

9.01

1,2,3-Triazines and their Benzo Derivatives

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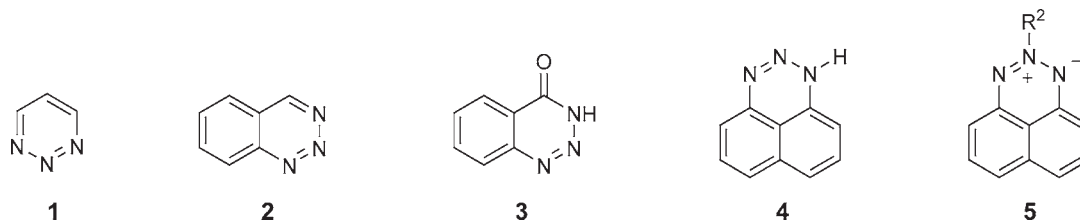
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9.01.1 Introduction

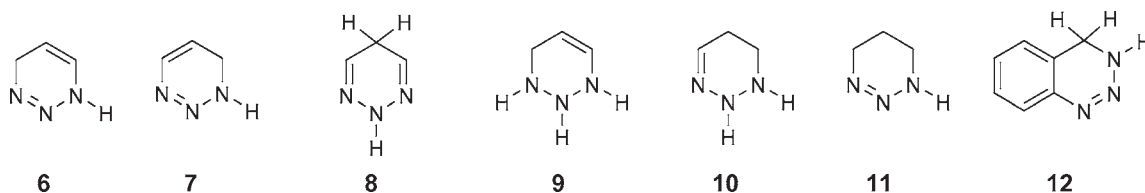
Both from experiment and theoretical predictions, 1,2,3-triazine **1**, also referred to as *vic*- or *v*-triazine, is the least stable of the monocyclic triazines. It became available in 1981 <1981CC1174>, while 3,4-dihydro-1,2,3-benzotriazin-

4-one **3** has already been known for 120 years <1887JPR262>. At present, interest is focused on four basic unsaturated structural types: the monocyclic 1,2,3-triazine **1**, its benzo-fused analogue **2**, the well-known benzotriazinone **3**, and the 1*H*-naphtho[1,8-*de*]triazine **4**, together with the symmetric 2-alkyltriazinium zwitterion **5**.



The benzotriazinones **3** will be treated among the fully conjugated systems in this chapter, because the 4-hydroxy tautomer and the delocalized anion are fully conjugated, and it would mean an undue fragmentation of the material to be covered if, for reasons of nomenclature usage, at N-3 substituted compounds **3**, which cannot form 4-hydroxy tautomers, were to be treated separately. Related considerations apply for the systems **4** and **5**.

Partially hydrogenated 1,2,3-triazines (prototypes **6–11**) and 3,4-dihydro-1,2,3-benzotriazines based on structure **12** are a second group of compounds of interest here. They did receive some consideration also in the previous editions; however, neither the prototypes **6** and **9** nor substituted derivatives there of are known, and except for **11** (being a cyclic triazene), prototypes **7**, **8**, **10**, and **12** are represented only in the form of numerous substituted derivatives.



In addition, a variety of iminium salts and *N*-oxides derived from structures **1**, **2**, **3**, **7**, and **12**, *N*-imines and ylides of **1**, and betaines of **3** have been prepared and studied.

In the past decade, a shift of emphasis in 1,2,3-triazine chemistry is to be noted from preparative to theoretical work. Interest in theoretical predictions of molecular properties of the parent **1** was evident from the literature over the past 40 years and has increased recently. On the other hand, benzotriazinones of type **3** receive attention primarily for the biological activity of many derivatives, and the 3-hydroxy derivative serves as a basis for active esters as coupling reagents in peptide synthesis. Via ring-chain tautomerism, 4-hydroxy-3,4-dihydrobenzotriazines derived from **12** are opened to triazenes which show cytotoxicity.

The literature in general until 1995 has been reviewed in the appropriate chapters of CHEC(1984) and CHEC-II(1996) <1984CHEC(3)369, 1996CHEC-II(6)483> and in earlier reviews quoted therein. The comprehensive review by Neunhoeffer <1978HC(33)3> and the chapter on 1,2,3-triazines in the book by Benson <B-1984MI96> (putting 1,2,3-triazine chemistry into the wider context of contiguous nitrogen chain compounds) should be mentioned especially. Preparative aspects have been treated in depth in Houben-Weyl's handbook <1998HOU(E9c)530> and its successor, *Science of Synthesis* <2004SOS(17)223>.

In the following sections, the prototypical compound numbers will be retained for **1–5** and **11** only; substituted derivatives will be numbered consecutively where needed for practicability. For consistency, substituents and other functions at ring positions will be numbered according to the ring atom where they are located (e.g., for 1,2,3-triazines: R⁴, R⁵, R⁶).

9.01.2 Theoretical Methods

The parent 1,2,3-triazine **1** has been the subject of the majority of theoretical investigations, while the fused systems **2–4** have been treated only occasionally. Knowledge of the molecular structure of targets from experiments and/or optimization of the geometry is of vital importance. Electron density and charge distributions, dipole moments and polarizabilities, photoelectron (PE) spectra and ionization potentials (IPs), electronic excitation, vibrational spectroscopy, energetics, aromaticity, fragmentation and bond dissociation, cycloadditions, N-protonation and metalation have been studied theoretically, as well as influences on properties arising from N-oxidation, -imination, and -methylenation. There are studies also on quantitative structure–activity relationships. Work prior to 1996 has been

(partly) treated in CHEC(1984) and CHEC-II(1996) and will be mentioned here only for purposes of comparison with recent calculation efforts, where appropriate.

9.01.2.1 Molecular Structure Parameters

For compilations of experimental and calculated bond distances and angles of substituted 1,2,3-triazines from the literature prior to the mid-1990s, see <1984CHEC(3)369> and <1996CHEC-II(6)483>. Recent material for the parent compound **1**, as well as results from older work not reviewed previously in this handbook, are contained in **Table 1**, which is meant to be a supplementary table to that in CHEC-II(1996). Experimental bond lengths and angles are listed in **Table 2**. AM1 and PM3 bond lengths and angles for the heteroring of 3,4-dihydrobenzo-1,2,3-triazin-4-one **3** have also been compared with experimental values <1973AXB1916>. PM3 bond lengths and angles have been calculated for three 6-X-substituted 3,4-dihydrobenzo-1,2,3-triazin-4-ones (X = OMe, Me, and NO₂) <2001JMT(535)199>.

Table 1 Calculated bond lengths and angles of 1,2,3-triazine **1** (see **Table 2** for experimental values)

Method and level	Bond lengths (Å) and angles (°) ^a							Reference
	N–N N–N–N	N–C N–N–C	C–C N–C–C	C–C–C	C(4)–H C(5)–C(4)–H	C(5)–H C(4)–C(5)–H	N(3)–C(4)–H	
DZ-SCF	1.3216 <i>120.82</i>	1.3416 <i>120.60</i>	1.3874 <i>121.27</i>	<i>115.44</i>	1.0674 <i>123.13</i>	1.0676 <i>122.28</i>	<i>115.60</i>	1998CPH(228)39
TZVP-SCF	1.2884 <i>121.90</i>	1.3196 <i>120.22</i>	1.3733 <i>121.72</i>	<i>114.22</i>	1.0726 <i>122.77</i>	1.0717 <i>122.89</i>	<i>115.51</i>	1998CPH(228)39
DZ-MP2	1.4127 <i>119.99</i>	1.3888 <i>119.36</i>	1.4182 <i>122.26</i>	<i>116.77</i>	1.0900 <i>123.00</i>	1.0905 <i>121.61</i>	<i>114.74</i>	1998CPH(228)39
TZVP-DZ	1.3337 <i>121.27</i>	1.3408 <i>119.56</i>	1.3841 <i>122.34</i>	<i>114.99</i>	1.0794 <i>122.58</i>	1.0788 <i>122.34</i>	<i>115.08</i>	1998CPH(228)39
LDA-DZVP	1.320 <i>121.3</i>	1.334 <i>119.8</i>	1.377 <i>122.1</i>	<i>114.9</i>	1.098 <i>122.6</i>	1.098 <i>122.5</i>		2000JCP6301
MSINDO	1.293 <i>125.4</i>	1.353 <i>118.4</i>	1.396 <i>121.5</i>	<i>114.8</i>	1.089 <i>122.4</i>	1.089 <i>122.4</i>		2000JCP6301
G3, G3MP2	1.340 <i>121.0</i>	1.345 <i>119.7</i>	1.387 <i>122.2</i>	<i>115.2</i>	1.087 <i>123.9</i>	1.085 <i>122.3</i>	<i>115.1</i>	2002JSC257
B3LYP/6-31G**	1.327 <i>121.6</i>	1.341 <i>119.6</i>	1.387 <i>121.8</i>	<i>115.4</i>	1.087 <i>123.9</i>	1.085 <i>122.6</i>		2006JMT(766)83
B3LYP/6-31++G**	1.326 <i>121.4</i>	1.342 <i>119.8</i>	1.388 <i>122.0</i>	<i>114.8</i>	1.087 <i>122.6</i>	1.085 <i>122.6</i>		2006JMT(766)83
B3LYP/cc-pVDZ	1.326 <i>121.6</i>	1.342 <i>119.7</i>	1.389 <i>122.1</i>	<i>114.7</i>	1.094 <i>122.5</i>	1.091 <i>122.6</i>		2006JMT(766)83
B3LYP/aug-cc-pVDZ	1.326 <i>121.6</i>	1.342 <i>119.8</i>	1.389 <i>121.9</i>	<i>115.0</i>	1.091 <i>122.6</i>	1.090 <i>122.5</i>		2006JMT(766)83
MP2/6-31G**	1.342 <i>121.1</i>	1.346 <i>119.6</i>	1.388 <i>122.2</i>	<i>115.3</i>	1.082 <i>122.6</i>	1.081 <i>122.4</i>		2006JMT(766)83
MP2/6-31++G**	1.341 <i>121.1</i>	1.347 <i>119.7</i>	1.389 <i>122.2</i>	<i>115.3</i>	1.082 <i>122.7</i>	1.081 <i>122.4</i>		2006JMT(766)83
CASSCF/6-31**	1.309 <i>121.5</i>	1.331 <i>120.3</i>	1.385 <i>121.5</i>	<i>114.8</i>	1.074 <i>122.8</i>	1.073 <i>122.6</i>		2006JMT(766)83

