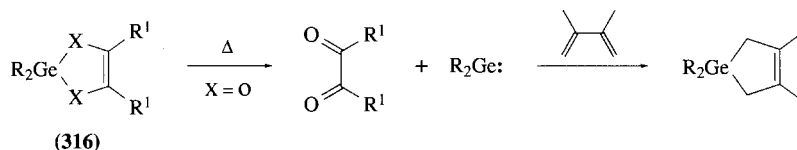
The study of inversion at phosphorus atom in a series of 2,5,1-dimetallaphospholanes and 2,1,3-metalladiphospholanes by ¹H and ³¹P dynamic NMR spectroscopy <82JOM(224)247> showed, in accordance with previous data <76AG445>, that the pyramidal inversion barriers increased with electronegativity of the neighboring metal in the order: Si < Sn < Ge.

4.24.2.5 Reactivity of Ring Systems Containing Germanium, Tin, and Lead

4.24.2.5.1 Thermal and photochemical reactions formally involving no other species

On thermolysis 1,3,2-dioxagermoles (316; X = O, R = Ph) decompose to germynes (which can be trapped as (4 + 1) adducts with dienes) and α-diketones, while 1,3,2-dithiagermoles (316; X = S) give six-membered cyclotrigermathianes (R₂GeS)₃, the latter being formed via a germanethione intermediate R₂Ge=S (Scheme 30) <85JOM(297)C17>.

Thermolysis and photolysis of 4,4-dimethyl-1,2,4-dithiagermolane (317) probably proceeds via



Scheme 30

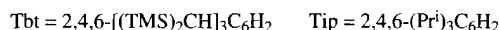
$$\text{Me}_2\text{Ge} \begin{array}{c} \diagup \text{S} \\ \diagdown \text{S} \end{array} \longrightarrow \text{Me}_2\text{Ge} \begin{array}{c} \diagup \text{S} \\ \diagdown \text{S} \end{array} \text{GeMe}_2 + \text{Me}_2\text{Ge} \begin{array}{c} \text{S} \\ \diagdown \text{S} \end{array} \text{GeMe}_2 + \text{Me}_2\text{Ge} \begin{array}{c} \text{S-Ge} \\ \diagdown \text{S-Ge} \end{array} \text{Me}_2 \quad (27)$$

(318)

(319)

(320)

(321)

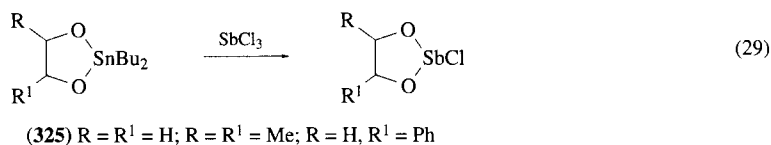


Scheme 31

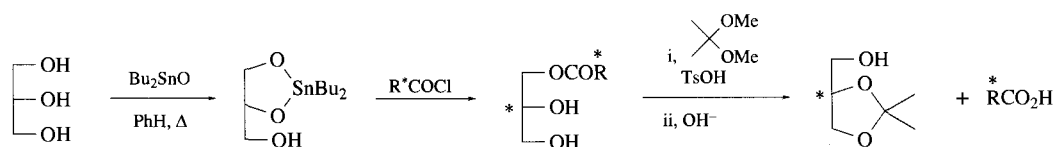
4.24.2.5.2 Electrophilic attack at ring oxygen, sulfur, and nitrogen

$$\begin{array}{c} \text{R}_2\text{Ge} \begin{array}{c} \diagup \text{X} \diagdown \\ \diagdown \text{X} \diagup \end{array} \begin{array}{c} \text{R}^1 \\ \text{R}^1 \end{array} \end{array} \xrightarrow{\text{ZCl}_2} \begin{array}{c} \text{Z} \begin{array}{c} \diagup \text{X} \diagdown \\ \diagdown \text{X} \diagup \end{array} \begin{array}{c} \text{R}^1 \\ \text{R}^1 \end{array} \\ (324) \end{array} + \text{R}_2\text{GeCl}_2 \quad (28)$$

Reactions of 1,3,2-dioxastannolanes (**325**) with electrophiles such as inorganic acid halides or organic acylation and alkylation agents are of great synthetic importance. Thus, 1,3,2-dioxastannolanes undergo exchange reaction with SbCl_3 (Equation (29)) to give the corresponding 1-chloro-1,3,2-dioxastibolanes ^[82JHC141].



Cleavage of 1,3,2-dioxastannolanes with acyl chlorides has been exploited extensively in various syntheses. In particular, (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol was prepared from glycerol in high yield and with high optical purity (Scheme 32) using acylation of 2,2-dibutyl-4-hydroxymethyl-1,3,2-dioxastannolane with an optically active acid chloride in the key step, the best results (*de* 90%) being obtained with (–)-camphanic acid <84CL401>. Some other examples deal with the cleavage of a chiral 2,2-dibutyl-1,3,2-dioxastannolane (obtained from *L*-dimethyl tartrate) with monoacyl chlorides <87CL141>.



Scheme 32

Diacyl chlorides have been studied in detail. Thus, 2,2-dibutyl-1,3,2-dioxastannolanes react with phosgene to give corresponding ethylene carbonates, the results of reaction with oxalyl chloride depends on substituents in positions 4 and 5: the 4,5-unsubstituted compound gives ethylene oxalate as the only product, but with methylated dioxastannolanes decarbonylation competes and the corresponding ethylene carbonates are also formed. Malonyl and succinyl chlorides give oligomeric ethylene malonates or succinates <83JOM(256)251> and higher diacyl chlorides lead mainly to macrocyclic tetraesters <84JHC577, 88JCS(P2)1617, 89JOC2643>. This cyclooligomerization involves transesterification equilibria and leads to a thermodynamic distribution of oligomeric esters, the dioxastannolane being both the reagent and an efficient transesterification (and equilibration) catalyst. As a result, the degree of regio- and stereospecificity is not high <88JCS(P2)1617, 89JOC2643>. A similar behavior is known for 2,2-dialkyl-1,3,2-oxathia- and -dithia- stannolanes <84S140, 92JOC766>.

Reactions of 2,2-dialkyl-1,3,2-dioxastannolanes with some alkylating reagents are of high synthetic potential. However, the low nucleophilicity of dioxastannolane oxygen demands some specific reagents or conditions. π -Allyl palladium intermediates, e.g. those formed from Pd(PPh₃)₄ and substituted allyl acetates, were successfully used <85JOC3558>. The reactivity of normal alkyl halides can be enhanced in the presence of caesium fluoride <87CL141>.

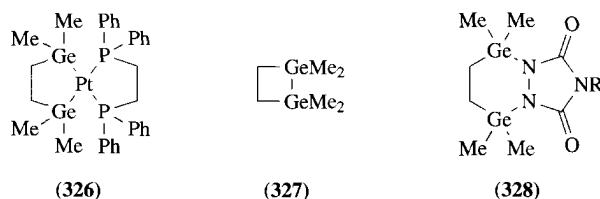
1,3,2-Oxazagermolidines and -diazagermolidines enter reactions with electrophiles of the type ZCl₂ (S=CCl₂, PhN=CCl₂, PhPCl₂, PCl₃, PhAsCl₂, O=SCl₂) analogous to those mentioned (see Section 4.24.2.5.2) for dioxagermolanes <89SRI49>. Spirogermanes are formed when tetrachloro-germane is used instead of covalent dihalides <89SRI49>.

4.24.2.5.3 Electrophilic attack at ring germanium or adjacent other metal atom

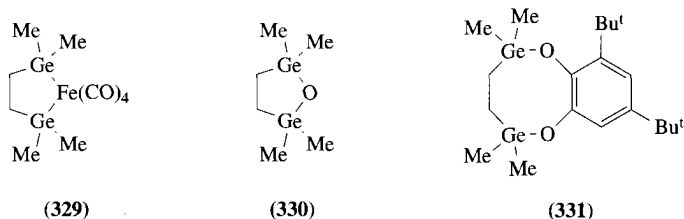
Reactions considered in this section can be classified in two groups. The first group contains those which can be regarded as proceeding via electrophilic attack at ring germanium (or nucleophilic attack at adjacent group VIII metal ring atoms), the second group of reactions consists of those that proceed (at least formally) via electrophilic attack at adjacent iron or ruthenium ring atoms.

Thus, a platinum spiro compound (326) <92ICA461> reacts with electrophiles, such as hydrochloric acid, bromine or methyl iodide with rupture of the Ge—Pt bond to give the corresponding platinum dihalide phosphine complex and the other products which result from the addition of the electrophile to the digermylethane fragment. Reaction of (326) with phenylacetylene is considered by the same authors <92ICA461> as proceeding via a nucleophilic attack at the platinum atom. Digermetane (327)

is proposed <92ICA461> as the intermediate in the reaction of (326) with triazolidinediones which leads to bicyclic systems (328).

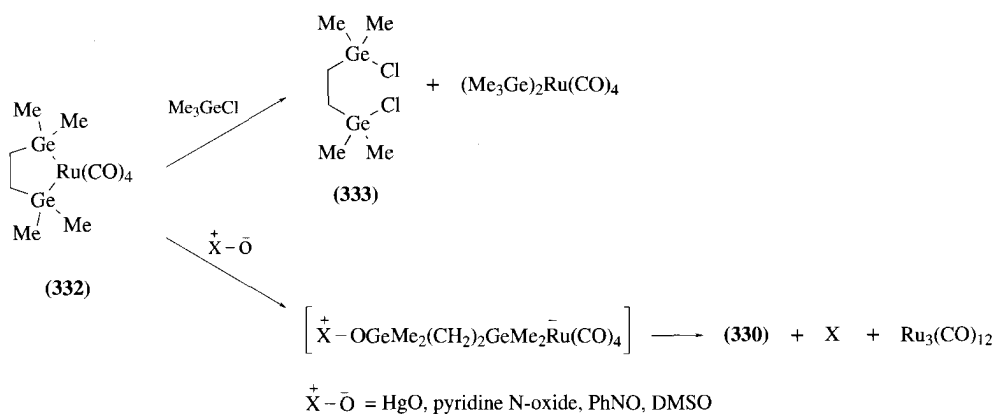


Some transformations of derivatives of 2-ferri- and 2-ruthena-1,3-digermacyclopentanes, i.e. bis(dimethylgermyl)ethane-iron and -ruthenium tetracarbonyls <89OM1585, 90IC1674, 90JOM(395)27, 91JOM(406)123> can be classified as involving electrophilic attack at the group VIII metal atom. For example, the iron derivative (329) undergoes an insertion-elimination process with aldehydes giving oxadigermolanes (330) via intermediate seven-membered heterocycles <90IC1674>. The exothermic reaction of compound (329) with 3,5-di-*t*-butyl-*O*-benzoquinone leads to the eight-membered heterocycle (331) with elimination of triiron dodecacarbonyl <90IC1674>. Reactions with germanium and tin halides <89OM1585> lead to the ring cleavage of (329) and formation of the dihalide (333) and four-membered Ge,Fe- and Sn,Fe-heterocycles.



The behavior of ruthenium derivative (333) resembles that of the iron analogue and reactions with some other electrophiles (CS₂, PhNCO, tetracyanoethylene) was also studied <91JOM(406)123>.

The ruthenium atom is the target for electrophilic attack in reactions <90JOM(395)27> of (333) with a number of "alkylating" reagents, such as trimethylgermyl chloride (Scheme 33) or ethylene dibromide.



Scheme 33

Results of reactions of bis(dimethylgermyl)ethane-ruthenium tetracarbonyl (332) <90JOM(395)27> with oxidants (which can be regarded as electrophiles) allow the electrophilic attack at Ru (or nucleophilic attack at Ge) to be presumed (Scheme 33).

4.24.2.5.4 Nucleophilic attack at ring germanium, tin, and lead

Coordination and self-association in the solid and in solutions of 1,3,2-dioxastannolanes and related compounds (see Section 4.24.2.3) can be regarded as the result of nucleophilic attack at

the ring tin atom. Various nucleophiles (pyridine, DMF, DMSO, sulfolane, THF, HMPT) form complexes with dioxastannolanes and related compounds playing the role of ligands at the tin atom <83JOM(258)7, 86JOM(309)273>.

In 1970 ring-opening and ring-closing reactions of 2,2-dialkyl-1,3,2-dioxo- and -1,3,2-oxathia-stannolanes with carbon disulfide and phenyl isothiocyanate involving nucleophilic attack at the tin atom were discovered <70CC235>. Since these reactions are described as proceeding via a cyclic transition state they will be considered in Section 4.24.2.5.10.

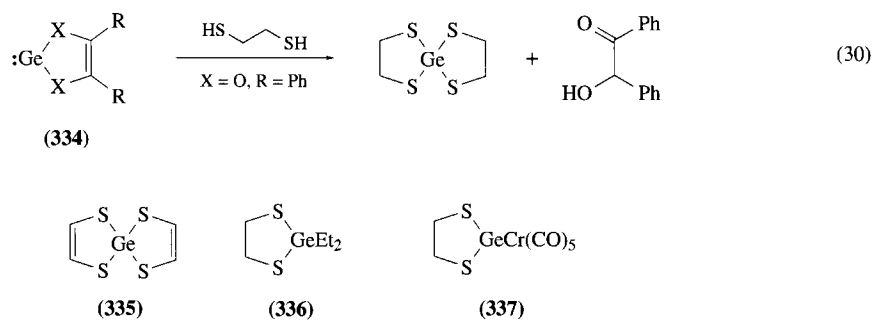
The bipolar molecule, 1,1,4,5,5-pentaethyl-2,2,3-trimethyl-1,2,5-azastannaborole, undergoes an exchange reaction with 2-trifluoromethylaniline to form (322) (see Section 4.24.2.5.1) which can be considered as the result of nucleophilic attack at the tin atom <87ZN(B)191>. Some ring-cleavage and ring-insertion reactions involving probably (or formally) nucleophilic attack at the germanium atom are known also for 2,5-digermaazolidines <86SR1991>.