^aAngular values in italics.

Dynamic aspects of structure have been scarcely treated. MP2/6-31G*(d,p) calculations for **1** predict a lowest out-of-plane ring vibration at 302 cm⁻¹ and a population of approximately 20% of the molecules in a nonplanar state at room temperature <2002JMT(616)159>. The rotational barrier of the Me group in 4-methyl-1,2,3-triazine in the S₀ and S₁ electronic states has been examined. When the torsional angle $\theta=0$ is defined to represent a conformation with one C–H bond in the ring plane, a minimum in S₀ and a maximum in S₁ is found for $\theta=60^\circ$ <2001JCP8357>.

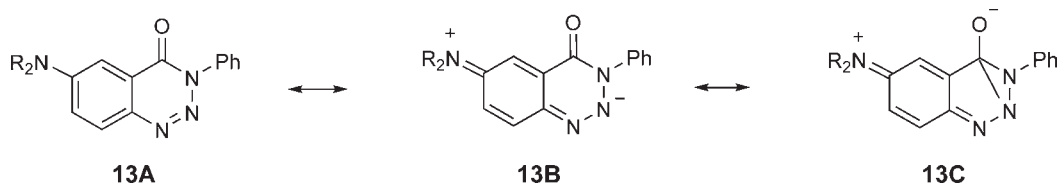
Table 2 Experimental bond lengths (Å) and angles (°) of 1,2,3-triazine **1** (standard deviations in parentheses)

Bond lengths	298 K ^a	100 K ^b	Bond angles	298 K ^a	100 K ^b
N(1)–N(2)	1.313(4)	1.326(2)	N(1)–N(2)–N(3)	121.8(3)	121.6(1)
N(2)–N(3)	1.322(4)	1.326(1)	N(2)–N(3)–C(4)	118.5(3)	119.6(1)
N(3)–C(4)	1.344(5)	1.346(1)	N(3)–C(4)–C(5)	122.4(3)	121.9(1)
C(4)–C(5)	1.348(5)	1.382(1)	C(4)–C(5)–C(6)	116.1(3)	115.4(1)
C(5)–C(6)	1.357(4)	1.388(1)	C(5)–C(6)–N(1)	121.8(3)	121.7(1)
C(6)–N(1)	1.339(5)	1.345(1)	C(6)–N(1)–N(2)	119.4(3)	119.8(1)
C(4)–H		1.085 ^c	C(5)–C(4)–H		124.5(1)
C(5)–H		1.085 ^c	C(4)–C(5)–H		120.2(1)
			C(5)–C(6)–H		123.3(1)
			C(6)–C(5)–H		124.4(1)
			N(3)–C(4)–H		113.6(1)
			N(1)–C(6)–H		115.0(1)

^a<1983CPB3762, 1992H(33)631>.^b<1985LA1732>.^cFixed at mean values from neutron diffraction experiments.

9.01.2.2 Electron Density and Charge Distributions

Early calculations on π -electron densities of **1** <1955MI173, 1967CPC880>, Pariser–Parr–Pople (PPP) calculations of localized atom charges and nonlocalized atom and bond charges <1968TCA240>, AVE (all valence electron) configuration interaction self-consistent field (CI SCF) effective charges on ring atoms <1972MI21>, SCF molecular orbital (MO) studies on net atomic charges including H-atoms <1983CPB3762> and for the ring atoms only <1992H(33)631>, as well as charge distributions and lowest unoccupied molecular orbital (LUMO) coefficients have been reported. Hückel molecular orbital (HMO) calculations of π -bond orders and charge densities of the skeleton of 6-dialkylamino-3-phenyl-3,4-dihydro-1,2,3-benzotriazin-4-one **13A** in the electronic ground and first excited states suggest a significant participation of electronic structures **13B** and **13C** to the excited state, but to a smaller extent to the ground state <1976LA946>.



9.01.2.3 Dipole Moments and Polarizabilities

For calculations of the dipole moment of **1** at various levels of theory from 1967 until the present, see **Table 3**. The orientation of μ is coinciding with the C-2 axis and the negative pole pointing to N-2 <1996IJQ1633>. Dipole moments of $\mu=4.65$ and 4.72 D, respectively, have been calculated also for 4- and 5-methyl-1,2,3-triazine <1996JME4065>. Quadrupole and octupole moments of **1** have also been predicted from MP2/C calculations <1999PCA10009>. For linear combination of atomic orbitals (LCAO) calculations of atom–atom, atom–bond, and bond–bond polarizabilities, see <1967TCA341>. MP2/C polarizabilities at MP2/6-31G* geometries <1996IJQ1633> and Hartree–Fock (HF)/6-311G(3d,2p) geometry <1997MI169> have been reported, also the average polarizability and second hyperpolarizability from CHF-PT-EB-CNDO (coupled Hartree-Fock perturbation energy extended basis-CNDO) studies <1985JCP1435> and, including polarizability anisotropy, from density functional theory (DFT) studies using MSINDO-optimized geometries <2000JCP6301>. Polarizabilities in their relation to aromaticity have been discussed for 42 heterocycles including **1** <2004MI427>; see also below.

Table 3 Calculated dipole moments of 1,2,3-triazine **1**

Method and level	μ (D)	Reference	Method and level	μ (D)	Reference
LCAO	4.91 ^a	1967CPC880	B3LYP/cc-pVTZ	4.88	1996JPC6973
PPP SCMO	^b	1968TCA240	HF/6-311G(3d,2p)	4.9227	1997MI169
AVE CI SCF	2.28 ^c , 6.18 ^d	1972MI21	DZ	6.010	1998CPH(228)39
<i>Ab initio</i> LCGO	4.41 ^c	1974J(P2)420	DZ + MP2	5.925	1998CPH(228)39
<i>Ab initio</i> SCF MO	6.24	1983CPB3762	TZVP	5.274	1998CPH(228)39
MNDO	4.60	1985JOC4894	TZVP + MP2	5.270	1998CPH(228)39
<i>Ab initio</i> 4-31G	6.09	1985JOC4894	MP2/C (MP2/6-31 G(d))	5.21	1999PCA10009
6-31G* at 6-31G geom.	5.25	1987JMT(150)135	CCSD/TZV//B3LYP/	5.7 ^f	2006PCP1385
MP2 ^g	5.20	1996IJQ1633	6-311++G(3d,f,3pd)		

^a $\mu_\sigma = 2.73$ D, $\mu_\pi = 2.18$ D.^b $\mu_\pi = 1.99$ D.^cWithin point charge approximation.^dIncluding sp correction.^e $\mu_\sigma = 3.87$ D, $\mu_\pi = 0.54$ D.^fThis value for S_0 drops to 3.0, 3.1, 3.3, and 3.6 D for the first low-lying excited states S_1 , S_2 , S_3 , and S_4 .^gAt MP2/6-31G* geometry.

9.01.2.4 PE Spectra, Ionization, and Electron Affinity

In the older literature, single calculated IPs have been reported for **1** without specification as to which type of orbital (n or π) is regarded as vacated; Pariser-Parr self consistent molecular orbital (PP-SCMO): 11.29 eV <1967TCA203>, LCAO-MO-SCF-CI: 10.61 eV <1968TCA240>, CI-SCF: 11.52 eV <1970TCA69> as quoted in <1972MI21>, AVE-CI-SCF: 10.78 eV <1972MI21>. The molecular energy levels of several azines including **1** have been calculated and correlated with PE spectroscopy <1973TL4659, 1974J(P2)778, 1987JMT(150)135>. Ionization energies (IEs) taken from the first five bands of the He(I_α) PE spectra of the parent **1** and 4-Me-, 5-Me-, 4,5-Me₂-, 4,6-Me₂-, and 4,5,6-Me₃-1,2,3-triazine have been reported with orbital assignments and band correlations within this series <1983CPL(97)94>. Experimental values of IEs of **1** and theoretically (HMO, energy-weighted maximum overlap (EWMO), HAM/3, Linear combination of Gaussian orbitals minimal basis (LCGO MB), outer valence Green's function (OVGF) (PM3)) estimated IPs have been compiled <1996CHEC-II(6)483>, so the table given there is now supplemented by **Table 4**, listing more recent calculated values.