4.24.2.5.5 Nucleophilic attack at other ring atoms

Substitution of carbon monoxide by phosphines has been observed for bis(dimethylgermylethane-iron tetracarbonyl <89OM1585>.

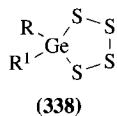
4.24.2.5.6 Reactions involving radicals, carbenes, carbenoids, reducing agents and at surfaces

Reactions of 2,2-dialkyl-1,3,2-dioxo- and -dithiagermoles (316) with GeCl_2 -dioxane complex give stable cyclic germynes, 1,3-dioxo- or 1,3-dithia-2-germa(II)-cyclopent-4-enes (334; $\text{X} = \text{O}, \text{S}$), which are able to undergo further transformations, particularly those shown in Equation (30) <85JOM(297)C17>. In the case of 4,5-unsubstituted 2,2-dialkyl-1,3,2-dithiagermoles (316; $\text{X} = \text{S}$, $\text{R}' = \text{H}$) reaction with GeCl_2 -dioxane complex leads to a mixture of the expected cyclic germylene (334; $\text{X} = \text{S}$, $\text{R} = \text{H}$) together with a germanium spirane molecule (335) <88RTC440>.

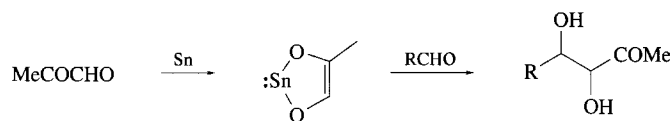


2,2-Diethyl-1,3,2-dithiagermolane (336) reacts with the chromium pentacarbonyl complex of dichlorogermylene (in the form of solvate with THF) to give a cyclic germylene complex (337) which can be further stabilized with an additional nitrene ligand <87JOM(331)11>.

Thermal reaction of 5-R-5-R'-1,2,3,4,5-tetrathiagermolane (338) ($\text{R} = \text{mesityl}$, $\text{R}' = 2,4,6\text{-}[(\text{Me}_3\text{Si})_2\text{CH}]_3\text{C}_6\text{H}_2$) with diphenyldiazomethane gives three unusual heterocycles, the 1,3,4,2-trithiagermolane and the 1,2,4,5-tetrathia-3-germa- and 1,3,4,5-tetrathia-2-germacyclohexanes <91TL6143>.



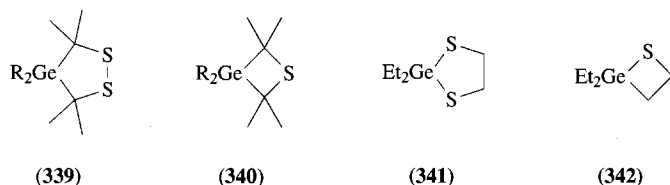
Cyclic stannylenes formed from activated tin and α -dicarbonyl compounds undergo a specific addition reaction (Scheme 34) with aldehydes to give ketodiol in high yields (83CL1825).



Scheme 34

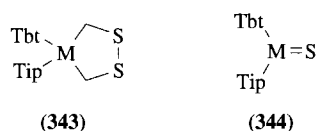
Reductive deoxygenation of 3,3,5,5-tetramesityl-1,2,3,5-dioxadigermolane with triphenylphosphine leads to the respective oxadigermetane in 95% yield (92CC457). Reduction of 1,3-di-*t*-butyl-2,2-dichloro-1,3,2-diazagermolidine with lithium metal gives the corresponding cyclic germylene (92AG(E)1485).

1,2,4-Dithiagermolanes (339) undergo desulfurization with $(\text{Et}_2\text{N})_3\text{P}$ to the corresponding 3,3-dialkyl-3-germathietanes (340) in high yield (83JOM(252)C73). Similar reaction of 1,3,2-dithiagermolanes (341) with trialkylphosphines is assumed to give the isomeric 2,2-dialkyl-2-germathietanes (342) as intermediates, the latter decomposing with the formation of ethylene and germathione trimer (81JOM(221)271).



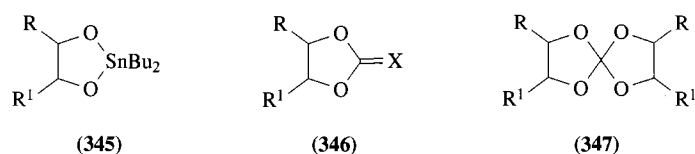
Reactions of bis(dimethylgermyl)ethane-iron and -ruthenium tetracarbonyls with *o*-quinones probably undergo a SET process to give eight-membered digermylated dioxocanes (90IC1674, 91JOM(406)123).

Okazaki and co-workers (93JA8855, 94PS(95-96)21) succeeded in generating all four sterically crowded metallothiones (344) by desulfurization of 1,2,3,4,5-tetrathiametallolanes (343) ($\text{M} = \text{Si}, \text{Ge}, \text{Sn}, \text{Pb}$); the first two compounds are quite stable crystalline substances which were studied by x-ray diffraction methods while the latter were identified only in solution.



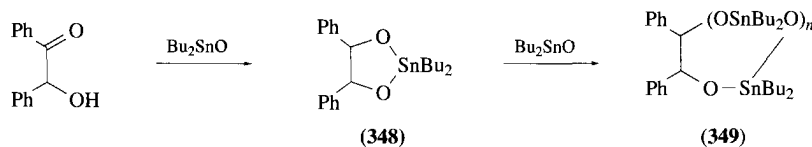
4.24.2.5.7 Reactions with cyclic transition states

It has been shown that ring-opening and ring-closing reactions of 2,2-dialkyl-1,3,2-dioxastannolanes (345) with carbon disulfide and phenyl isothiocyanate are effectively promoted with equimolar amounts of Lewis bases such as tributylphosphine, HMPT and triethylamine to give products (346; $\text{X} = \text{S}$ or NR) under mild conditions ($40\text{--}50^\circ\text{C}$) in high yields (91CB1881). It should be noted that in the presence of a base 1,3-dioxolane-2-thiones (346) ($\text{X} = \text{S}$) are obtained in the reaction with carbon disulfide while spiro compounds (347) are predominantly formed in the absence of bases. The reaction with isothiocyanates gives in both cases cyclic imines in high yields. It seems evident that the base forms a complex or ion pair with carbon disulfide enhancing the nucleophilicity of the latter (in particular, Bu_3P is known to form an ion pair with CS_2) (91CB1881).



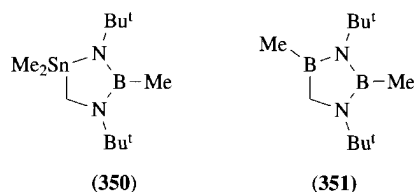
4.24.2.5.8 Other reactions

Unsaturated tin(IV) derivatives, 2,2-dialkyl-1,3,2-dioxastannoles (**348**), undergo a telomerization reaction with dialkyltin oxide to give a set of cyclic oligomers (**349**) <82JOM(224)C37, 83JOM(251)203>. This telomerization can be combined with the synthesis of 2,2-dialkyl-1,3,2-dioxastannoles (Scheme 35).



Scheme 35

1,3-Di-*t*-butyl-2,4,4-trimethyl-1,3,4,2-diazastannaborolidine (**350**) reacts with methylboron dichloride to give the 1,3,2,4-diazadiborolidine (**351**), the product of tin-boron exchange, in 15% yield <87JOM(326)307>.



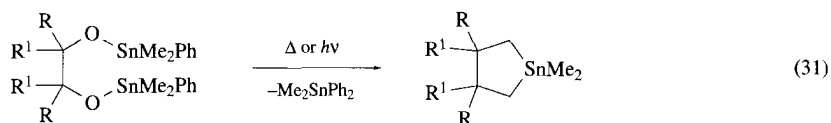
4.24.2.6 Ring Synthesis from Acyclic Compounds

This section also includes syntheses of annelated rings in which the annelating ring remains intact throughout the process, for example, formation of benzannelated rings from the appropriate benzene derivatives.

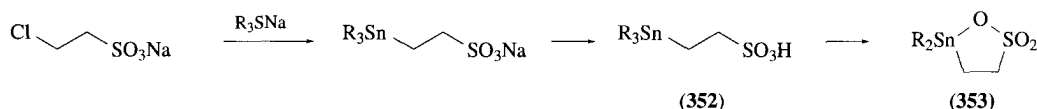
4.24.2.6.1 Formation of one bond between two heteroatoms

This route is used rather rarely for the synthesis of particular types of group IV heterocycles.

Tin glycolates or *o*-diphenolates undergo photochemical or thermal radical cyclization (Equation (31)) to 1,3,2-dioxastannolanes or benzo-1,3,2-dioxastannolenes in high yields <86JOM(303)87>.



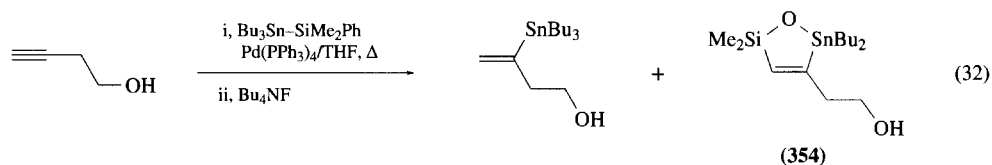
β -Triorganotinethylsulfonic acids (obtained by ion-exchange from their readily available sodium salts) are of limited stability and undergo cyclocondensation (Scheme 36) to give 5,5-diorgano-1,2,5-oxathiastannolane 2,2-dioxides <91ZAAC(603)41>.



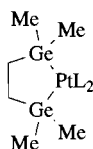
R = Me, Ph

Scheme 36

In Pd(0) mediated addition of trialkyl[dimethyl(phenyl)silyl]stannane to acetylenes <89S218> the product obtained from 1-hydroxybut-3-yne after normal workup contained the substituted 1,2,5-oxasilastannolene (**354**) in addition to the expected 2-tributylstannylalk-1-ene (Equation (32)).



A ligand-stabilized five-membered cycle (355) containing two germanium atoms and one platinum atom <92ICA461> was obtained by depolymerization–cyclization of $[\text{Me}_2\text{GeCH}_2\text{CH}_2\text{GeMe}_2\text{Pt(PPh}_3)_2]_n$ with diphos.



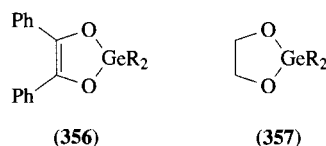
(355)



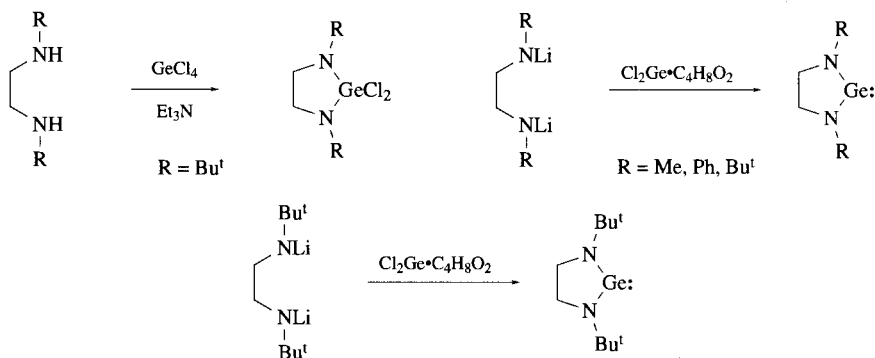
4.24.2.6.2 Formation of two bonds: Four-atom fragments and group IV elements

Formation of two bonds between a four-atom fragment and a group IV element atom provides a route to various germanium, tin and lead heterocycles, especially to 1,3-diheterametallacyclopentanes and -cyclopentenes. Different types of reactants and reactions are used depending on target molecule structures.

Substitution reactions of diorganodihalogermanes, -stannanes or -plumbanes with various bifunctional compounds are very useful for syntheses of both saturated and unsaturated heterocycles. Thus, diphenyl- and diethyldichlorogermane react with benzoin (as its dipotassium salt) to give respective 2,2-disubstituted 4,5-diphenyl-1,3,2-dioxagermolenes (356) <85JOM(297)C17>. Diorganodichlorogermanes react with ethylene glycol in the presence of triethylamine to give corresponding 1,3,2-dioxagermolanes (357) <83JOM(246)227>.

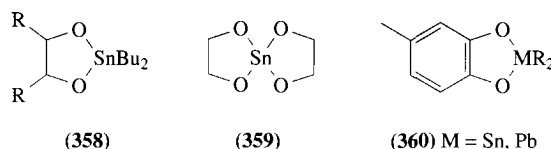


1,3,2-Dioxa- and -dithiagermoles as well as their benzannelated derivatives were prepared from diorganodihalogermanes and α -hydroxyketones, 1,2-ethenediolates, 1,2-ethenedithiolates and -benzenedithiolates <88RTC440>. Similar reactions (Scheme 37) can be used for the synthesis of diazagermolidines <92AG(E)1485> and cyclic germylenes <85CB2020, 90PS(53)411, 92AG(E)1485>.

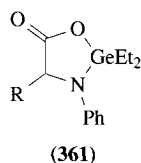


Scheme 37

The same reaction pattern is useful for dioxastannolanes and oxathiastannolanes. Thus, dioxastannolanes (**358**) were prepared from Bu_2SnCl_2 and mixtures of meso- and ($\pm$)-diols $(\text{RCHOH})_2$ with $\text{R} + \text{R} = (\text{CH}_2)_4$, $(\text{CH}_2)_3$, and $\text{R} = \text{Ph}$ in the presence of sodium carbonate, these compounds being separable by fractional crystallization $\langle 83\text{G}73 \rangle$. Analogously, starting from thioglycol and tin tetrachloride, spiro oxathiastannolane (**359**) was obtained $\langle 83\text{MI} 424\text{-}01 \rangle$. Dithiastannolanes and -plumbolanes, e.g. (**360**), can also be obtained in the same manner $\langle 85\text{JOM}(290)41 \rangle$.

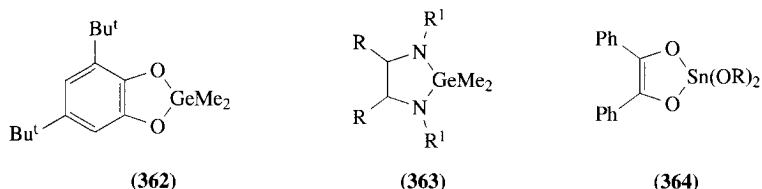


Instead of diorganodihalogermanes or -stannanes such compounds as diorgano-bis(dialkylamino)germanes $\langle 82\text{JOM}(240)335, 82\text{PS}(12)279, 85\text{JOM}(297)\text{C}17, 91\text{PS}(63)341 \rangle$, dialkyldimethoxystannanes $\langle 82\text{ZOB}1820, 83\text{JCS}(\text{P}1)875 \rangle$ and tin tetraacetate $\langle 82\text{JJC}(\text{A})983 \rangle$ can be used; acyloins can be substituted by their enediol carbonates $\langle 83\text{JCS}(\text{P}1)875 \rangle$ and dithiols by respective thiol acetates $\langle 82\text{ZOB}1820 \rangle$. Diorganogermanium imines $\langle 83\text{RTC}21 \rangle$ and possibly dialkyltin oxides $\langle 82\text{JOM}(224)\text{C}37, 83\text{JCS}(\text{P}1)875, 88\text{BSB}873 \rangle$ can interact according to a $[4 + 1]$ scheme. Thus, diethylgermylimine, $\text{Et}_2\text{Ge} = \text{NH}$, (as its cyclic trimer which is considered to be in an equilibrium with the monomer $\langle 83\text{RTC}21 \rangle$) gives with *N*-phenylglycine and -alanine 1,3,2-oxazagermolidinones (**361**; $\text{R} = \text{H}, \text{Me}$) but not -diazagermolidinones $\langle 77\text{JOM}(137)\text{C}37 \rangle$. 4-Oxo-1,3,2-dioxastannolanes were prepared by cyclocondensation of Bu_2SnO with α -hydroxycarboxylic acids $\langle 88\text{BSB}873 \rangle$.



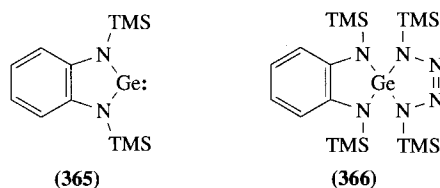
The other important type of reaction leading to the formation of two bonds between a metal and four-atom fragment is addition of carbenoids, i.e. germylenes and stannylenes, to α -dicarbonyl and related compounds. The process can be classified as redox $(4 + 1)$ cycloaddition since the dicarbonyl fragment is reduced while the carbenoid is oxidized. Formally the simplest example of such reactions is the interaction of methylglyoxal with activated tin metal to give a cyclic stannylene, $\text{Sn}(\text{II})$ enediolate (see Scheme 34) $\langle 83\text{CL}1825 \rangle$.

Cycloaddition of dimethylgermylene ($\text{Me}_2\text{Ge:}$) to α -diketones $\langle 86\text{TL}2455, 92\text{OM}2330 \rangle$ or *o*-quinones gives 1,3,2-dioxagermoles in high yields, in the case of 3,5-di-*t*-butyl-1,2-benzoquinone the yield of annelated dioxagermole (**362**) being 100% $\langle 86\text{TL}2455 \rangle$. Cyclic germylenes give spiro systems $\langle 91\text{JOM}(406)303, 91\text{PS}(63)341 \rangle$. Besides α -dicarbonyl compounds their nitrogen analogues also enter into the reaction to give 1,3,2-diazagermoles (**363**) $\langle 89\text{TL}6669, 91\text{JOM}(406)303 \rangle$. Similar reactions of stannylenes give related 1,3,2-dioxastannolene systems. Among variously generated stannylenes which take part in the reaction dialkylstannylenes $\langle 82\text{OM}1017, 86\text{MI}424\text{-}01, 86\text{TL}5347 \rangle$, diarylstannylenes $\langle 92\text{CB}563 \rangle$ and dialkoxystannylenes $\langle 81\text{BCJ}2345 \rangle$ should be mentioned. As an example, the reaction of benzil with $\text{Sn}(\text{OR})_2$ ($\text{R} = \text{CH}_2\text{CH}_2\text{NMe}_2$) gives (**364**) $\langle 81\text{BCJ}2345 \rangle$.

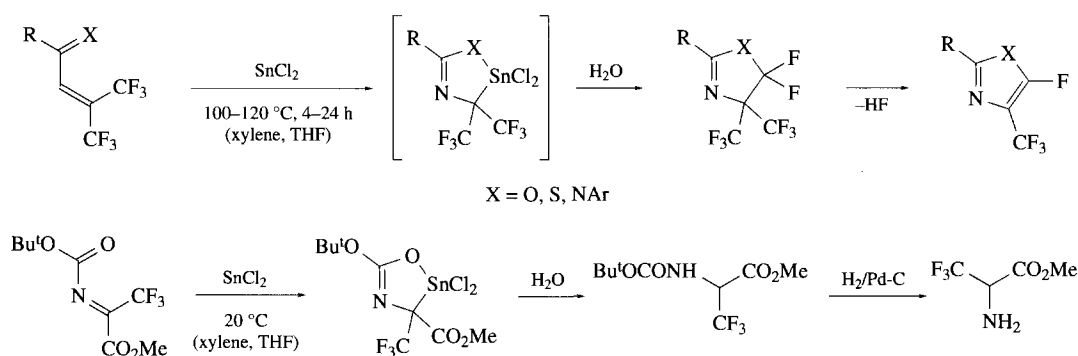


The reaction of 1,3-bis(trimethylsilyl)-1,3-diaza-2-germa(II)-indane (**365**) with trimethylsilyl azide to give (**366**) may seem to be reminiscent of several preceding transformations but, as was shown with open-chain germylenes, the process is not a cycloaddition and probably involves nitrene intermediates $\langle 89\text{CB}245 \rangle$.

A $[4 + 1]$ cycloaddition involving SnCl_2 $\langle 90\text{JFC}(46)105 \rangle$ is presumed to be the first step in some new syntheses (Scheme 38) of trifluoromethyl-substituted compounds, particularly those of 1,3-

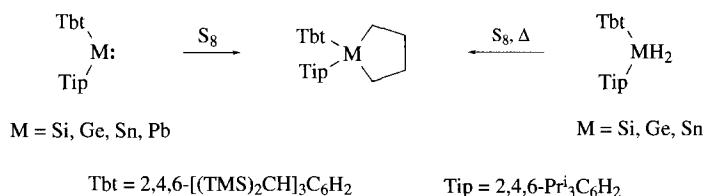


azoles <88S189> and α -aminoacids <91ZN(B)361>. In the latter case the 4,5-dihydro-1,3,5-oxazastannol was isolated.



Scheme 38

The syntheses of 1,2,3,4,5-tetrathiametallolanes (**343**) by Okazaki and co-workers belong to the same category since all procedures involved the generation of the respective carbene analogues and subsequent reaction of the latter with sulfur (Scheme 39) <91TL6143, 93JA8855, 94PS(95-96)21>. The thermal syntheses using the corresponding hydrides also probably proceed via carbenoids.

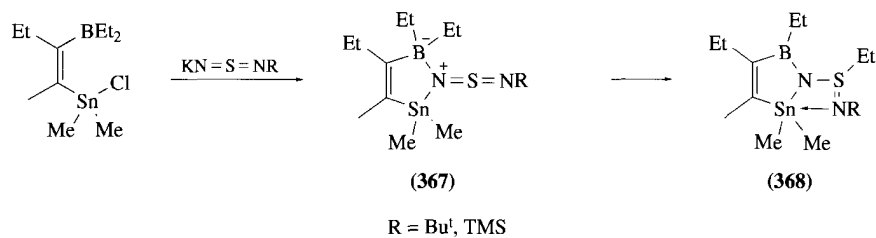


Scheme 39

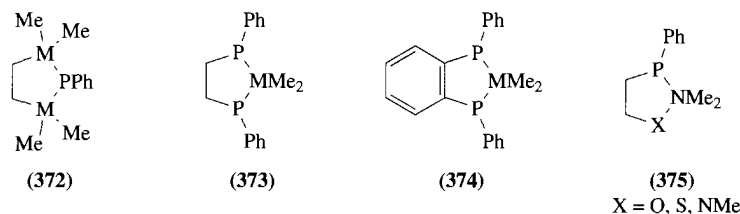
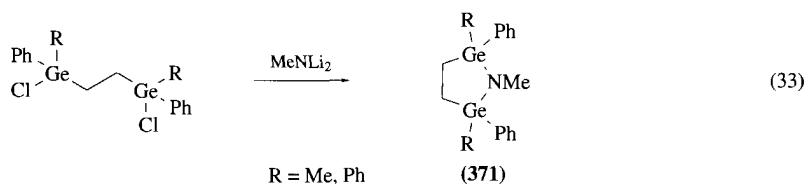
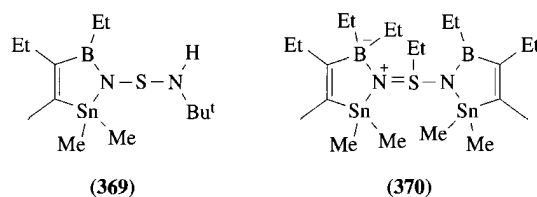
4.24.2.6.3 Formation of two bonds: Four-atom fragments and nitrogen, phosphorus, or group VIII metal

Reaction of 2-(chlorodimethylstannyl)-3-(diethylboryl)pent-2-ene with sulfur diimide anions below -30°C (Scheme 40) gives zwitterionic unstable 2,5-dihydro-1,2,5-azastannaboratoles (**367**). At higher temperatures these undergo rearrangement with transfer of one ethyl group from boron to sulfur atom to give azastannaboroles (**368**) which are additionally stabilized by intramolecular N $\rightarrow$ Sn coordination <91CB691>. Compound (**368**; R = Bu^t) undergoes elimination of ethylene with the formation of a diaminosulfane derivative (**369**). Reaction of the same pent-2-ene derivative with dipotassium sulfur diimide gives the product (**370**) with both azastannaboratole and azastannaborole rings <91CB691>.

Methodologies used for syntheses of 1,2,5-azadigermolindines (**371**) <86SRI991>, 2,5-dimetallaphospholanes (**372**), 2-metallo-1,3-diphospholanes (**373**) and (**374**) <82PS(12)265>; as well as 2-metallo-3-heteraphospholanes (**375**) (M = Si, Ge, Sn) <82PS(12)279> are illustrated by the formation of (**371**) in Equation (33).



Scheme 40

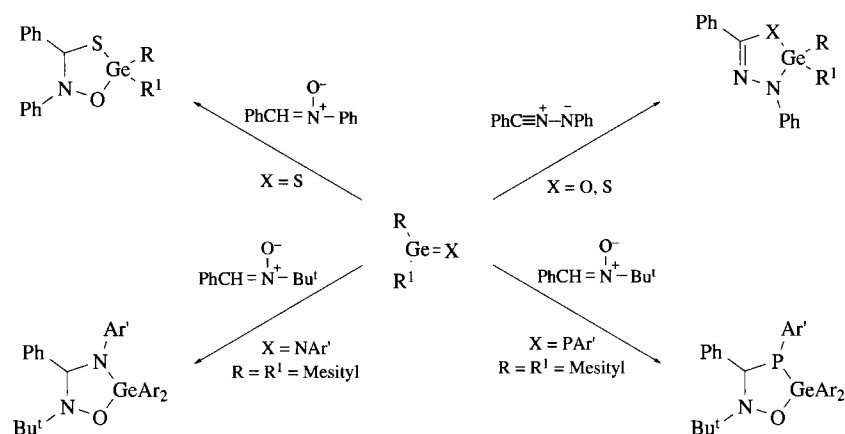


A five-membered heterocycle (329) with two germanium atoms and one iron atom <89OM1585>, was obtained from $\text{H}(\text{Me})_2\text{GeCH}_2\text{CH}_2\text{Ge}(\text{Me})_2\text{H}$ and $\text{Fe}(\text{CO})_5$. Its ruthenium analogue (332) was prepared by a similar route <90JOM(395)27>. Analogous methodology but with platinumacyclopentatriphenyl phosphine complex <92ICA461> gave an oligomeric product which could be transformed to stable spiro compound (326) on treatment with 1,2-diphenylphosphinoethane (diphos as ligand).

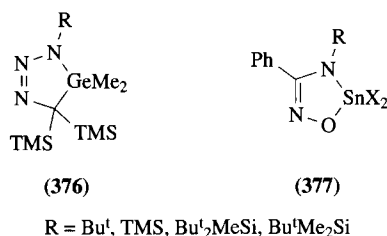
4.24.2.6.4 Formation of two bonds: [3 + 2] Atom fragments by cycloaddition

1,3-Dipolar cycloadditions were studied for germanones and germathiones as dipolarophiles with traditional dipoles, nitrile imines and nitrones <82AG455, 82JOM(240)335>. Results are presented in Scheme 41. Stable germainines react with α -phenyl-*N*-*t*-butylnitrone to give 1,2,4,5-oxadiazagermolanes <93JOM(462)89>. Using a stable germaphosphene and α -phenyl-*N*-*t*-butylnitrone <91JOM(415)327> the respective heterocycle with four heteroatoms was obtained.

The substituted germaethene $\text{Me}_2\text{Ge}=\text{C}(\text{SiMe}_3)_2$ undergoes 1,3-dipolar cycloaddition reactions with azides to give 1,2,3,4-triazagermolanes (376) <86CB2980> and the free stannamine ($\text{X}_2\text{Sn}=\text{NR}$; $\text{X} = \text{N}(\text{TMS})_2$, $\text{R} = 2,6\text{-Pr}^i\text{C}_6\text{H}_3$) (stable below -30°C) reacts with benzonitrile oxide giving the 1,2,4,5-oxadiazastannoline derivative (377) <93CB2247>.