Table 4 Experimental and theoretically estimated ionization energies (eV) for 1,2,3-triazine **1**

1991J(P2)1865						1998CPH(228)39					
<i>Exp.</i> ^a	<i>MO</i>	<i>PM3</i>	<i>OVGF</i> ^b (<i>PM3</i>)	<i>AMI</i>	<i>OVGF</i> ^b (<i>AMI</i>)	<i>MO</i>	<i>DZ GF</i>	<i>GF</i>	<i>TZVP</i> <i>TDA</i> ^c	<i>MRD-CI</i>	<i>State</i>
10.0	n_1	10.48	9.87	11.30	10.35	11a ₁	9.449	9.632	9.597	9.66	² A ₁ (LP _N)
10.4	n_2	10.85	10.21	11.76	10.87	7b ₂	9.862	10.208	10.354	10.02	² B ₂ (LP _N)
11.6	π_1	11.65	11.51	11.66	11.44	2b ₁	11.656	11.395	12.300	11.92	² B ₁ (π)
12.0	π_2	11.69	11.53	11.98	11.67	1a ₂	11.847	11.731	12.602	12.15	² A ₂ (π)
13.1	n_3	13.31	12.46	14.02	12.87	10a ₁	13.184	13.640	13.607	12.93	² A ₁ (LP _N)
15.0						6b ₂	15.431	15.087	15.650	14.68	² B ₂ (σ)

^a<1983CPL(97)94>.^bOuter valence Green's function.^cTamm–Dancoff approximation.

The interpretation of the experimental spectrum of **1** <1983CPL(97)94> has been reconsidered using Green's function (GF) and the nondiagonal Tamm–Dancoff approximation (TDA), as well as with multireference double-excitation configuration interaction (MRD-CI) calculations <1998CPH(228)39>. This paper also offers the following information about the parent **1**:

- figures of the vacuum ultraviolet (VUV) spectrum between 5 and 11.5 eV (248–108 nm), the most intense band of which at 7.4 eV (168 nm) is assigned to a ¹ π, π^* -transition;

- tables of calculated singlet states between 4 and 13.4 eV, of triplet and possible Rydberg states and valence states in accord with VUV absorption and electron energy loss (EEL) data (figures of EEL spectra given);
- calculations of molecular properties.

Valence and Rydberg states have been studied by multireference, multiroot CI studies (using MRD-CI techniques) and the electronic properties of **1** have been determined at equilibrium geometry for a large basis set at both the SCF and MP2 levels <1998CPH(228)39>. In a recent DFT study, vertical IPs have been calculated using Koopman's theorem and as the difference of single point energies of the neutral and the corresponding cation for the first n - and π -type orbitals (7.0135 and 8.9270 eV, respectively) with the RB3LYP/6-31G** method at optimized geometries <2003IJQ432>. For early calculations of the electron affinity of **1**, see <1972MI21>. The 7–12 eV PE spectra of 1,2,3-benzotriazine **2** and 4-methyl-1,2,3-benzotriazine have been depicted and the five lowest IEs have been calculated at the HAM/3 level at HF/6-31G** geometries (**2**: 8.87, 9.70, 9.84, 10.55, 11.64 eV; 4-Me: 8.59, 9.48, 9.60, 10.31, 11.64 eV) <1995CJC146>.

The PE spectrum of 2-methylnaphtho[1,8-*de*]triazin-2-ium-1-ide (**5**; R² = Me) with the first four ionizations ($a_2(\pi)$, 6.79 eV; $b_2(n_-)$, 8.65 eV; $b_1(\pi)$, 9.55 eV; $a_1(n_+)$, 9.82 eV) has also been reported <1978AGE468>.

9.01.2.5 $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Electronic Excitation

From 1965 to 1968, $^1(\pi, \pi^*)$ transition energies and intensities of **1** have been calculated using the PPP method <1965TCA45, 1965TCA418>, a modified Hückel-Wheland method <1966MI71>, SCMO <1967TCA203>, and LCAO-MO-SCF-CI <1968TCA240> methods. For more recent computations <1997CPH(221)11>, see **Tables 5** (π, π^* transitions) and **6** (n, π^* transitions).

Table 5 Calculated and observed transition energies (eV) and oscillator strengths f for the lowest excited $^1(\pi, \pi^*)$ states of 1,2,3-triazine (**1**, C_{2v}) <1997CPH(221)11>

State	CIS[6,31G(d)			CASSCF(6,12)/DZP		CASSCF(6,6)/DZP		CASPT2(6,6)/DZP		Experimental	
	Adiab. ^b	Vert. ^a	f	Adiab. ^b	Vert. ^a	Adiab. ^b	Vert. ^a	Adiab. ^b	Vert. ^a	Vert.	f
(1) ¹ B ₂	6.54	6.67	0.001	5.03	5.10	4.97	4.96	4.66	5.04	5.39	0.004
(1) ¹ A ₁	6.83	6.82	0.022	7.04	7.60	7.05	7.76	6.56	6.75	>6.2	
(2) ¹ B ₂		8.67	0.689		8.50		8.50		8.50	>6.2	
(2) ¹ A ₁		8.87	0.694		8.67		9.14		7.14	>6.2	

^aAt MP2/6-311G(d,p) optimized ground state geometry.

^bAt CAS(6,6)/6-31G(d) optimized geometries.

Besides the UV data obtained later for **1** by Ohsawa *et al.* in ethanol solution <1981CC1174>, new measurements of the UV spectrum in hexane solution and in the vapor phase have become available and have been interpreted extensively by *ab initio* calculations <1997CPH(221)11> (see **Table 6**). From these, the first three excited singlet states are n, π^* in nature and energetically close. By comparison with the experimental value (4.28 eV) of the energy of the allowed first n, π^* transition <1997CPH(221)11>, it is apparent from **Table 6** that computational methods predict this energy closely and which do not. The UV spectrum of **1** is sensitive to the water content of the solvent (hexane) and a hypsochromic shift of the 298 nm maximum to 281 nm is observed, but there is only a weak effect by added water on the shoulder at 325–330 nm and the 230 nm band. The spectrum in methanol is less resolved (main maximum at 288 nm) and clearly much less influenced by added water <1995JPH135>.

More recently, the influence on the $^1B_1(a_1 \rightarrow b_1)$ (n, π^*) excitation of **1** in water was studied starting from *ab initio* CASSCF (complete active space self consistent field) estimates of the gas-phase electronic excitation properties, followed by Monte Carlo simulations to elucidate the structures of the liquid around the ground and excited state solute. Finally, the solvent shift was evaluated based on gas-phase charge distributions and solvent structures. One linear H-bond to each N-atom of **1** is predicted for diluted solutions <2003CPL(368)377, 2004JCC813>, and three H-bonds to the ground state

are regarded as consistent with observed solvent shifts. Upon electronic excitation, one H-bond is broken completely while two H-bonds remain to N-1 and N-2. H-Bonding of the ground and lowest excited singlet states of **1** has also been studied with DFT B3LYP and *ab initio* MP2-optimized geometries of the ground state <2005MI891>.

Table 6 Calculated vertical excitation energies E_v (eV) of the lowest $^1(n,\pi^*)$ excitations of 1,2,3-triazine **1**; where available, oscillator strengths are given in parentheses