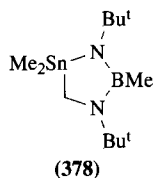


Scheme 41



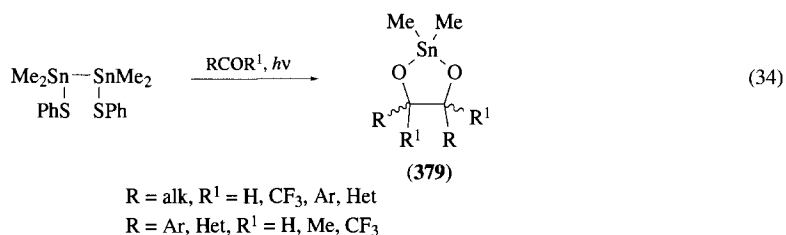
4.24.2.6.5 Formation of two bonds: [3 + 2] Atom fragments by other processes

Cyclocondensation of a secondary diamine, (di-*t*-butylamino)methylborane, with an organotin dibromide, $\text{Me}_2\text{Sn}(\text{CH}_2\text{Br})\text{Br}$, in the presence of butyllithium gives 1,3-di-*t*-butyl-2,4,4-trimethyl-1,3,2,4-diazastannaborolidine (**378**) in 60% yield [87JOM(326)307].

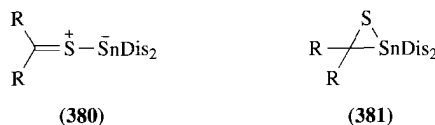


4.24.2.6.6 Formation of three bonds

Photolysis of 1,2-bis(phenylthio)tetramethyldistannane or 1,1,2,2-tetramethyl-1,2-diphenylstannane in the presence of aldehydes or ketones leads to 1,3,2-dioxastannolanes (**379**) in high yield (Equation (34)) [82OM1017, 86JOM(303)87]. The reaction involves dimethylstannylene and formation of a stannacarbonyl ylide intermediate (or the corresponding biradical). Reductive cyclization with the formation of three new bonds is very efficient for transformation of 2,2'-diacetylbiphenyl and 1,8-diacetylnaphthalene into corresponding tetra- and heptacyclic annelated 1,3,2-dioxastannolanes [86JOM(303)87].

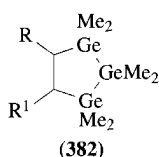


Some thioketones are reported to give 1,3,2-dithiastannolanes in moderate to high yields in reactions with a stannylene Dis_2Sn [$\text{Dis} = \text{CH}(\text{SiMe}_3)_2$] <93OM4>. The key difference with the process discussed above is inversed polarization of intermediate ylide (**380**) which can exist in an equilibrium with a thiastannirane (**381**).



4.24.2.6.7 Formation of four bonds

Dimethylgermylene generated on thermolysis (70°C) of 7,7-dimethyl-7-germa-2,3-benzonorbadiene reacts with alkynes to give 1,2,3-trigermolenes (**382**) in 30–68% yields <92OM2069>.



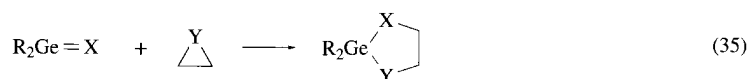
$\text{R} = \text{R}^1 = \text{H}, \text{CF}_3, \text{Ph};$

$\text{R} = \text{H}, \text{R}^1 = \text{Bu}, \text{Bu}^t, 4\text{-MeC}_6\text{H}_4$

4.24.2.7 Ring Synthesis by Transformation of Another Ring

4.24.2.7.1 Ring synthesis from three-membered heterocycles

Oxiranes, thiiranes and aziridines are known as useful precursors of five-membered germanium heterocycles, the other reaction partner being germanones, germathiones or germainines. These are mostly generated *in situ*, e.g. by thermal destruction of their dimers or trimers <83JOM(246)227, 83RTC21> or 1,2-oxa- and -thiagermacyclobutanes <83JOM(243)281> or some germanium analogues of cyclic thio- and aminothioacetals <83JOM(246)227, 83RTC21>. Several examples of this approach are presented in Equation (35) <83JOM(246)227, 83RTC21>. Better preparative results have been obtained for combinations $\text{X} = \text{O}, \text{Y} = \text{S}; \text{X} = \text{S}, \text{Y} = \text{O}, \text{S}, \text{NH}, \text{NAlk}$.

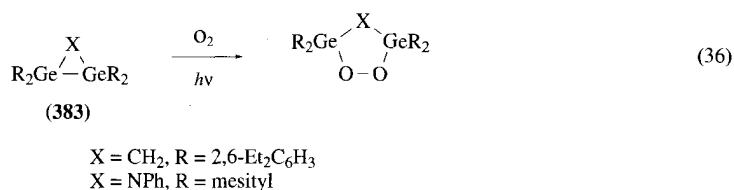


$\text{X} = \text{O}; \text{Y} = \text{O}, \text{S}, \text{NR}^1$

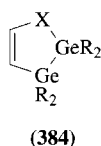
$\text{X} = \text{S}; \text{Y} = \text{O}, \text{S}, \text{NR}^1$

$\text{X} = \text{NMe}; \text{Y} = \text{O}$

Tetraphenylporphyrin-sensitized photooxygenation of 1,2-disubstituted digermirane (**383**; $\text{X} = \text{CH}_2$) and 1,2,3-disubstituted azadigermiridine (**383**; $\text{X} = \text{NPh}$) (Equation (36)) leads to corresponding cyclic peroxides <92CC457>.

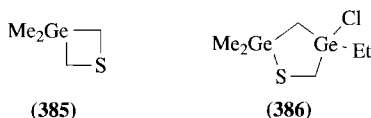


Palladium-catalyzed reactions of thia- and selenadigermiranes (**383**; $\text{X} = \text{S}, \text{Se}, \text{R} = \text{mesityl}$) with alkyne afford 1,2,3-thia- and -selenadigermolenes (**384**) <89OM2286>.

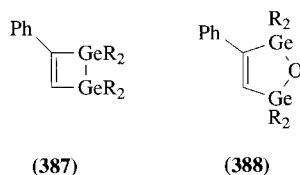


4.24.2.7.2 Ring synthesis from four-membered heterocycles

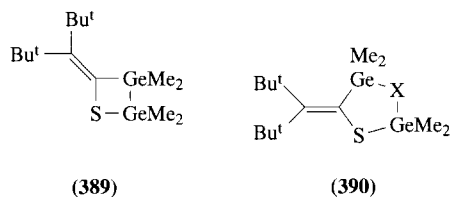
1,2-Oxa- and -thiagermacyclobutanes formed from dialkylgermylene-triethylamine complexes and oxiranes or thiiranes act as sources of germylene oxide or sulfide in syntheses of five-membered germanium heterocycles (see above) <83JOM(243)281>. The same role can be played also by 1,3,2,4-dioxa- and -dithiadigermetanes <87OM659>. 3,3-Dimethyl-1,3-thiagermetane (**385**) with ethylchlorogermane, EtGeH₂Cl, gives an insertion product, 2-chloro-2-ethyl-4,4-dimethyl-1,2,4-thiadigermolane (**386**) <84SR121>.



1,2,5-Oxadigermolene (**388**) and 1,2,3,6-dioxagermine were obtained by photosensitized and radical cation-catalyzed electron-transfer oxygenations of 3-phenyl-1,1,2,2-tetramesityl-1,2-digermetene (**387**), the five-membered compound being the main product (ratio of five- to six-membered rings 79:2) when the reaction was carried out in the presence of (*p*-BrC₆H₄)₃NSbCl₆ radical cation in dichloromethane <92CC458>.



4-Alkylidene-3,3,4,4-tetramethyl-1,2,3-thiadigermetane (**389**) reacts with molecular oxygen or sulfur to give, respectively, the oxathia- or dithiadigermolanes (**390**) <86TL5105, 89OM1467>.

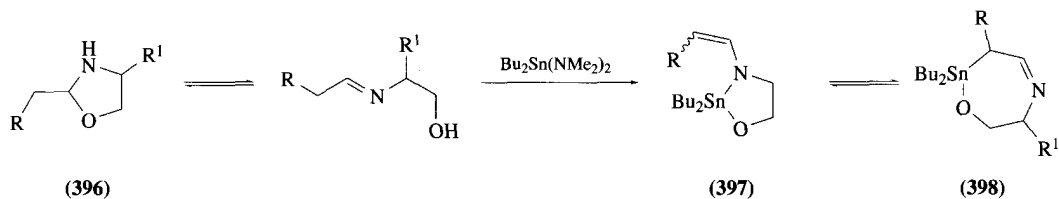
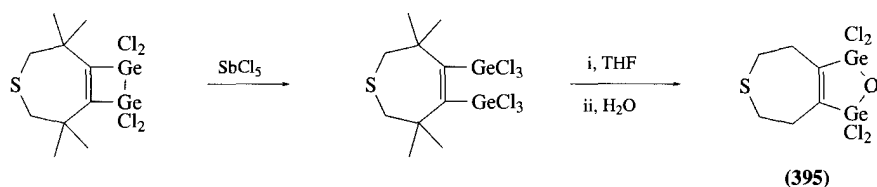
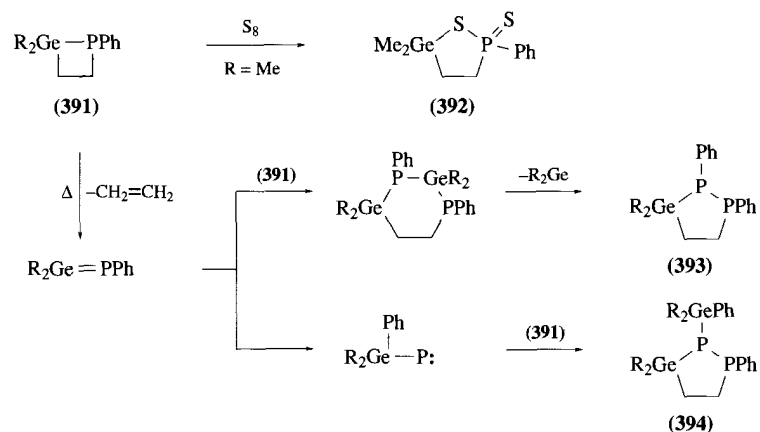


Similarly 2,2-dimethyl-1-phenyl-1,2-phosphagermetane (**391**) reacts exothermically with sulfur with the formation of a five-membered Ge,P,S-heterocycle (**392**); on thermolysis both phosphagermetane (**391**) and its diethyl homologue undergo ethylene extrusion to form unstable germaphosphimines which undergo further transformations (Scheme 42) leading to mixtures of two other heterocycles (**393**) and (**394**) which could not be separated but were characterized by NMR and GLC data <82OM1261>. Analogous insertion reactions of phosphagermetane (**391**) CR = Me, Et) with (PhP)₃ affords 1,2,3-diphosphagermolane (**393**) <82PS(12)265>.

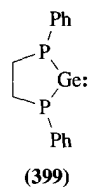
Conversion of a four- to five-membered ring (Scheme 43) was used in the preparation of Δ^{1,7}-8,8,10,10-tetrachloro-2,2,6,6-tetramethyl-9-oxa-4-thia-8,10-digermabicyclo[5.3.0]decene (**395**) <89M1 424-02>.

4.24.2.7.3 Ring synthesis from five-membered heterocycles

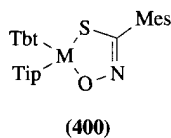
Ozazolidines (as their open-chain tautomers) react with bis(dimethylamino)dibutyltin to give *N*-vinyl-1,3,2-oxazastannolanes (**397**) which exist in equilibrium with 1,4,7-oxazastannepines (**398**) (Scheme 44) <86JOM(299)319>.



This group of syntheses includes those involving metal-metal exchange. Thus, a 1,3,2-diphosphasilolane (**373**; $M = \text{Si}$) was converted into germanium and tin analogues by the action of Me_2MCl_2 ($M = \text{Ge}, \text{Sn}$); reaction of (**373**; $M = \text{Si}$) with GeCl_2 -dioxane complex made possible the preparation of the first stable diphosphorus germylene (**399**) $\langle 82\text{PS}(12)265 \rangle$.

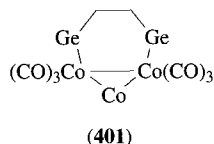


1,2,3,4,5-Tetrathiametallolanes (**343**) $\langle 94\text{PS}(95-96)21 \rangle$ are useful precursors of analogues of thio-ketones (**343**) which act as dipolarophiles in (3 + 2)-cycloaddition reactions to give, for example, (**400**) with mesitonitrile oxide.

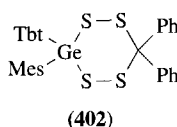


4.24.2.7.4 Ring synthesis from six-membered heterocycles

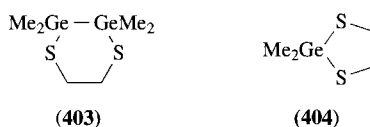
Bis(dimethylgermyl)ethane dicobalt heptacarbonyl (**401**) obtained from bis(dimethylgermyl)ethane and dicobalt octacarbonyl reacts with various oxygen-containing compounds (RCHO, HgO, pyridine N-oxide, PhNO) to give 1,2,5-oxadigermolane (**330**); similar desulfurization of carbon disulfide results in 1,2,5-thiadigermolane (**330**; S for O) <91NJC657>. These reactions proceed in high yields (72–94% for oxygen and 62% for sulfur compounds).



The 3,3,5,5-tetrasubstituted 1,2,4,3-trithiagermolane (**318**) was obtained quantitatively by desulfurization with $P(NMe_2)_3$ of the 1,2,4,5-tetrathia-3-germacyclohexane (**402**) which is one of the products formed from the corresponding 1,2,3,4,5-tetrathiametallolane (**388**) and diphenyldiazomethane <91TL6143>.



2,2,3,3-Tetramethyl-2,3-digerma-1,4-dithiane (**403**) decomposes with extrusion of dimethylgermylene very slowly at room temperature but readily on thermolysis or photolysis to yield 2,2-dimethyl-1,3,2-dithiagermolane (**404**) <84JOM(277)323>.



4.24.2.8 Synthesis of Particular Classes of Compounds

Main data on various routes for the synthesis of particular classes of five-membered germanium, tin and lead heterocycles with three and more heteroatoms were given and compared in Sections 4.24.2.6 and 4.24.2.7. In Tables 3–8 the synthetic routes are classified according to the nature and number of heteroatoms. Some references are included for completeness from the monograph <B-71MI 424-01>.

4.24.2.9 Important Compounds and Applications

4.24.2.9.1 Germanium heterocycles

Biological activity of organogermanium compounds including various heterocycles is well known and documented <B-90MI 424-04>. Some five-membered germanium heterocycles with three heteroatoms also manifest different types of bioactivity. Thus, 2,2-disubstituted 1,3,2-thiazagermalidines have higher radioprotective activity than cysteamine but are more toxic than the latter <82EJM433>. Similar activity is associated with bicyclic compounds of the type (**405**) (as hydrochlorides) and related trithiagermatranes (**406**) having three “1,3,2-thiazagermolidines” rings with one common coordination $N \rightarrow Ge$ bond <91EJM291>.

1,3,2-Dithiagermolanes <85JAP8511494> and -oxathiagermolanes <86JAP86100588>, variously substituted at germanium, are claimed as anticancer, antiinflammatory and antibacterial agents.

2,2-Disubstituted 1,3,2-dioxagermoles (as well as -siloles and stannoles) obtained from diethyl tartrate can be used as silica gel modifiers <88MI 424-06>.

Table 3 Synthetic routes to heterocycles with one germanium and two other heteroatoms.

Type of compound	Ref.
<i>Derivatives of divalent germanium</i>	
1,3-Diaza-2-germa(II)-cyclopentane	85CB2020, 92AG(E)1489
1,3-Diaza-2-germa(II)-cyclopentene	92AG(E)1489
1,3-Dioxa-2-germa(II)-cyclopentane	90PS(53)411
1,3-Dithia-2-germa(II)-cyclopentene	88RTC440
1,3-Diaza-2-germa(II)-indane	89CB245
1,3-Diphospha(III)-germa(II)-cyclopentane	82PS(12)265
<i>Derivatives of tetravalent germanium</i>	
1,2,3-Diphosphagermole	82OM1261
1,2,3-Diphosphagermolane	82PS(12)265
1,2,5-Thiaphosphagermole	82OM1261
1,3,2-Azaphosphagermolidine	82PS(12)279
1,3,2-Diazagermolidine	82JOM(240)335, 83JOM(246)277
1,3,2-Diazagermoline	89TL6669
1,3,2-Dioxagermolane	83JOM(243)281, 83JOM(246)227, 83JOM(246)277, 90PS(53)411
1,3,2-Dioxagermolene	85JOM(297)C17, 86TL2455, 92OM2330
Annulated 1,3,2-dioxagermolene	63ZN(B)846, 86TL2455
1,3,2-Dithiagermolane	83JOM(243)281, 83JOM(246)227, 83JOM(246)277, 87JOM(331)11
1,2,4-Dithiagermolane	83JOM(252)C73
1,3,2-Dithiagermolene	85JOM(297)C17, 88RTC440
1,3,2-Oxazagermolidine	77JOM(137)C37, 83JOM(246)227, 83JOM(246)277, 83RTC21, 90PS(53)411
1,3,2-Oxathiagermolane	83JOM(246)227, 83JOM(246)277, 94PS(95-96)21
1,3,2-Oxaphosphagermolidine	82PS(12)279
1,3,2-Thiazagermolidine	83JOM(246)227
1,3,2-Thiaphosphagermolidine	82PS(12)279
1,3,2-Diphosphagermolane	82PS(12)265
Benzo-1,3,2-diphosphagermolene	82PS(12)265
Spiro compounds	62CB2276, 64IC1329, 65JOM(3)285, 67IC163, 85CB2020, 85JOM(297)C17, 88RTC440, 89CB245, 89SRI49, 91JOM(406)303

Table 4 Synthetic routes to heterocycles with one germanium and three or four other heteroatoms.

Type of compound	Ref.
1,3,5,2-Oxathiazagermole	82JOM(240)335
1,2,4,5-Oxathiazagermolidine	93JOM(462)89
1,2,4,5-Oxazaphosphagermolidine	91JOM(415)327
1,3,5,2-Oxathiazagermolidine	82AG455, 82JOM(240)335
1,3,4,2-Oxadiazagermoline	82AG455, 82JOM(240)335
1,3,4,2-Thiadiazagermoline	82AG455, 82JOM(240)335
1,2,3,4-Triazagermoline	86CB2980
1,2,4,3-Trithiagermolane	91TL6143, 94PS(95-96)21
Tetrazagermolene	89CB245
Tetrathiagermolane	91JA7047
Tetrasilagermolane	66M1309

4.24.2.9.2 Tin heterocycles

Applications of five-membered tin heterocycles with three heteroatoms are widespread and the subject of numerous papers and patents. However, practically all publications are devoted to only one type of compound, the readily available 1,3,2-diheterastannolanes.

In contrast to their germanium analogues, the main applications of tin heterocycles are not concerned with their biological activity although several 1,3,2-dioxastannolane derivatives exhibit *in vitro* antitumor activity (88BSB873, 92H(34)549). The two most important fields involve technical uses of 1,3,2-diheterastannolanes and their use in organic synthesis.

1,3,2-Dioxastannolanes (82JAP8224393, 91EGP295174) and 1,3,2-oxathiastannolanes (85JAP8513849,

Table 5 Synthetic routes to heterocycles with two or more germanium atoms.

Type of compound	Ref.
1,2,3-Thiadigermole	89OM2286
1,2,3-Selenadigermole	89OM2286
1,2,4-Thiadigermolane	84SRI21
1,2,5-Oxadigermolane	91JOM(406)123, 91NJC657
1,2,5-Oxadigermole	92CC458
1,2,5-Azadigermolidine	86SRI991
1,2,5-Phosphadigermolane	92PS(12)265
1,3,2-Digermiferrolane	89OM1585, 90IC1674
1,3,2-Digermaplitanolane	92ICA461
1,3,2-Digermaruthenolane	91JOM(406)123
1,3,2,5-Oxathiadigermolane	86TL5105, 89OM1467
1,2,3,5-Dioxadigermolane	89OM1585, 92CC457
1,2,3,5-Dithiadigermolane	89OM1585
1,3,2,4-Dithiadigermolane	86TL5105, 89OM1467
1,3,4,5-Diazadigermolidine	92SRI1431
1,2,4,3,5-Dioxazadigermolidine	92CC457
9-Oxa-4-thia-8,10-digermabicyclo[5.3.0]decene	89MI 424-02
Spirotricyclic compounds	89CB245
1,2,5-Ferradigermolane	89OM1585
1,2,5-Platinadigermolane	92ICA461
1,2,5-Ruthenadigermolane	90JOM(395)27
1,2,3-Trigermole	92OM2069
1,3,2,4,5-Dithiatrigermole	84JOM(277)323
Oxatetragermolane	65LA(683)1
Pentagermolane	63TL1541, 65LA(683)1

Table 6 Synthetic routes to heterocycles with one tin and two other heteroatoms.

Type of compound	Ref.
<i>Derivatives of divalent tin</i>	
1,3-Diaza-2-stanna(II)-cyclopentane	90ICA205
1,3-Diaza-4,5-disila-2-stanna(II)-cyclopentane	90ICA205
1,3-Dioxastanna(II)-cyclopentane	83CL1825
<i>Derivatives of tetravalent tin</i>	
1,2,3-Diphosphastannolane	82PS(12)265
1,3,2-Dioxastannolane	82OM1017, 82ZN(B)1144, 82IJC(A)983, 83G73, 83JOM(258)7, 86JOM(303)87, 86JOM(315)277, 87JOM(328)61
1,3,2-Dioxastannolene	81BCJ2345, 82JOM(224)C37, 82OM1017, 83JCS(P1)875, 86MI 424-01, 86TL5347, 92CB563
Annelated 1,3,2-dioxastannolene	86MI 424-01
1,3,2-Oxathiaastannolane	87USP4816593, 91EUP423643, 93JA2065
1,3,2-Diphosphastannolane	82PS(12)265
Benzo-1,3,2-diphosphastannole	82PS(12)265
1,3,5-Oxazastannoline	90JFC(46)105
1,3,2-Oxazastannolidine	86JOM(299)319
1,3,5-Thiazastannoline	90JFC(46)105
1,3,5-Diazastannoline	90JFC(46)105
1,3,2-Dithiaastannolane	82ZOB1820, 91JOM(411)99, 91JOM(414)71, 93OM4
Benzo-1,3,2-dithiaastannole	85JOM(290)41
1,2,5-Azastannaborole	87ZN(B)191, 91CB691
1,2,5-Oxasilastannolene	89S218
1,2,5-Oxathiaastannolane-2,2-dioxide	91ZAAC(603)41
Spirobicyclic compounds	82IJC(A)983, 83MI 424-01

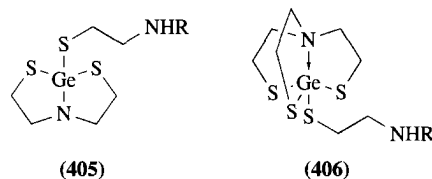
85MI 424-01, 87USP4816593, 92MI 424-01 are claimed as stabilizers for polypropylene and halogen-containing vinyl polymers. Dioxastannolanes are described as components of polyester plasticizers <82JAP82153024>, polymerization <86MAC543> and cross-linking agents for polymers <91MIP9109899>, as well as curing accelerators for polyurethane sealants <90EUP370164> and agents for creating hydrophobic surfaces on hydrophilic inorganic materials <85EUP133702>. 2,2-Dibutyl-1,3,2-oxathia-

Table 7 Synthetic routes to heterocycles with one tin and three other heteroatoms, or with two tin and two or more other heteroatoms.

Type of compound	Ref.
1,2,4,5-Oxadiazastannole	93CB2247
1,3,5,2-Oxathiazastannole	93JA2065, 94PS(95-96)21
1,3,4,2-Diazastannaborolidine	JOM(326)307
1,2,4,3-Trithiastannolane	94PS(95-96)21
Tetrathiastannolane	91JA7047
1,3,2-Phosphadistannolane	82PS(12)265
1,2,4,3,5-Trioxadistannolane	90CC1461

Table 8 Synthetic routes to lead heterocycles.

Type of compound	Ref.
<i>Derivatives of divalent lead</i>	
1,3-Dithia-2-plumba(II)-cyclopentene	89ZN(B)1531
Benzo-1,3,2-dithiaplumb(II)ole	85JOM(290)41
1,3-Dithia-2-plumba(II)-cyclopentane	91MI 424-03
1,3-Diaza-4,5-disila-2-plumba(II)-cyclopentane	90ICA205
<i>Derivatives of tetravalent lead</i>	
Benzo-1,3,2-dithiaplumbole	85JOM(290)41
Quinoxalino-1,3,2-dithiaplumbole	85JOM(290)41
1,3,5,2-Oxathiazaplumbole	94PS(95-96)21
Tetrathiaplumbolane	94PS(95-96)21



stannolane can be used as a catalyst in a cationic electrodepositable polyurethane composition <91EUP423643>. Dozens of patents claim 1,3,2-dioxastannolanes <86JAP86278863, 87JAP8775547> and 1,3,2-dithiostannolanes <86JAP86217063, 86JAP86258272> as components of charge-donating materials (toners) for development of electrostatic images.

The extensive use of 1,3,2-dioxastannolanes and their thioanalogues in organic synthesis is well documented although it has only been developed relatively recently. For example, the well-known monograph <B-80MI 424-01> includes no data concerning the synthetic potential of 1,3,2-dioxastannolanes. Their broad applications, mainly as protecting groups, are based on the formation of dioxastannolanes from 1,2-diols (Section 4.24.2.6.2) and ring opening under the action of electrophiles (Section 4.24.2.5.2).

It should be noted particularly that in some cases *cis*- and *trans*-isomers of 4,5-disubstituted 1,3,2-dioxastannolanes can be separated by simple crystallization allowing separation of isomeric 1,2-diols after ring opening <83G73, 90MI1>. Dioxastannolanes formed from various 1,2-diols (including partially protected carbohydrates) undergo highly regio- and stereoselective ring opening on alkylation <83MI 424-02, 84MI 424-03, 85JOC3558, 87CL141, 87JAP87185052, 87TL2183, 88TL2927, 89CPB861, 91LA765, 92LA47, 92TL4979>, acylation <82OM1017, 84CL49, 84CL401, 84MI 424-03, 85CC1457, 87JAP87185052, 89CAR(187)154, 89CPB861, 91EUP448413> or sulfonylation <84MI 424-03, 87JAP87185052> to give respective half-ethers or half-esters which are important intermediates and can be further transformed to various derivatives of carbohydrates <81CAR(96)21, 85JCS(P1)1067, 86TL611>, including glyceroglycolipids <83MI 424-02, 91LA765>, glycerophosphonolipids <86JCS(P1)765>, glycopeptides <92TL4979>, a modified 16-membered macrolide tylosin <87JAP87234093, 89CPB861>, as well as to compounds of other classes, e.g. to (*R*)-(+)- α -lipoic acid <87TL2183> and (*R*)- and (*S*)-isomers of acetoin <83JCS(P1)2435>.

Regioselective oxidation by brominolysis of dioxastannolane obtained from methyl β -L-arabinopyranoside made it possible to accomplish (after subsequent oximation and reduction) a facile synthesis of 4-amino-4-deoxy-L-arabinose, an amino-sugar found in lipopolysaccharides of some *Salmonella R.* mutant strains <83CPB3778>.

Condensation of 1,3,2-dioxastannolanes with 2,6-di(bromomethyl)anisole gave corresponding diols which were used in the synthesis of macrocyclic polyethers <82CC655>. 1,3,2-Dioxastannolanes found widespread use in the synthesis of macrocyclic polylactones by ring opening with dicarboxylic acid dichlorides <82JA4220, 84JCR(S)38, 84JHC577, 84JHC1789, 85JHC1129, 86T3503, 88JCS(P2)1617, 88T5845, 89JOC2643, 89M3275, 90CC58, 92JOC1472>. Analogous reactions with 1,3,2-dithiastannolanes <84S140, 88T5845, 92JOC766> and 1,3,2-oxathiastannolanes <85JOC5476> give thiolactones while the interaction of diacyl dichlorides with a 1,3,2-diazastannolane <88T5845> leads to di- and tetralactams.