Method	Geometry	E_v			
		$(1)^1B_1$	$(1)^1A_2$	$(2)^1A_2$	$(2)^1B_1$
2006JMT(766)83					
TDDFT/6-31G**	B3LYP/6-31G**	3.70	3.90		
TDDFT/6-31G**	MP2/6-31G**	3.76	3.86		
TDDFT/6-31++G**	B3LYP/6-31++G**	3.68	3.89		
TDDFT/6-31++G**	MP2/6-31++G**	3.75	3.85		
CASSCF/6-31G**	CASSCF/6-31G**	4.30	5.00		
CASSCF/6-31++G**	CASSCF/6-31++G**	4.54	5.29		
1997CPH(221)11					
CIS/6-31G(d) ^a		4.93 (0.019)	5.52 (0.0)	5.95 (0.0)	6.59 (0.007)
CASSCF(6,12)/DZP ^a		4.51	5.55	4.82	5.38
CASSCF(6,6)/DZP ^a		4.61	6.00	5.29	5.29
CASPT2(6,6)/DZP ^a		3.32	2.60	2.90	3.55
1998CPH(228)39					
MRDC1/DZPR		4.095 (0.008 5)	4.24 (0)	4.59 (0)	4.70 (0.007 5)
RPA/DZPR		4.63 (0.011 2)	5.49 (0)	6.19 (0)	5.81 (0.004)
TDA/DZPR		4.85 (0.017 5)	5.65 (0)	6.33 (0)	5.975 (0.005 9)
2006JMT(764)87					
PBE1PBE/DZPR		3.70 (0.005 8)	3.98 (0.0)	4.04 (0.0)	4.32 (0.005 6)
PBE1PBE/6-31G(d)		3.74 (0.005 5)	4.03 (0.0)	4.10 (0.0)	4.39 (0.005 9)
PBE1PBE/6.31G(d,p)		3.74 (0.005 5)	4.02 (0.0)	4.09 (0.0)	4.37 (0.005 9)
PBE1PBE/6-311++G(2d,2p)		3.72 (0.005 3)	4.03 (0.0)	4.07 (0.0)	4.37 (0.004 9)
PBE1PBE/6-311++G(3df,3pd)		3.70 (0.005 0)	4.01 (0.0)	4.06 (0.0)	4.35 (0.004 6)
BLYP/DZPR		3.31 (0.003 2)	3.24 (0.0)	3.47 (0.0)	3.73 (0.006 4)
BLYP/6-31G(d)		3.37 (0.002 5)	3.30 (0.0)	3.55 (0.0)	3.81 (0.005 6)
BLYP/6-31G(d,p)		3.36 (0.002 5)	3.30 (0.0)	3.54 (0.0)	3.79 (0.005 6)
BLYP/6-311++G(2d,2p)		3.35 (0.003 0)	3.30 (0.0)	3.52 (0.0)	3.78 (0.005 5)
BLYP/6-311++G(3df,3pd)		3.32 (0.002 7)	3.29 (0.0)	3.50 (0.0)	3.76 (0.004 9)
B3LYP/DZPR		3.64 (0.005 3)	3.86 (0.0)	3.97 (0.0)	4.24 (0.005 7)
B3LYP/6-31G(d)		3.71 (0.005 1)	3.91 (0.0)	4.04 (0.0)	4.30 (0.005 9)
B3LYP/6-31G(d,p)		3.70 (0.005 1)	3.90 (0.0)	4.03 (0.0)	4.29 (0.005 9)
B3LYP/6-311++G(2d,2p)		3.68 (0.005 0)	3.91 (0.0)	3.99 (0.0)	4.27 (0.004 9)
B3LYP/6-311++G(3df,3pd)		3.66 (0.004 8)	3.90 (0.0)	3.97 (0.0)	4.25 (0.004 7)
CCSD/DZV		3.96 (0.011 1)	4.19 (0.0)	4.26 (0.0)	4.48 (0.011 9)
CCSD/DZPR		4.22 (0.008 9)	4.40 (0.0)	4.58 (0.0)	4.69 (0.006 6)
CCSD/TZV		3.86 (0.006 7)	3.90 (0.0)	4.10 (0.0)	4.38 (0.006 4)

^aAt MP2/6-311G(d,p)-optimized ground-state geometry.

On the basis of calculations using DFT/B3LYP and MP2 with the 6-31++G** basis set for the electronic ground state and the CASSCF method with 6-31G** and 6-31++G** basis sets for the lowest $^1(n,\pi^*)$ excited state, other authors favor two ground-state minima (I, II) and one excited state minimum for the **1**:water 1:1 complex. Interaction energies ΔE (kcal mol⁻¹) for I (linear H-bond to N-2, 2.033 Å) of -5.22 (DFT/B3LYP) and -5.19 (MP2), as well as for II (distorted H-bond to N-1, 2.041 Å) of -6.10 (DFT/B3LYP) and -6.07 (MP2) have been calculated using a full-counterpoise-corrected (FCP) basis set superposition error. Excitation energies for the complex models I and II are predicted to be 4.52 and 4.66 eV, respectively <2006JMT(766)83>; for reference values of excitation energies of free **1**, see Table 6.

Time-dependent density functional theory (TDDFT) using different gradient-corrected density functionals, the BLYP and B3LYP functionals, and a hybrid DFT/HF approach based on the Perdew–Burke–Ernzenhofer exchange correlation functional (PBE1PBE) were recently applied to calculate vertical transitions to low-lying excited states of

1 in vacuum (see Table 6) and in aqueous solution (using the conductor-like polarizable continuum model (CPCM) <1998PCA1995>) for the following hydration models of **1** (symmetry and **1**:water ratio given): C_s 1:1, C_{2v} 1:2, C_s 1:3, C_1 1:4 <2006JMT(764)87>. The results show the potential of the methods used and will be of value for the study of structural and spectroscopic properties in the liquid phase.

The low lying vertical transitions of **1** in the vapor phase have also been calculated on the BLYP/*B3*, B3LYP/*B3*, PBEO/*B3*, and CCSD/TZV//B3LYP/*B3* levels (with *B3* corresponding throughout to 6-311++G(3df,3pd) basis sets), and shifts of these transitions between 0.24 and 0.81 eV in methanol at 298 K have been predicted from PMM/- and SCRF/CCSD/TZV//B3LYP/6-311++G(3df,3pd) calculations (CCSD=coupled-cluster singles and doubles; TZV=triple zeta valence; PMM=polarizable molecular mechanics; SCRF=self-consistent reaction field) <2006PCP1385>. Solvent effects on the ground state were found to be rather low. The pure generalized gradient-corrected functional BLYP strongly underestimates the experimental and the MRCD-CI transition energies (see Table 6). Calculated spectra of the low-lying transitions in methanol have also been depicted in this paper.

Short-wavelength (240–110 nm) absorptions of **1** have been measured and singlet states in that range have been calculated with the DZPR basis set <1998CPH(228)39>. π -Electron correlation has also been addressed <2001CPH(269)11>.

The first five transitions in the ultraviolet/visible (UV/Vis) spectra of 2-methylnaphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide (**5**: $R^2 = \text{Me}$) and its 6,7-ethano analogue were assumed to be $\pi \rightarrow \pi^*$ in nature and have been calculated using the PPP-CI model (including polarization) to provide a basis for spectral assignment <1978AGE468>.

9.01.2.6 Vibrational Spectroscopy

For compound **1**, well-resolved infrared (IR) spectra (estimated frequency error $\pm 2 \text{ cm}^{-1}$) from KBr and CsI disks and Raman spectra ($\pm 5 \text{ cm}^{-1}$) of the pure solid have become available and assignments were based on a refined Urey–Bradley force field and computations at the MP2/6-31G* and HF/6-31G* levels <1993JSP388> and by using the B3LYP density functional with correlation consistent basis sets of spd and spdf quality (cc-pVDZ and cc-pVTZ) <1996JPC6973>. More recently, DFT calculations of anharmonic force fields and vibrational frequencies using the B97-1 exchange correlation functional and a TZ2P basis set have been made. The fundamental frequencies computed using second-order rovibrational perturbation theory were in good agreement with experimental data, revealed the tendency of certain bands to Fermi resonance, and led to an interchanged assignment of the $5a_1$ and $5b_2$ in-plane bending modes <2004PCA3085>.

Further DFT computations (B3LYP/6-31G(d) level) using an extended basis set (obtained by adding polarization functions <2003JCC1582> to the 6-31G set) led to a better agreement of calculated and experimental frequencies <2004PCA4146>. For a compilation of experimental and calculated vibrational frequencies, see Table 7. The performance of the B3LYP density functional has been studied in general for a set of semirigid molecules including **1** <2005JCC384>.

Table 7 Observed and calculated vibrational frequencies ($\tilde{\nu}$, cm^{-1}) of 1,2,3-triazine **1** (relative intensities in parentheses, sh = shoulder)

1993JSP388		Observed		Calculated		
Assignment		IR (KBr)	Raman (solid)	UBFF ^a	MP2/6-31G*	HF/6-31G* ^b
<i>In-plane</i>						
1a ₁	CH stretch	3107 (1.2)	3110 (2.9)	3107	3079 (1.0)	3054 (0.9/54)
2a ₁	CH stretch		3045 (3.4)	3045	3056 (0.2)	3031 (0.2/35)
3a ₁	CH bend, ring stretch	1597 (0.6)	1594 (1.2)	1597	1514 (0.7)	1597 (0.4/3.7)
4a ₁	Ring stretch	1336 (5.8)	1329 (0.9)	1336	1306 (3.7)	1401 (2.7/0.0)
5a ₁	Ring bend	1080 (0.5)	1088 (2.5)	1080	1044 (0.3)	1122 (0.5/1.1)
6a ₁	Ring stretch	1069 (sh)	1064 (2.1)	1057	1077 (0.0)	1053 (0.0/3.5)
7a ₁	Ring stretch	979 (3.5)	977 (10.0)	979	927 (1.4)	1007 (1.1/10)
8a ₁	Ring bend	660 (sh)	660 (1.3)	660	633 (0.2)	662 (0.0/1.7)
1b ₂	CH stretch	3046 (1.4)		3046	3062 (2.7)	3040 (2.3/13)

(Continued)

Table 7 (Continued)

1993JSP388

Assignment		Observed		Calculated		
		IR (KBr)	Raman (solid)	UBFF ^a	MP2/6-31G [*]	HF/6-31G ^{*b}
<i>In plane</i>						
2b ₂	Ring stretch, CH bend	1545 (10)	1547 (1.5)	1545	1524 (10)	1585 (10/0.1)
3b ₂	Ring stretch	1410 (2.3)		1410	1370 (2.7)	1422 (1.2/0.0)
4b ₂	Ring stretch	1195 (0.6)	1198 (1.3)	1329	1193 (0.8)	1201 (0.1/1.6)
5b ₂	CH bend	1124 (0.5)	1127 (1.0)	1124	1088 (1.0)	1075 (0.0/1.6)
6b ₂	CH bend	935 (2.8)		935	989 (3.0)	899 (0.8/2.0)
7b ₂	Ring bend	653 (4.3)		653	621 (1.9)	649 (1.0/1.1)
<i>Out-of-plane</i>						
1a ₂	CH bend	c		1123	915 (0.0)	966 (0.0/0.5)
2a ₂	Ring bend	c	365 (0.9)	365	310 (0.0)	401 (0.0/0.4)
1b ₁	CH bend			1300	907 (0.1)	1015 (0.0/0.1)
2b ₁	Ring bend	819 (3.6)		821	761 (6.0)	819 (1.2/0.4)
3b ₁	CH bend	769 (3.3)		767	713 (1.9)	762 (2.5/0.1)
4b ₁	Ring bend	318 ^d		318	286 (0.5)	358 (0.3/0.1)

1996JPC6973

2004PCA4146

2004PCA3085

	<i>B3LYP</i>		<i>6-31G(d)</i> ^c		<i>6-31G(d)</i> ^g		<i>B97-1/TZ2P</i>		
<i>Assignment</i>	<i>cc-pVDZ</i>	<i>cc-pVTZ</i>		<i>Ext.</i> ^{c,f}		<i>Ext.</i> ^{f,g}	<i>Harmon.</i>	<i>Fundam.</i>	<i>Experimental</i> <i>IR reassigned</i>
<i>In plane</i>									
1a ₁	3204 (6.5)	3199 (7.5)	3224	3219	3138	3133	3195	3032 ^h	3046
2a ₁	3170 (1.4)	3167 (2.0)	3196	3190	2997	2992	3165	3028	
3a ₁	1596 (0.02)	1592 (0.01)	1605	1595	1563	1553	1589	1548	1546
4a ₁	1383 (14.1)	1387 (15.3)	1396	1388	1359	1351	1384	1347	1336
5a ₁	1137 (1.1)	1139 (0.5)	1144	1138	1127	1121	1136	1122	1124 (5b ₂) ⁱ
6a ₁	1091 (0.5)	1099 (0.7)	1096	1092	1083	1079	1092	1081 ^h	1080
7a ₁	1013 (5.0)	1010 (4.3)	1012	1012	991	991	1006	985	979
8a ₁	678 (0.2)	682 (0.1)	680	679	671	670	675	667	660
1b ₂	3175 (12.6)	3172 (11.5)	3201	3196	3054	3050	3171	3042 ^h	3046
2b ₂	1596 (45.4)	1591 (47.1)	1602	1596	1557	1551	1584	1538	1545
3b ₂	1428 (4.4)	1444 (3.6)	1451	1434	1422	1405	1438	1410	1410
4b ₂	1218 (0.03)	1225 (0.2)	1234	1222	1211	1199	1219	1199	1195
5b ₂	1098 (0.1)	1105 (0.1)	1110	1102	1086	1078	1101	1078	1080 (5a ₁) ⁱ
6b ₂	991 (13.0)	965 (12.7)	990	997	944	951	974	929	935
7b ₂	663 (6.1)	668 (6.5)	666	665	664	663	662	659 ^h	660
<i>Out-of-plane</i>									
1a ₂	988	1001	994	989	973	968	992	973	c
2a ₂	360	366	363	365	355	357	358	350	c
1b ₁	1017 (10 ⁻³)	1031 (10 ⁻⁴)	1015	1015	996	996	1017	998	
2b ₁	823 (3.4)	832 (4.2)	822	824	809	811	824	811	819
3b ₁	780 (13.2)	789 (19.1)	780	781	767	768	783	769	769

^aUrey–Bradley force field normal coordinate analysis. Frequencies in italics: No attempt has been made to fit these to observed frequencies.

^bRelative intensities (IR/Raman).

^cElectric dipole forbidden.

^dIn Csl.

^eHarmonic.

^fPolarization functions optimized for correlated methods have been added to 6-31G(d).

^gPT2 with anharmonic terms.

^hBands affected by Fermi resonance.

ⁱPrevious assignment <1993JSP388>.

9.01.2.7 Magnetic Properties

Second-order magnetic properties, such as magnetic susceptibility and chemical shift tensors, have been calculated <1988MRC394> using the individual gauge for localized orbitals (IGLO) method <1980ISJ789, 1982JCP1919>, which provides absolute shieldings for conversion into the common scale with reference to trimethylsilane (TMS) for C and to NH₃ for ¹⁴N, ¹⁵N. Inclusion of electron correlation effects is probably important for improving the discrepancies between theory and experiment for N chemical shifts (see Table 8).

Table 8 Calculated and experimental N and C chemical shifts (δ , ppm) for 1,2,3-triazine **1** <1988MRC394>

Atom	IGLO DZ ^a	IGLO IF ^a	Exptl.	Reference (exptl.)
N-1,3	459.8	459.9	393.9 ^b	1985LA1732
N-2	588.6	581.8	461.0 ^b	1985LA1732
C-4,6	162.6	158.4	149.7 ^c	1981CC1174
C-5	120.6	123.8	117.9 ^c	1981CC1174

^aThe method does not differentiate between ¹⁴N and ¹⁵N. δ_C with ref. to TMS, δ_N with ref. to NH₃ (r_z geometry).

^b $\delta(^{15}\text{N})$ in DMSO-*d*₆ solution with ref. to liquid NH₃. Originally $\delta(^{15}\text{N}) = -13.7$ (¹H decoupled: -16.05) had been given for N-1,3 and -80.76 (¹H decoupled: -80.04) for N-2 with reference to nitromethane <1985LA1732>.

^cCDCl₃, TMS.

¹⁴N Chemical shifts for the oxygenated N-atoms of the mono-*N*-oxides of **1** and **2** relative to the shifts for the parent structures have been calculated (SCF-PPP) <1976SAA345>. Calculations of the diamagnetic susceptibility of **1** have been carried out at the SCF and MP2 levels <1998CPH(228)39>. The diamagnetic susceptibility anisotropy (DSA, being the difference between in-plane and out-of-plane contributions) decreases as the number of N-atoms in an azine ring increases and is related linearly to the binding energy <1974TL253>.

9.01.2.8 Energetics and Aromatic Character, Aromaticity Criteria

Total energies have been calculated for **1** using several methods and at various levels: nonempirical <1973TL4659>, LCGO <1974J(P2)778>, 4-31G/MNDO (MNDO = modified neglect of diatomic overlap) <1985JOC4894>, 3-21G and 3-21+G <1988JCC784>, STO-3G, 3-21G, 6-31G, 6-31G*/6-31G (STO = Slater-type orbital) <1987JMT(150)135>, 4-31G and 6-31G <1997JMT(393)9>, G3 and G3(MP2) at 0 and 298 K <2002JSC257>. Comparison with total energies of 1,2,4- and 1,3,5-triazine demonstrates **1** to be the least stable of the monocyclic triazines <1985JOC4894>. For older estimates of the binding energy of **1**, see <1966JCP759> (PPP, SPO) and <1973TL4659> (LCGO).

The heat of formation ΔH_f° of **1** has been calculated by several groups (see Table 9). An experimental value is not available, but a value of 99 kcal mol⁻¹ has been estimated from increments <B-1988MI110>, and 97.3 kcal mol⁻¹ has been estimated <1997T13111> by applying the group additivity method <1996T14335>.

Table 9 Calculated heats of formation (kcal mol⁻¹) of 1,2,3-triazine **1**

Method	ΔH_f°	Reference	Method	ΔH_f°	Reference
MNDO	56.5	1985JOC4894	4-31G	98.4 ^a	1997JMT(393)9
AM1	81.6	1988JCC784	6-31G**	98.0 ^a	1997JMT(393)9
MNDO	55.7 (101.5) ^b	1997JMT(393)9	G3	97.7 (101.0) ^c	2002JSC257
AM1	81.6 (104.0) ^b	1997JMT(393)9	G3 (MP2)	97.5 (100.9) ^c	2002JSC257
PM3	81.7 (102.7) ^b	1997JMT(393)9			

^aMean values from four isolobal reactions.

^bValues in parentheses: correction terms have been applied.

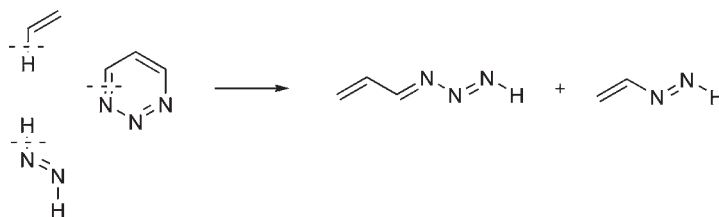
^cValues in parentheses: calculated for 0 K.