Some chiral 1,3,2-dioxastannolanes were used as catalysts in asymmetric Diels-Alder reactions of cyclopentadiene with methyl acrylate <90JCR(S)278>. *N*-Alkenyl- and -cycloalkenyl 1,3,2-oxazastannolanes, generated *in situ* from chiral amino alcohols, gave optically active 2-substituted aldehydes and ketones in modest to high chemical and optical yields after alkylation with methyl acrylate or acrylonitrile (which is usual for enamines) and subsequent hydrolysis <85CC504, 85JOC3863>.

4.25

Pentazoles

RICHARD N. BUTLER

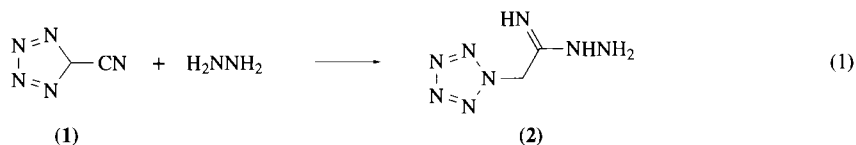
University College, Galway, Ireland

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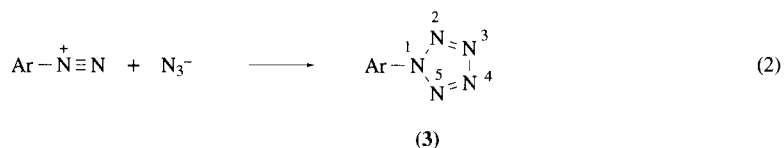
4.25.1 INTRODUCTION

The pentazoles are the final members of the azole series, the isoelectronic nitrogen analogues of the cyclopentadienylide anion. Among the metastable nitrogen species which attract theoretical chemists the pentazoles provide a bridge with experimental reality with many of their properties and derivatives still awaiting discovery. Knowledge of the firm experimental existence of pentazoles is due to the pioneering work of Huisgen and Ugi who proved the existence of the ring <56AG705, 57CB2914> and measured its stability and rate of decomposition <58CB531>. This eventually led to the determination of an x-ray crystal structure of the ring by Wallis and Dunitz <83CC910> which showed it to be aromatic in the physical sense and hence a true azole. The history of the early debates about pentazoles has been described <93AG(E)230> and for an insider account of the discovery and true beginning of experimental pentazole chemistry the excellent account by Ugi in *Comprehensive Heterocyclic Chemistry, First Edition* <84CHEC-I(5)839> must be consulted. Unsuccessful attempts to prepare phenylpentazole were made by Hantzsch <03CB2056> and Dimroth and de Montmollin <10CB2904>. Lifschitz <15CB410> believed he had obtained the pentazole derivative (2) from the reaction of 'tetrazolecarbonitrile' (1) with hydrazine (Equation (1)) but the inevitable correction by Curtius <15CB1614> was so critical that pentazole chemistry froze for about 40 years. Since the experimental work of Huisgen and Ugi most theoretical papers on azoles have included the pentazole ring in tables of calculated parameters. The availability of an x-ray crystal structure with ring dimensions has added new meaning and impetus to these calculations. The position of the pentazole ring as a viable member of the azole series has been enhanced by the measurement of ¹⁴N and ¹⁵N NMR signals and spectra <75MI 425-01, 85AG(E)513>. The status of the ultimate azine, hexazine

(N₆), among the azines is now quite different to that of the ultimate azole and we will make a brief comparison of the current status of the two all-nitrogen rings.



The known pentazoles are aryl derivatives which have the structure (3). They are obtained from the reaction of aryl diazonium ions with azide ion (Equation (2)). No alkylpentazoles are known and the reaction of diazomethane with HN₃ which gives methyl azide has been shown by ¹⁵N-labelling not to pass through a pentazole intermediate <58HCA1823>. The parent NH-pentazole is unknown. The numbering system shown in (3) will be used in this chapter.



4.25.2 THEORETICAL METHODS

4.25.2.1 Pentazole: Dimensions and Stability

Calculated molecular dimensions for pentazole (4) are summarized in Table 1. These may be compared with x-ray crystal structure dimensions of the ring in 1-(*p*-dimethylaminophenyl)pentazole (16) (see Section 4.25.3).

Table 1 Theoretical calculations on pentazole: dimensions.

Method	Bond length ($\times 10^{-1}$ nm)				Bond angles ($^\circ$)				Ref.
	1-2	2-3	3-4	N-H	51H	512	123	234	
6-31G	1.323	1.276	1.367	0.989		111.3	105.6	108.7	86JPC5597
3-21G	1.356	1.279	1.427	0.995		110.7	106.3	108.3	89JPC3929
STO-3G	1.37	1.32	1.40			111	105	109	79NJC607
INDO	1.308	1.280	1.307	1.000		112.8	103.7	109.9	84CS84
MBPT (<i>n</i>)	1.333	1.333	1.352	1.014	122.9				92JA8302
SCF	1.298	1.264	1.330	0.996	124.05				92JA8302

The heat of formation of pentazole was calculated at 21.622 eV by Dewar and Gleicher. This compares with a similarly calculated value of 39.388 eV (measured at 39.391) for pyrazole <66JCP(44)759>. Calculated dipole moments for pentazole are 3.95 <84CS84>, 3.70 <69BSF1097>, and 4.10 D <86JPC5597>. The polarizability α of pentazole has been calculated as 19.4 on a scale where pyrrole has an α value of 53.5 and 2H-tetrazole of 27.7 <90JPC1755>. A calculated total energy for pentazole has been quoted at -272.69873 au <89JPC3929> (1 au = 1 hartree = 627.51 kcal mol⁻¹). HMO calculated π -electron densities for pentazole are N-1, 1.518, N-2, 1.085, and N-3, 1.156 <77JJC(B)168>. An assessment of the possible existence of cyclic HN₅ has been made using *ab initio* calculations such as the *n*th order many-body perturbation theory (MBPT(*n*)). The procedure gave the structural values in Table 1 and suggests that pentazole is a minimum on the HN₅ hypersurface. It has C_{2v} symmetry and its vibrational spectral frequencies have also been calculated <92JA8302>. The transition states for gas phase fragmentation to HN₃ and N₂ were assessed (Figure 1). The activation barrier for the lower energy pathway, asymmetric cleavage of the N(1)—N(2) and N(3)—N(4) bonds, structure (5), was calculated at 19.8 kcal mol⁻¹ thus making pentazole a reasonable target in the gas phase or in a low temperature lattice <92JA8302>. Using a number of theoretical levels, Janoschek reviewed the activation barrier from (4) to (5). He suggested that

MBPT calculated barriers are too high, and gave a revised range of 13.7–20.9 kcal mol⁻¹ with the lower values more likely. Triplet states with intersystem crossing could also lead to other lower energy decomposition mechanisms <93AG(E)230>.

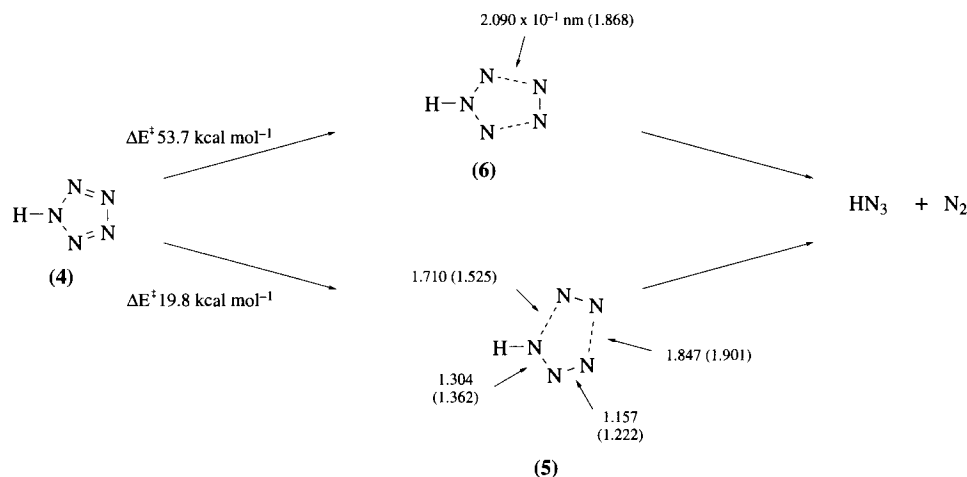
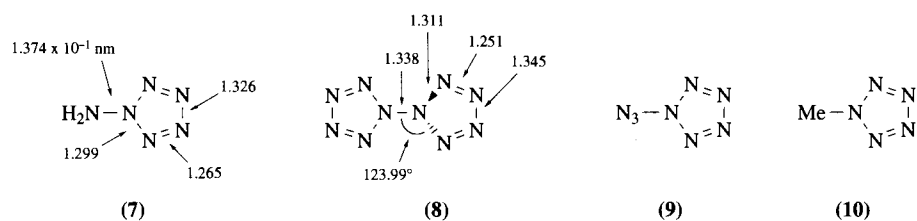


Figure 1 Symmetric and asymmetric decomposition of pentazole from SCF and (MBPT2) calculations <92JA8302>.

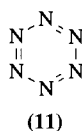
4.25.2.2 Substituted Pentazoles

Calculated structural parameters and properties have been reported for the pentazole derivatives (7)–(10). The total energy for 1-methylpentazole (10) was estimated as -311.53772 au and its dipole moment was 5.54 D from calculations at the 6–31 G level <93MRC791>. Dimensions are shown for the interesting bipentazole (8) in which the rings are twisted at 90° and for the 1-aminoderivative (7) <92JA8302>. The electron donating amino group lowered the barrier to fragmentation by $7.9 \text{ kcal mol}^{-1}$ and it was suggested that pentazole with electron withdrawing substituents such as (8) are more likely to be isolated <92JA8302>. *Ab initio* and MNDO results for 1-azidopentazole (9) suggest that it is a true energy minimum with a total energy of -434.56376 au and ΔH_f° of $184 \text{ kcal mol}^{-1}$. It is estimated to be $32.8 \text{ kcal mol}^{-1}$ more stable than the fused bicyclic pentazolopentazole form and an acyclic N_8 chain was found to be $6.6 \text{ kcal mol}^{-1}$ higher in energy than (9) <86CC959>.

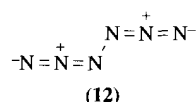


4.25.2.3 Pentazole vs. Hexazine

It is of interest to compare the present status of the ultimate azole and the ultimate azine, hexazine (11).



A report that a yellow compound of composition N_6 , showing no ESR signal, was formed on UV irradiation of $cis-[Pt(N_3)_2(PPh_3)_2]$ in a frozen matrix of EtOH or THF at 77 K aroused interest in the possibility that (11) might have been formed. On warming the yellow color disappeared and N_2 was evolved (80AG(E)717). Many calculations followed and in an assessment of these Huber (82AG(E)64) concluded that (11) is ca. 239 kcal mol⁻¹ higher in energy than 3N₂ and that there is no activation barrier between them. It has since been claimed that (11) cannot exist because the D_{6h} symmetry would give two imaginary frequencies for out-of-plane vibrations (92JPC1173). The acyclic N_6 structure (12), formed from a combination of two azido radicals, was calculated to be 35 kcal mol⁻¹ more stable than (11). It is now generally considered to be the yellow N_6 compound (90JPC6923, 93AG(E)230). Prospects for cyclic hexazine are not good while clearly those for cyclic HN₅ are promising.



4.25.2.4 Basicity, Protonation and Complexation

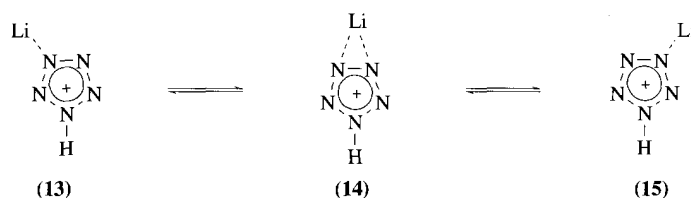
The pentazoles are weak bases with an estimated pK_a of -8.9 for compound (10) (93MRC791). A number of calculated protonation energies have been reported (Table 2). It is generally agreed that the protonation site is N-3 (84CS84, 86JPC5597, 91JPC7694, 93MRC791). Similar results have been obtained for 1-methylpentazole with protonation energies at N-3 of 201.5 kcal mol⁻¹ (6-31 G) (93MRC791) and 228.8 (STO-3 G) (84CS84). Two accounts of the interaction of pentazole with Li⁺ have been reported (89JPC3929, 92JA8302). This is different to protonation since it involves the interaction of two closed-shell systems and no new covalent bond is formed in contrast to the sigma bond formation in protonation.

Table 2 Theoretical calculations on pentazole: protonation energies (kcal mol⁻¹)^a.

Method	H ⁺ at N-3	H ⁺ at N-2	Ref.
STO-3G	223.4	200.3	86JPC5597
STO-3G	220.3	202.5	84CS84
6-31G**/6-31G	191.6	170.9	86JPC5597
6-31G**/6-31G	191.6		91JPC7694

^aDifference in energy between pentazole and the cation.

The potential energy curve for the approach of Li⁺ to pentazole showed a double minimum for a direct single coordination at N-3 as in (13) and (15) with the bridging structure (14) higher in energy by 1.8 kcal mol⁻¹ (Scheme 1) (89JPC3929). The bridged structure with C_{2v} symmetry has been reported with dimensions (92JA8302). There have been a number of theoretical assessments of the prospects for generating ferrocene-type metal complexes of the pentazole anion, N₅⁻ (83CJC1435, 85POL1721, 88MI 425-01).