MNDO, AM1, and PM3 notoriously underestimate azine heats of formation; thus, correction terms have been suggested <1997JMT(393)9> (see Table 9). PM3 appears to be the most accurate semi-empirical method for calculation of nitrogen heterocycle heats of formation.

The concept of aromaticity is of great importance in heterocyclic chemistry. Today, it rests largely on energetic, geometric, and magnetic criteria; see recent reviews by Krygowski *et al.* <2000T1783> and by Balaban *et al.* <2004CRV2777>.

Electron delocalization of **1** has been estimated previously by SCF MO calculations based on crystallographic data <1983CPB3762>. A novel procedure for constructing a localized fragment MO basis set has been developed to allow new insights into aromaticity and conjugation. The effects that π -delocalization have on the σ -framework need to be taken into account <2000PCA1736>. For **1** as an example of a benzene-like compound, it is demonstrated that both the π - and the σ -system are stabilized by π -delocalization.

For the resonance energy of **1**, Dewar and Gleicher had presented values of 14 kcal mol⁻¹ using PPP at fixed geometry ($r_{\text{N-N}} = 1.344$ Å) and 13.6 kcal mol⁻¹ using SPO (split p-orbital method, $r_{\text{N-N}} = 1.244$ Å), respectively <1966JCP759>. More recently, the resonance energy of **1** has been calculated to 43.1 kcal mol⁻¹ using the HOSE (Harmonic oscillator stabilisation energy) approach <1997T13111>. A vertical resonance energy of -0.083 hartree (with its two components $\Delta E_{\pi}^v = -0.0488$ and $\Delta E_{\sigma}^v = -0.0345$ hartree) has been predicted <2000PCA1736>. The energy of homodesmotic ring opening (energy difference of the cyclic compound and its open-chain counterpart taken as the aromatic stabilisation energy) of **1** according to Scheme 1 has been calculated to 11.7 (MP2(fc)/6-31G*) and 6.1 kcal mol⁻¹ (B3LYP/6-31G*) <2004CJC50>.



Scheme 1 Homodesmotic ring opening of 1,2,3-triazine **1** <2004CJC50>.

Bird's aromaticity index I_x (based on statistical evaluation of peripheral bond orders and, thus, based on experimental bond lengths) has been calculated for **1** as $I_6 = 76.9$ (reference benzene: $I_6 = 100$) <1986T89>; the bond lengths used, however, had been taken from the X-ray crystal structure analysis of 4,5,6-tris(4-methoxyphenyl)-1,2,3-triazine <1972CB3704>. The calculation method has been described in <1985T1409>. I_x' (based on AM1-predicted geometries) is given as 76.1 <1993QSA146>. Since for 1,2,4- and 1,3,5-triazine, $I_6 = 86.1$ and 100, respectively, **1** is indicated to be the least aromatic of the monocyclic triazines.

The bond energy E_b and the bond length r are related by $E_b = 1/r^2$; thus, there should be a correlation between aromaticity indexes and resonance energies. Accordingly, a unified aromaticity index I_A has been defined (reference benzene: $I_A = 100$), and $I_A = 77$ for **1**, 86 for 1,2,4- and 100 for 1,3,5-triazine <1992T335>. From molecular dimensions, $I_A = 77$ has also been calculated for both 4,6-dimethyl- and 4-methyl-6-phenyl-1,2,3-triazine, 73.4 for 4,6-dimethyl-1,2,3-triazine 2-oxide, 76.0 for 4-methyl-6-phenyl-1,2,3-triazine 2-oxide, and 68.95 for 6-methyl-4-phenyl-1,2,3-triazine 1-oxide <1993T8441>. In this sense, N-oxidation is accompanied by a reduction in aromatic character.

An MO multicenter bond index involving σ - and π -electron population is related to both energetic and magnetic criteria. Since aromaticity is certainly related to the mutual simultaneous interaction of all bonds of an aromatic ring, I_{ring} is defined as a measure of aromaticity <2000PCP3381>. I_{ring} values for **1**, 1,2,4- and 1,3,5-triazine are 0.087 5, 0.087 1, and 0.084 0, respectively; thus, I_{ring} decreases in this line while I_A increases.

Bird's aromaticity indexes I_x and I_x' , Jug's aromaticity index RC and Pozharskii's ΔN (both calculated from AM1 geometries), Dewar and Hess-Schaad resonance energies (both per π -electron), predicted heats of formation, predicted diamagnetic susceptibilities for 23 mono-heterocycles including **1** have been compiled and treated by principal component analysis <1990JPR885>. General trends observed are: pyridine-like N-atoms have a relatively small effect on classical aromaticity, five-membered rings are less aromatic than six-membered rings, and aromaticity decreasing effects of the most common heteroatoms follow the order $O \gg S > N$.

For an earlier discussion of the relation of magnetic susceptibility and aromaticity on the basis of calculated diamagnetic susceptibilities of 28 carbo- and heterocyclic unsaturated compounds including **1**, see <1974TL253>. Magnetic susceptibility χ_{iso} , its anisotropy χ_{aniso} , its component χ_{zz} perpendicular to the ring plane, the exaltations Λ ,

$\Delta\chi_{\text{aniso}}$, and $\Delta\chi_{zz}$ (differences between the observed values and the calculated values for a hypothetical structure in which the electron distribution is completely localized) of these three characteristics, and the nucleus-independent chemical shifts (NICSs, in ppm) at ring centers and 1 Å above these centers have been calculated and their role as aromaticity criteria have been discussed. Some magnitude characteristics may be orthogonal to others, so the group of these characteristics is most heterogeneous. The optimized geometries and the magnetic properties (except NICS) were calculated using the gauge-independent atomic orbital (GIAO) and individual gauges of atoms in molecules (IGAIM) methods at the B3LYP/6-311++G** level <2004JPO303>. Ring current effects, as predicted from NICS values obtained from GIAO HF/6-31G* calculations on MP2(fc)/6-31G* geometries, and electron distribution derived from bond orders and bond lengths indicate azabenzenes to be aromatic in the sense of sustaining a diatropic ring current <2004CJC50>.

Polarizability anisotropy of the π -electrons is regarded as the best available polarizability-based aromaticity index from a comparison of Pozharskii's index ΔN , Bird's index I_A , the harmonic oscillator model of aromaticity (HOMA) index, the parallel polarizability $\alpha_{\parallel}$, the polarizability anisotropy, and the π -electron counterparts $\alpha_{\parallel}^{\pi}$ and $\Delta\alpha^{\pi}$ <2004MI427>.

The π -electron correlation energy E_{π} in planar heteroatomic molecules follows simple additivity rules. The nondynamical component $E(\text{ND})_{\pi}$ of aromatic compounds is lower than that of their open-chain counterparts and (in comparison with benzene) regarded as another useful aromaticity index <2001CPH(269)11>.

9.01.2.9 Quantitative Structure–Activity Relationships

The dipole moment and its orientation, HOMO and LUMO energies, lowest point charges on a heteroatom and highest point charges on a hydrogen atom, the van der Waals length, width and volume, and also the octanol/water partition coefficient (measure of lipophilicity) have been calculated (MNDO, complete neglect of differential overlap (CNDO)) for 100 methylated and fused fully unsaturated heterocycles, including 4- and 5-methyl-1,2,3-triazine. The results were subjected to principal component analysis aimed at predicting biological activities <1996JME4065>.

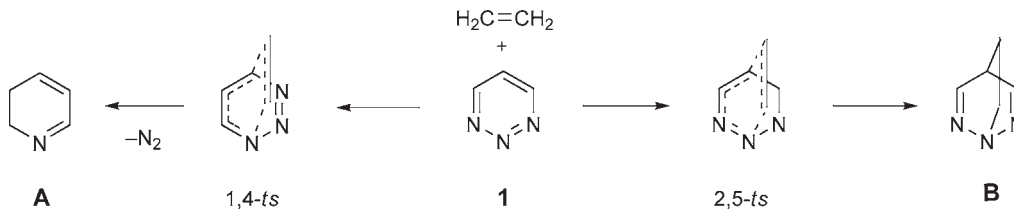
9.01.2.10 Fragmentation and C–H Bond Dissociation

Both thermodynamic and kinetic stability (the latter from overlap population being related to bond strength) have been discussed for **1** on the basis of LCGO calculations <1974J(P2)778>. For 4-methyl-1,2,3-triazine, it was concluded on the basis of HF/4-31G-optimized geometry and overlap population that the ground-state geometry predetermines the preferred path of thermal fragmentation. From calculated total energies of reactant and products, the less exothermic ($-28.00 \text{ kcal mol}^{-1}$) pathway (forming propyne, HCN, and N_2) is the preferred one (and found by flash vacuum thermolysis (FVT)) over the alternative one forming ethyne, CH_3CN , and N_2 ($-32 \text{ kcal mol}^{-1}$) <1992H(34)1183>. Heats of dissociation (ΔH_d) into ethyne, HCN, and N_2 may be predicted from heats of formation ΔH_f° of the respective azine and those of the fragments ethyne, HCN, and N_2 ($\Delta H_f^\circ = 54.5, 32.3$, and 0 kcal mol^{-1}). Thus, with $\Delta H_f^\circ = 97.3 \text{ kcal mol}^{-1}$ (from group additivities), a ΔH_d of $-10.5 \text{ kcal mol}^{-1}$ is derived for **1** <1997T13111> and, accordingly from the viewpoint of ΔH_d , **1** is the least stable isomer of the monocyclic triazines (ΔH_d for 1,2,4- and 1,3,5-triazine is 17.0 and $42.9 \text{ kcal mol}^{-1}$, respectively). Generally, from calculations on the MP2, B3LYP, and CCSD(T) levels, fragmentation energies become negative for molecules with three contiguous or four noncontiguous nitrogen atoms, and again **1** is found to be the least stable monocyclic triazine <2004CJC50>. While MP2 and CCSD(T) reaction energies and activation energies of fragmentation come quite close, the B3LYP values tend to be considerably larger.

Bond-dissociation energies (BDEs) for the C(4)–H and C(5)–H bonds have been calculated using composite *ab initio* methods and were found to be dependent on the N–C(4)–H or C(4)–C(5)–H bond angle, spin (carried by the C-radical formed), and charge (natural bond orbital, NBO) carried by the H-atom in the C–H bond. BDEs (kcal mol^{-1}) predicted for C(4)–H (C5–H) are 110.1 (113.2) using G3//MP2, 107.6 (111.2) using G3//B3LYP with structures and zero-point vibrational energy calculated at B3LYP/6-31G(d) level (recommended method), and 104.5 (108.2) using the UB3LYP/6-311G++G(2df,p)// UB3LYP/6-31G(d) method. These BDE estimates are regarded to be within $1\text{--}2 \text{ kcal mol}^{-1}$ of the real BDEs <2003JPO883>. The latter two methods have also been used for BDE calculation of benzylic C–H bonds in 4-methyl- (5-methyl-) 1,2,3-triazine, namely 95.9 (94.0) (recommended values) and 89.2 (87.5) kcal mol^{-1} . Benzylic C–H BDEs are regarded as important criteria for evaluating the metabolic stability of methyl groups in heterocyclic compounds having potential as drug candidates <2005JPO353>.

9.01.2.11 Cycloadditions and Ring Closure

The two *a priori* possible pathways for the (prototypical) [4+2] cycloaddition of ethene to **1** involve either a 1,4- or a 2,5-bridged transition state (*ts*); see [Scheme 2](#).



Scheme 2 Pathways for the prototypical [4+2] cycloaddition of ethene to 1,2,3-triazine **1**.

G3(MP2) calculations indicate that the 1,4-addition *ts* is slightly favored by 2.4 kcal mol⁻¹ ($E_a(1,4) = 23.7$, $E_a(2,5) = 26.1$ kcal mol⁻¹) and that the 1,4-addition (including the liberation of N₂) is considerably more exothermic (−69.9 kcal mol⁻¹) than the formation of the 2,5-bridged 2,5-dihydrotriazine (−5.4 kcal mol⁻¹) [<2005JMT\(723\)195>](#). In the original publication, however, this ordering has been reversed in the discussion, contradicting the energy profiles shown. 1,4-Addition is also observed as expected in the microwave-assisted cycloaddition of an enamine to 4,6-dimethyl-1,2,3-triazine [<2001SL236>](#). This case has been studied by *ab initio* SCF-MO calculations aimed at elucidating a potential stepwise pathway and at evaluating a totally different mechanism, namely ring contraction to an azete and its cycloaddition to said enamine. The latter option was ruled out due to the high activation energy (around 116 kcal mol⁻¹) needed for ring contraction in the first step compared to ca. 30 kcal mol⁻¹ (in the gas phase) for the concerted process. From the calculations, there is little solvent influence on the concerted pathway and its variant involving an open bipolar intermediate [<2002J\(P2\)1257>](#).

From PM3 studies, the ring closure of 2-(aminocarbonyl)benzenediazonium ion to 3,4-dihydro-1,2,3-benzotriazin-4-one **3** has been proposed to proceed through an enol-type intermediate. A 6-NO₂ group in the starting material is predicted to accelerate and a 6-MeO group to retard the cyclization [<2001JMT\(535\)199>](#).

9.01.2.12 N-Protonation and -Alkylation, Hydration via Hydrogen Bonds from Water

6-31G-optimized geometries of **1** and its N-1- and N-2-protonated forms as well as protonation energies for these sites using STO-3G, 3-21G, 6-31G, and 6-31G*/6-31G basis sets have become available [<1987JMT\(150\)135>](#). Other authors determined the 3-21G and 3-21+G total energies as well as MNDO and AM1 heats of formation (ΔH_f in kcal mol⁻¹) for the neutral **1** and its N-1- and N-2-protonated forms (MNDO: 56.5, 237.9, 248.2; AM1: 81.6, 255.1, 263.7) as well as for benzo-1,2,3-triazine **2** and its N-1-, N-2-, and N-3-protonated species (MNDO: 70.7, 245.0, 252.4, 240.1; AM1: 99.1, 255.6, 272.9, 261.5). Heats of formation are always highest for the N-2-protonated form [<1988JCC784>](#). From this point of view, N-2 would be the preferred site of protonation in both **1** and **2**. The picture is less clear-cut, however, when protonation energies are compared: STO-3G notoriously overestimates these, whereas 3-21G, 6-31G, and 6-31G*/6-31G protonation energies come close to each other, and N-2 protonation is favored by 2–3 kcal mol⁻¹ over N-1 protonation for **1** [<1987JMT\(150\)135>](#). The same trend is observed for 3-21G and 3-21+G proton affinities, but MNDO and AM1 proton affinities, when corrected for underestimation of lone pair repulsion, either come out equal for **1** or point to N-3 as the preferred protonation site of **2** [<1988JCC784>](#). Calculations at the B3LYP/6-311G*/HF/6-31G* + 0.89ZPE (HF/6-31G*) level also predict the N-2-protonated form as the thermodynamically favored one for 4- and 5-phenyl-1,2,3-triazine (ZPE = zero-point energy) [<2003S413>](#). Within an ensemble of nine azabenzenes and sixteen azanaphthalenes, calculated (*ab initio* HF theory at 3-21 + G//3-21G level) proton affinities correlate well with a calculated function of electronic potential of a given atom. For **1** the proton affinity is predicted to be 214.2 and 216.4 kcal mol⁻¹ at N-1 and N-2, respectively, and the calculated pK_a is given as −0.96 (−0.77) for the species protonated at N-1 (N-2) [<1995JPO496>](#).

Alkylation parallels protonation and, thus, at the above level of theory, 2-ethyl-1,2,3-triazinium ions are thermodynamically more stable than their 1-ethyl isomers [<2003S413>](#). The latter may, however, be regarded as kinetically favored from natural population analysis (NPA) charge studies [<2003TH1>](#). Calculations using molecular reactivity parameters based on the concept of an effective electronic potential, and defined as a function of molecular charge distribution, gave excellent linear correlations for proton affinities, pK_a values, and H/D exchange rate exponents for twenty-three monocyclic and fused azines, including **1** [<1995JPO496>](#).

The many-body interaction of **1** in an aqueous environment via hydrogen bonds from water to triazine N-atoms was studied using the DFT B3LYP method at the 6-31++G** basis set for up to three water molecules. Two 1:1, three 1:2, and six 1:3 ground-state minima have been discussed <2005CHJ1314, 2006MI401>. A strong hydrogen bond ($-4.3 \text{ kcal mol}^{-1}$) has been found for the 1:1 complex after basis set superposition error and zero-point vibrational energy correction <2006MI209>. Further studies on the ground-state interaction of **1** and water using DFT B3LYP and *ab initio* MP2 in accord with previous results have appeared recently <2005MI891, 2005MI225>. Hypsochromic shifts in the UV spectrum of **1** in water have been discussed earlier in this chapter.

9.01.2.13 Lithiation

1,2,3-Triazines should also be susceptible to lithiation in absence of typical *ortho*-directing groups <2003TH1>. Calculations on the B3LYP/6-311+G**//B3LYP/6-311+G*+0.89ZPE (HF/6-31G*) level predict the 5-lithio-1,2,3-triazine to be $10.17 \text{ kcal mol}^{-1}$ less stable than the 4-lithio isomer. N-3 participates in the chelation of the metal; the distances Li–C(4) and Li–N(3) in 4-lithio-1,2,3-triazine have been calculated (B3LYP/6-311+G) to be 1.937 and 1.849 Å, respectively, while 1.975 Å for the Li–C(5) distance in 5-lithio-1,2,3-triazine has been predicted <2003TH1>. 4-Methoxy-1,2,3-triazine is lithiated at both C-5 and C-6 and calculations on the B3LYP/6-311+G**//B3LYP/6-311+G* + 0.89ZPE (HF/6-31G*) level predict almost equal stability for both products. The 6-lithio derivative (three-membered chelate with N-1) is predicted to be only $0.5 \text{ kcal mol}^{-1}$ less stable than the 5-isomer (four-membered chelate with the methoxy oxygen). Oxygen-chelated 4-lithio-5-methoxy-1,2,3-triazine is, however, $11.6 \text{ kcal mol}^{-1}$ less stable than with N-3 chelation. The Li–C bond polarity has been estimated to be close to that in vinylolithium by natural population analysis (NPA) at the HF/6-31G* level. Geometries of precomplexation (using lithium amide), lithiation transition states, and end complexes (containing one molecule of NH_3 coordinated to Li) have also been studied <2003TH1>.