Scheme 1

The pentazole anion is estimated to be 31 kcal mol⁻¹ higher in energy than N₃⁻ + N₂ but the decomposition activation barrier is 22 kcal mol⁻¹ and the anion could probably be isolated in a

low temperature matrix. Comparisons between extended Hückel calculations on $(N_5)M(CO)_3$ and $(C_5H_5)M(CO)_3$ for $M = Fe^{2+}$, Mn^{+} , and Cr , suggest that such complexes should form if the pentazole anion (unknown) could be generated in the presence of the metal carbonyl $\langle 83CJC1435, 85POL1721 \rangle$.

4.25.3 EXPERIMENTAL STRUCTURAL METHODS

4.25.3.1 Molecular Dimensions

The most stable solid pentazole derivative isolated was 1-(*p*-dimethylaminophenyl)pentazole (**16**), reported to decompose at 50°C but whose crystals rapidly deteriorate at ambient temperatures $\langle 58CB531 \rangle$. An x-ray crystal structure on this compound measured at 128 K was a considerable achievement $\langle 83CC910 \rangle$. The structure (Figure 2) displays N—N bond lengths intermediate between single and double bond values indicating an aromatic structure. The effect of the pentazole ring on the dimensions of the dimethylaminophenyl group were comparable to the influence of a nitro group and it was suggested that pentazole has an inductive effect comparable to an NO_2 group $\langle 83CC910 \rangle$.

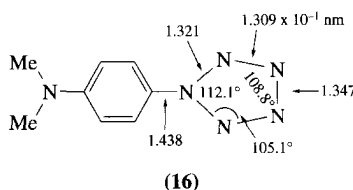


Figure 2 X-ray crystal structure dimensions of the pentazole ring $\langle 83CC910 \rangle$.

4.25.3.2 NMR Spectroscopy

The first reported NMR signal from a pentazole in solution was a ^{14}N signal at -70 ppm (upfield from external $MeNO_2$) for the N-1 atom $\langle 75MI 425-01 \rangle$. The ^{14}N signals for the pyridine-type nitrogens were too broad to be observed and although the sample was decomposing at probe temperature in a mixture of methanol and dichloromethane (1 : 1 v/v) the signal was consistently observed and the decomposition products had no signals in this region. Although it has subsequently been established that N_2 gas could give a signal at -70.5 (measured at 233 K) $\langle 77JA1264 \rangle$ it seems unlikely that N_2 could build up to such a concentration at 32°C in the probe. A full ^{15}N NMR spectrum of compound (**16**) in $CDCl_3$ at 238 K has been obtained and the assignments confirmed by using a ^{15}N -labelled sample $\langle 85AG(E)513 \rangle$. The chemical shifts were N-1, -80.0 ppm; N-2, -27.1 ppm; N-3, $+4.9$ ppm, and *p*- NMe_2 , -324.6 ppm (from external $MeNO_2$). The spectrum confirmed the pentazole structure in solution $\langle 85AG(E)513 \rangle$. It also allowed an observation of the ring degradation to arylazide and N_2 . The effect of the pentazole ring on the Me_2N nitrogen-15 shift was similar to that of CN and $CH=O$ at the *para*-position. Thus the ^{15}N shift for *N,N*-dimethylaniline is -338 ppm; for *p*-CN, -326.4 ppm; and for *p*- $CH=O$, -323.1 ppm. For *p*- NO_2 -*N,N*-dimethylaniline the NMe_2 shift is -316.5 ppm and the ^{15}N NMR data conflict somewhat with the x-ray dimensions as to the electron withdrawing power of the pentazole ring. The decreasing progression of the ^{15}N shift of the pyrrole-type singly bound nitrogen in the azole series is completed with the pentazole datum, 1-methylpyrazole, -180.8 ppm; 1-methyltetrazole, -151 ppm; 2-methyl-1,2,3-triazole, -134 ppm; 2-methyltetrazole, -104 ppm; 1-substituted pentazole, -80 ppm $\langle 85AG(E)513 \rangle$. For ^1H and ^{13}C NMR spectra of arylpentazoles, see $\langle 96JCS(P2)000 \rangle$.

4.25.3.3 IR and UV Spectra

Calculated IR vibrational frequencies for HN_5 have been listed to assist with its possible discovery $\langle 92JA8302 \rangle$. UV spectra in EtOH of 1-phenylpentazole (λ_{max} , ca. 335 nm), 1-*p*-ethoxyphenylpentazole

($\lambda_{\max}$, ca. 270 nm), and 1-*p*-dimethylaminophenylpentazole (**16**) ($\lambda_{\max}$, ca. 250 nm) were similar to those of the corresponding 1-aryltetrazoles. These values suggested the presence of a strong resonance interaction from the pentazole ring with electron donating substituents in the 1-aryl ring with the pentazole behaving like a nitro group <58CB2324>.

4.25.4 THERMODYNAMIC ASPECTS

The known solid pentazoles are unstable compounds which give off N₂ at ambient conditions. Decomposition temperatures quoted for substituted 1-*N*-aryl derivatives are given in Table 3. In the solid crystal the molecules are stacked in parallel planes separated by ca. 3.4–3.6 Å (3.4–3.6 × 10⁻¹ nm) and the N-(1) of one molecule lies over the (N3)—N(4) bond of the one stacked below it <83CC910>. There may be a weak intermolecular interaction, possibly of the HOMO–LUMO type at these sites. In solutions the pentazoles evolve N₂ at room temperature. This N₂ evolution is reported to be slowest for 1 : 1 (v/v) methanol–dichloromethane solutions <75MI 425-01>. The compounds are soluble in normal organic solvents such as methanol, chloroform, dichloromethane, carbon tetrachloride, diethyl ether, and acetone <75MI 425-01>. Solvents have a large influence on the rate of decomposition of phenylpentazole, the rate constant being 45.2 × 10⁻⁴ s⁻¹ in *n*-hexane and almost 10 times lower, 5.7 × 10⁻⁴ s⁻¹ in MeOH : H₂O (1 : 1 v/v) <58CB2324>.

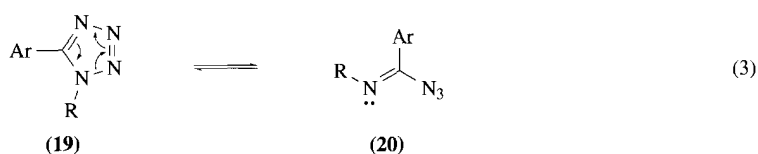
Table 3 Solid substituted 1-phenylpentazoles^a.

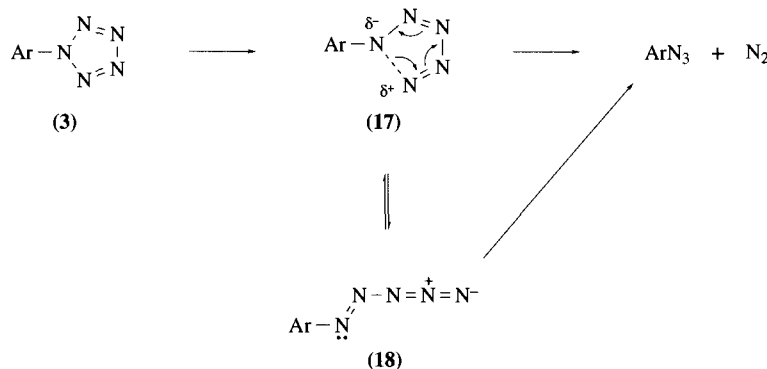
<i>p</i> -Substituent	Decomposition range (°C)	Yield (%)
H	–5 to 3	27
Me	2–5	32
Cl	8–10	21
MeO	13–15	38
EtO	26–29	42
Me ₂ N	50–54	52

^a<58CB2324>.

4.25.5 REACTIVITY

The main experimental reaction of pentazoles is thermal degradation to aryl azides and N₂. Hypothetical reactions of protonation and complexation with metals have been discussed in Section 4.25.2.4. A theoretical analysis and calculated transition state for the gas-phase thermal degradation of parent 1-*H*-pentazole is shown in Figure 1. It involves simultaneous cleavage of the N(1)—N(2) and N(3)—N(4) bonds and is enhanced by electron withdrawing substituents <92JA8302>. However, measured experimental data on substituted 1-arylpentazoles in solution give a different picture. The reaction shows a Hammett ρ of +1.01 and arylpentazoles are stabilized by electron donating substituents <58CB531>. Analogies should be sought between the behavior of pentazoles and that of their closest azole neighbors, the tetrazoles (cf. <96JCS(P2)999>). A ring opening as in Scheme 2 would satisfy a positive Hammett ρ and would accommodate the stabilizing effect of donating substituents on the ring. It would be a formal nitrogen analogue of the imido-azide–tetrazole isomerism; compare (17), (18) and (19), (20) (Scheme 2 and Equation (3)). It merits theoretical assessment as a possible mechanism for pentazole degradation in solution. The reverse of the transition state in Figure 1, the cycloaddition of N₂ with ¹⁵N-labelled *p*-ethoxyphenyl azide was tested on a charcoal surface but no exchange of ¹⁵N occurred <84CHEC-I(5)839>. Ozonization of compound (16) at –60°C caused decomposition of both the aryl ring and the pentazole ring and reduction of 1-phenylpentazole with sodium in NH₃(l) gave aniline and N₂ <61AG172>.





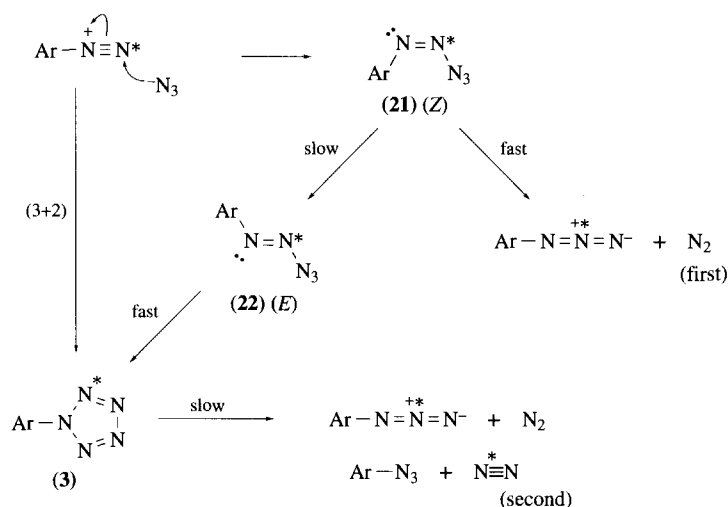
Scheme 2

4.25.6 SYNTHESIS

A key feature of pentazole chemistry is the formation of the pentazole ring and the route by which this might arise. The history of the discovery and the involvement of laboratories in Munich and Zurich has been thoroughly described by Ugi $\langle 84\text{CHEC-I}(5)839 \rangle$.

The ring was first discovered as an intermediate in the conversion of aryl diazonium ions into aryl azides using β - ^{15}N -labelled diazonium ion and normal azide ion $\langle 54\text{HCA}798, 57\text{CB}2914 \rangle$. Treatment of phenyldiazonium chloride with LiN_3 at -40°C in MeOH gave a first N_2 evolution of 76% followed by a second of 24%, indicating two separate processes. Labelling of the diazonium β -N with ^{15}N resulted in an isotope distribution consistent with that shown in Scheme 3 $\langle 57\text{CB}2914 \rangle$. At -12°C the first evolution of N_2 occurred and the influence of substituents on the rate of the second evolution was measured by raising the temperature to 0°C after this first evolution had subsided $\langle 58\text{CB}531 \rangle$. The rate was higher with electron withdrawing substituents in the aryl ring and lower for electron donating groups and showed a Hammett ρ of +1.01. *ortho*-Substituents also increased the rate. Eventual isolation of the pentazole intermediates confirmed that they were the source of the second N_2 evolution $\langle 58\text{CB}2324 \rangle$. Ugi has discussed the mechanistic alternatives to explain these observations $\langle 84\text{CHEC-I}(5)839 \rangle$.

The most likely explanation is as outlined in Scheme 3. Following a well-known stereoelectronic effect $\langle \text{B-83MI } 425\text{-01} \rangle$, wherein addition of nucleophiles to triple bonds places the developing new lone pair *trans* to the incoming nucleophile, a fast addition of azide ion to the diazonium ion would give the *Z*-diazoazide (21) which cannot form a pentazole. This is analogous to the stable imidoyl azide of tetrazole chemistry. Rapid loss of N_2 from this produces the first N_2 evolution.

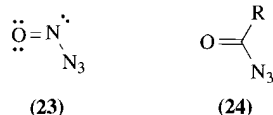


Scheme 3

At lower temperatures there is time for *Z* $\rightarrow$ *E* isomerization to the *E*-form (22) which has the correct stereoorientation of the azide and the diazo lone pair for a Huisgen cyclization (1,5-

electrocyclization) $\langle 80\text{AG(E)947} \rangle$. This is a nitrogen analogue of the imidoyl azide tetrazole ring closure and should be enhanced by electron donation from the aryl group. It gives the relatively stable pentazole from which the second N_2 evolution eventually arises. An alternative possible route to the pentazole is a $(3 + 2)$ cycloaddition of the diazonium ion and the azide ion. An assessment of orbital compatibility and HOMO–LUMO gaps needs to be made in order to explore the viability of this. However, in the final analysis the reaction is an ionic process likely to be dominated by charge control.

It is of interest that an oxygen analogue of (22), N_4O (a new oxide of nitrogen, which is NO-N_3 (23), has been obtained as a pale yellow solid by vacuum sublimation of the products from the reaction of NaN_3 and NOCl at -196°C $\langle 93\text{AG(E)1610} \rangle$. Its low temperature Raman spectrum confirmed an open-chain azide structure, although the cyclic form (1-oxopentazole) was computed to be 13 kcal mol^{-1} more stable than (23). Bending of the azide in the cyclization process would apparently require an activation energy of 49 kcal mol^{-1} $\langle 93\text{AG(E)1610} \rangle$. By comparison with the carbamoyl azide structure (24), which does not cyclize due to the low electron density of the C=O , the species (23) would also not be expected to cyclize and it could be looked upon as an extreme case of the electron-withdrawing effect of the substituent in inhibiting the cyclization in (22). The behavior of the systems (20), (22), (23), and (24) provide interesting comparisons and it may be anticipated that the sulfur analogues of (22) and (23) should cyclize as with 1,2,3,4-thiadiazoles, the sulfur analogues of (24).



4.25.7 APPLICATIONS

A perusal of the *Chemical Abstracts* index since the 1970s shows a number of unexpected claimed usages for 'pentazines' and 'pentazoles' in biochemical and agricultural literature. In all cases these turn out to be very poor misuse of nomenclature and no pentazole or pentazine compounds are involved. The best stimulant to renew experimental pentazole chemistry would be an industrial use.

As a prelude to this review the author made 1-*p*-dimethylphenylaminopentazole and 1-*p*-chlorophenylpentazole ($\langle 96\text{JCS(P2)000} \rangle$). The most striking feature was the easy evolution of N_2 at room temperature and below. Molecules which allow controlled evolution of N_2 are used in industry as blowing agents in the manufacture of cellular materials such as sponge rubber, rubber foam, and cellular plastics. An arylpentazole could be expected to give controlled successive N_2 evolutions at different temperatures (the second via the ArN_3). Hence pentazoles which could be held stable at 0°C or slightly below might yet find practical use.

References

EXPLANATION OF THE REFERENCE SYSTEM

Throughout this work, references are designated by a number–lettering coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted; the advantages of this system are outlined in the Introduction. The system has been used previously in the first edition of *Comprehensive Heterocyclic Chemistry*, eds A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984 and is based on that used in the following two monographs: (a) A. R. Katritzky and J. M. Lagowski, “Chemistry of the Heterocyclic N-Oxides,” Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, “The Tautomerism of Heterocycles,” in “Advances in Heterocyclic Chemistry,” Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer, is given immediately following these notes. Journal names are abbreviated throughout using the CASSI (Chemical Abstracts Service Source Index) system.
2. Each volume contains all the references cited *in that volume*; no separate lists are given for individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For nontwentieth-century references the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are *not* included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code “MI” for miscellaneous with the whole code for books prefixed by the letter “B-”.
11. Where journals have changed names, the same code is used throughout, e.g. CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

Journal Codes

AAC	Antimicrob. Agents Chemother.
ABC	Agric. Biol. Chem.
AC	Appl. Catal.
AC(P)	Ann. Chim. (Paris)
AC(R)	Ann. Chim. (Rome)
ACH	Acta Chim. Acad. Sci. Hung.

ACR	Acc. Chem. Res.
ACS	Acta Chem. Scand.
ACS(A)	Acta Chem. Scand., Ser. A
ACS(B)	Acta Chem. Scand., Ser. B
AF	Arzneim.-Forsch.
AFC	Adv. Fluorine Chem.
AG	Angew. Chem.
AG(E)	Angew. Chem., Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AHCS	Adv. Heterocycl. Chem. Supplement
AI	Anal. Instrum.
AJC	Aust. J. Chem.
AK	Ark. Kemi
AKZ	Arm. Khim. Zh.
AM	Adv. Mater. (Weinheim, Ger.)
AMLS	Adv. Mol. Spectrosc.
AMS	Adv. Mass. Spectrom.
ANC	Anal. Chem.
ANL	Accad. Naz. Lincei
ANY	Ann. N. Y. Acad. Sci.
AOC	Adv. Organomet. Chem.
AP	Arch. Pharm. (Weinheim, Ger.)
APO	Adv. Phys. Org. Chem.
AQ	An. Quim.
AR	Annu. Rep. Prog. Chem.
AR(A)	Annu. Rep. Prog. Chem., Sect. A
AR(B)	Annu. Rep. Prog. Chem., Sect. B
ARP	Annu. Rev. Phys. Chem.
ASI	Acta Chim. Sin. Engl. Ed.
ASIN	Acta Chim. Sin.
AX	Acta Crystallogr.
AX(A)	Acta Crystallogr., Part A
AX(B)	Acta Crystallogr., Part B
B	Biochemistry
BAP	Bull. Acad. Pol. Sci., Ser. Sci. Chim.
BAU	Bull. Acad. Sci. USSR, Div. Chim. Sci.
BBA	Biochim. Biophys. Acta
BBR	Biochim. Biophys. Res. Commun.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BJ	Biochem. J.
BJP	Br. J. Pharmacol.
BMC	Bioorg. Med. Chem. Lett.
BP	Biochem. Biopharmacol.
BPJ	Br. Polym. J.
BRP	Br. Pat.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
BSF(2)	Bull. Soc. Chim. Fr., Part 2
C	Chimia
CA	Chem. Abstr.
CAN	Cancer
CAR	Carbohydr. Res.
CAT	Chim. Acta Turc.
CB	Chem. Ber.

CBR	Chem. Br.
CC	J. Chem. Soc., Chem. Commun.
CCA	Croat. Chem. Acta
CCC	Collect. Czech. Chem. Commun.
CCR	Coord. Chem. Rev.
CE	Chem. Express
CEN	Chem. Eng. News
CHE	Chem. Heterocycl. Compd. (Engl. Transl.)
CHEC-I	Comp. Heterocycl. Chem., 1st edn.
CI(L)	Chem. Ind. (London)
CI(M)	Chem. Ind. (Milan)
CJC	Can. J. Chem.
CJS	Can. J. Spectrosc.
CL	Chem. Lett.
CLY	Chem. Listy
CM	Chem. Mater.
CMC	Comp. Med. Chem.
COC	Comp. Org. Chem.
COMC-I	Comp. Organomet. Chem., 1st edn.
COS	Comp. Org. Synth.
CP	Can. Pat.
CPB	Chem. Pharm. Bull.
CPH	Chem. Phys.
CPL	Chem. Phys. Lett.
CR	C. R. Hebd. Seances Acad. Sci.
CR(A)	C. R. Hebd. Seances Acad. Sci., Ser. A
CR(B)	C. R. Hebd. Seances Acad. Sci., Ser. B
CR(C)	C. R. Hebd. Seances Acad. Sci., Ser. C
CRAC	Crit. Rev. Anal. Chem.
CRV	Chem. Rev.
CS	Chem. Scr.
CSC	Cryst. Struct. Commun.
CSR	Chem. Soc. Rev.
CT	Chem. Tech.
CZ	Chem.-Ztg.
CZP	Czech. Pat.
DIS	Diss. Abstr.
DIS(B)	Diss. Abstr. Int. B.
DOK	Dokl. Akad. Nauk SSSR
DP	Dyes Pigm.
E	Experientia
EC	Educ. Chem.
EF	Energy Fuels
EGP	Ger. (East) Pat.
EJM	Eur. J. Med. Chem.
EUP	Eur. Pat.
FCF	Forstchr. Chem. Forsch.
FCR	Fluorine Chem. Rev.
FES	Farmaco Ed. Sci.
FOR	Fortschr. Chem. Org. Naturst.
FRP	Fr. Pat.
G	Gazz. Chim. Ital.
GAK	Gummi Asbest Kunstst.
GEP	Ger. Pat.
GEP(O)	Ger. Pat. Offen.

GSM	Gen. Synth. Methods
H	Heterocycles
HAC	Heteroatom Chem.
HC	Chem. Heterocycl. Compd.
HCA	Helv. Chim. Acta
HOU	Methoden Org. Chem. (Houben-Weyl)
HP	Hydrocarbon Process
IC	Inorg. Chem.
ICA	Inorg. Chim. Acta
IEC	Ind. Eng. Chem. Res.
IJ	Isr. J. Chem.
IJC	Indian J. Chem.
IJC(A)	Indian J. Chem., Sect. A
IJC(B)	Indian J. Chem., Sect. B
IJM	Int. J. Mass Spectrom. Ion Phys.
IJQ	Int. J. Quantum Chem.
IJS	Int. J. Sulfur Chem.
IJS(A)	Int. J. Sulfur Chem., Part A
IJS(B)	Int. J. Sulfur Chem., Part B
IS	Inorg. Synth.
IZV	Izv. Akad. Nauk SSSR, Ser. Khim.
JA	J. Am. Chem. Soc.
JAN	J. Antibiot.
JAP	Jpn. Pat.
JAP(K)	Jpn. Kokai
JBC	J. Biol. Chem.
JC	J. Chromatogr.
JCC	J. Coord. Chem.
JCE	J. Chem. Ed.
JCED	J. Chem. Eng. Data
JCI	J. Chem. Inf. Comput. Sci.
JCP	J. Chem. Phys.
JCPB	J. Chim. Phys. Physico-Chim. Biol.
JCR(M)	J. Chem. Res. (M)
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(A)	J. Chem. Soc. (A)
JCS(B)	J. Chem. Soc. (B)
JCS(C)	J. Chem. Soc. (C)
JCS(D)	J. Chem. Soc., Dalton Trans.
JCS(F1)	J. Chem. Soc., Faraday Trans. 1
JCS(F2)	J. Chem. Soc., Faraday Trans. 2
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JCS(S2)	J. Chem. Soc. (Suppl. 2)
JEC	J. Electroanal. Chem. Interfacial Electrochem.
JEM	J. Energ. Mater.
JES	J. Electron. Spectrosc.
JFA	J. Sci. Food. Agri.
JFC	J. Fluorine Chem.
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JINC	J. Inorg. Nucl. Chem.
JLC	J. Liq. Chromatogr.

JMAS	J. Mat. Sci.
JMC	J. Med. Chem.
JMOC	J. Mol. Catal.
JMR	J. Magn. Reson.
JMS	J. Mol. Sci.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPJ	J. Pharm. Soc. Jpn.
JPO	J. Phys. Org. Chem.
JPP	J. Pharm. Pharmacol.
JPR	J. Prakt. Chem.
JPS	J. Pharm. Sci.
JPS(A)	J. Polym. Sci., Polym. Chem., Part A
JPU	J. Phys. Chem. USSR (Engl. Transl.)
JSC	J. Serbochem. Soc.
JSP	J. Mol. Spectrosc.
JST	J. Mol. Struct.
K	Kristallografiya
KFZ	Khim. Farm. Zh.
KGS	Khim. Geterotsikl. Soedin.
KO	Kirk-Othmer Encyc.
KPS	Khim. Prir. Soedin.
L	Langmuir
LA	Liebigs Ann. Chem.
LC	Liq. Cryst.
LS	Life Sci.
M	Monatsh. Chem.
MAC	Macromol. Chem.
MC	Mendeleev Chem. J. (Engl. Transl.)
MCLC	Mol. Cryst. Liq. Cryst.
MI	Miscellaneous [book/journal]
MIP	Miscellaneous Pat.
MM	Macromolecules
MP	Mol. Phys.
MRC	Magn. Reson. Chem.
N	Naturwissenschaften
NAT	Nature
NEP	Neth. Pat.
NJC	Nouv. J. Chim.
NKK	Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)
NKZ	Nippon Kagaku Zasshi
NZJ	N. Z. J. Sci. Technol.
OCS	Organomet. Synth.
OM	Organometallics
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OPP	Org. Prep. Proced. Int.
OR	Org. React.
OS	Org. Synth.
OSC	Org. Synth., Coll. Vol.
P	Phytochemistry
PA	Polym. Age
PAC	Pure Appl. Chem.

PAS	Pol. Acad. Sci.
PB	Polym. Bull.
PC	Personal Communication
PCS	Proc. Chem. Soc.
PHA	Pharmazi
PHC	Prog. Heterocycl. Chem.
PIA	Proc. Indian Acad. Sci.
PIA(A)	Proc. Indian Acad. Sci., Sect. A
PJC	Pol. J. Chem.
PJS	Pak. J. Sci. Ind. Res.
PMH	Phys. Methods Heterocycl. Chem.
PNA	Proc. Natl. Acad. Sci. USA
POL	Polyhedron
PP	Polym. Prepr.
PRS	Proceed. Roy. Soc.
PS	Phosphorus Sulfur
QR	Q. Rev., Chem. Soc.
QRS	Quart. Rep. Sulfur. Chem.
QSAR	Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.
RC	Rubber Chem. Technol.
RCM	Rapid Commun. Mass Spectrom.
RCP	Rec. Chem. Prog.
RCR	Russ. Chem. Rev. (Engl. Transl.)
RHA	Rev. Heteroatom Chem.
RJ	Rubber J.
RP	Rev. Polarogr.
RRC	Rev. Roum. Chim.
RS	Ric. Sci.
RTC	Recl. Trav. Chim. Pays-Bas
RZC	Rocz. Chem.
S	Synthesis
SA	Spectrochim. Acta
SA(A)	Spectrochim. Acta, Part A
SAP	S. Afr. Pat.
SC	Synth. Commun.
SCI	Science
SL	Synlett
SM	Synth. Met.
SR	Sulfur Reports
SRI	Synth. React. Inorg. Metal-Org. Chem.
SS	Sch. Sci. Rev.
SST	Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]
SUL	Sulfur Letters
SZP	Swiss Pat.
T	Tetrahedron
T(S)	Tetrahedron, Suppl.
TA	Tetrahedron Asymmetry
TAL	Talanta
TCA	Theor. Chim. Acta
TCC	Top. Curr. Chem.
TCM	Tetrahedron, Comp. Method.
TFS	Trans. Faraday Soc.
TH	Thesis
TL	Tetrahedron Lett.
TS	Top. Stereochem.

UK	Usp. Khim.
UKZ	Ukr. Khim. Zh. (Russ. Ed.)
UP	Unpublished Results
URP	USSR Pat.
USP	US Pat.
WCH	Wiadom. Chem.
YGK	Yuki Gosei Kagaku Kyokaishi
YZ	Yakugaku Zasshi (J. Pharm. Soc. Jpn.)
ZAAC	Z. Anorg. Allg. Chem.
ZAK	Zh. Anal. Khim.
ZC	Z. Chem.
ZN	Z. Naturforsch.
ZN(A)	Z. Naturforsch., Teil A
ZN(B)	Z. Naturforsch., Teil B
ZOB	Zh. Obshch. Khim.
ZOR	Zh. Org. Khim.
ZPC	Hoppe-Seyler's Z. Physiol. Chem.
ZPK	Zh. Prikl. Khim.

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