9.01.2.14 N-Oxides, N-Imines, and N-Ylides

Attempts to oxygenate 1,2,3-benzotriazines with hydrogen peroxide have been made, but only in one case (4-(2,4,6-trinitrophenyl)sulfanyl-) was an *N*-monoxide isolated and tentatively assigned as a 3- or 1-oxide <1971JHC785>, mainly on the basis of HMO charge density calculations <1966JSP25> on the unsubstituted parent **2**. These calculations were, however, misleading in their prediction which oxide is eventually isolated, since in this case it was later found to be the 2-oxide <1988J(P1)1509>. SCF MO calculations were performed for 4,6-dimethyl-1,2,3-triazine 2-imine based on the crystallographic coordinates. The unit cell was found to contain three pairs of molecules, one intermolecularly bonded by an $\text{N(1)} \cdots \text{HN}_{\text{imino}}$ hydrogen bond, the other two pairs by nonbonded interactions, which were also calculated using van der Waals potential functions <1988YZ1040>.

The MNDO LUMO energy (-0.787 eV) of **1** is lowered to -1.825 eV by N-2 dicyanomethenylation, which means a rise in the electrophilic reactivity of the triazine ring <1993CPB1644>; see Section 9.01.5.4.

9.01.2.15 Dihydro- and Tetrahydro-1,2,3-triazines

Intermolecular $\text{O-H} \cdots \text{N}$ hydrogen bonds have been found in crystalline 4-ethyl-3-methyl-3,4-dihydro-1,2,3-benzotriazin-4-ol. *Ab initio* STO-3G MO calculations of atomic charges rule out N-2 as the proton acceptor since this atom is nearly neutral, and point to N-1 (-190 millielectrons) for that role <1987AXC2209>.

The acid-sensitive 1,4,5,6-tetrahydro-1,2,3-triazine **11** and its N-1-protonated form (although not stabilized by charge delocalization) were investigated within the HF approximation. Total energies of -279.35169 (SCF 3-21G) and -280.943554 (SCF 6-31G*) hartree for the neutral and -279.71364 hartree (SCF 3-21G) for the protonated form were calculated. N-1 is the preferred site of protonation. Optimized geometrical parameters for the neutral and the N-1-protonated species were given <1991JA7893>.

9.01.2.16 Valence Isomers of 1,2,3-Triazine

The bicyclic structure **14** (no calculations available) has been suggested tentatively as an intermediate in the photolysis of **1** <1995JPH135>. Azatriprismanes have received some interest, and the strained 1,2,3-triazatriprismane **15** is predicted to be more stable by $66.2 \text{ kcal mol}^{-1}$ than the parent triprismane C_6H_6 from comparison of 3-21G isodesmic reaction energies. This finding has been interpreted in terms of favorable σ -delocalization of the nitrogen lone pairs being partially dampened by repulsive interactions <1990JMT(207)193>. In general, placement of N-atoms on diagonally opposite sites is more favorable than placing them on a single triangular face <2005THA167>.

Compound **16** is the second triazatriprismane structurally related to **1**. Molecular electrostatic potential (MESP) minima and dipole moments of **15** (4.98 D) and **16** (3.93 D) have been calculated. Interest in high-energy compounds has also stimulated the investigation of nitro-substituted azatriprismanes <2005THA167>.

**14**(1,2,3)
15(1,2,5)
16

9.01.3 Experimental Structural Methods

In this section, structural and spectroscopic data of various 1,2,3-triazines and related compounds are presented and discussed. Selected data and references from the literature prior to 1995 may be included for purpose of comparison, especially when such work has not been covered in CHEC(1984) and CHEC-II(1996). When they represent real compounds, the formula numbers of the prototypes from Section 9.01.1 are retained. Otherwise, current numbers have been assigned for individual compounds or groups of compounds (e.g., **17**, which means 1,2,3-triazines, which may bear Rⁿ (H, alkyl, aryl acyl, etc.) or a heteroatom substituent Xⁿ at ring atom *n*. If not given next to the formula, the meaning of Rⁿ and Xⁿ is specified in the text or tables.

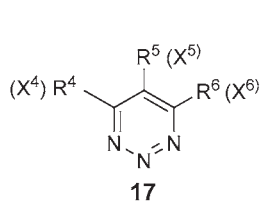
Necessarily there will be overlap with the preceding section on theoretical investigations, especially since the structure of the parent 1,2,3-triazine **1** <1983CPB3762, 1985LA1732> (see also <1996CHEC-II(6)483>) and its spectroscopic properties have been the subjects of numerous calculations.

9.01.3.1 Single Crystal X-Ray Structure Determinations

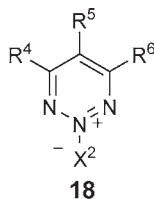
In addition to several structures of 1,2,3-triazine derivatives reviewed in previous editions <1984CHEC(3)369 and 1996CHEC-II(6)483>, single crystal X-ray structural analyses have become available for the following compounds:

- 4-methyl-6-phenyl-1,2,3-triazine-5-carboxamide **17a** (forming two polymorphs, namely as colorless prisms and as colorless needles, both when crystallized from methanol) <1991AXC2256>;
- 4-methoxy-6-(phenylhydroxymethyl)-1,2,3-triazine **17b** <1998MI119>;
- 5-diethylamino-4,6-diphenyl-1,2,3-triazine **17c** (showing torsion angles of 50° for the phenyl groups relative to the triazine main plane) <2005AXE93>;
- 5-diethylamino-4,6-di(4-fluorophenyl)-1,2,3-triazine **17d** (only crystal data given) <2002HCO325>;
- 4,5,6-tris(dimethylamino)-1,2,3-triazine **17e** <1993ZK310>;
- methyl 6-phenyl-1,2,3-triazine-4-carboxylate **17f** <1994ZK196>;
- 4,5,6-triphenyl-1,2,3-triazine 2-oxide **18a** <1986CPB109>;
- 4,5,6-tris(4-methylphenyl)-1,2,3-triazine 2-oxide **18b** (Ar=4-MeC₆H₄) <1991AXC2193>;
- 4,6-dimethyl-1,2,3-triazine 2-imine **18d**, the crystals of which contain eight geometrically slightly different molecules in the unit cell, therefore averaged bond lengths (Å) and angles (°) are given: N(1)–N(2) 1.36, N(2)–N(3) 1.35, N(3)–C(4) 1.33, C(4)–C(5) 1.38, C(5)–C(6) 1.38, C(6)–N(1) 1.33; N(1)–N(2)–N(3) 125, N(2)–N(3)–C(4) 116, N(3)–C(4)–C(5) 124, C(4)–C(5)–C(6) 114, C(5)–C(6)–N(1) 124, C(6)–N(1)–N(2) 114 <1988YZ1040, 1988YZ1056> (this compound is unique insofar as its molecules in the crystal occupy eight systems of equivalent positions (*P*₁, *Z* = 8 (1⁸)) <1995AXA473>; while the structure in the crystal is well stabilized by H-bonds, **18d** is monomeric in chloroform solution <1983CPB3759>);
- 4-phenylamino-2-propyl-1,2,3-benzotriazin-4-ones **19a** (R³ = CONPh₂) <1991T8917>, **19b** (R³ = CH₂SP(S)(OMe)₂, Azinphos methyl) <1976JFA713>, **19c** (R³ = CH₂SP(S)(OEt)₂, Azinphos ethyl) <1995AXC521>, **19d** (X³ = OH) <1983AXC738>, **19e** (X³ = OP(O)(OEt)₂) <1999OL91>;
- 3,4-dihydro-1,2,3-benzotriazin-4-ols **20a** and **20b** <1985CJC581> and **20c** <1987AXC2209> with discussion of intermolecular hydrogen bonds in the crystal;

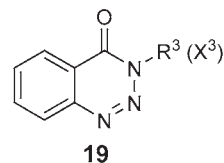
- 2,5-dihydro-1,2,3-triazines **21a** and **21b** where crowding and twisting of the 4,5,6-substituents suspend the symmetry otherwise present in the crystal lattice so that different lengths and angles are found for corresponding bonds and angles <2006TL1721, 2006JOC5679>;
- the dihydrotriazinone **22a** <2002HCO325>;
- the bridged tetrahydro-1,2,3-triazinone **23** <1988JOC391>;
- the spirotriazinium zwitterion **24** <1987CC1697, 1990J(P1)2379>;
- the phenanthro[9,10-*d*]fused triazin-2-ium-3-ide **25** (E = COOMe, R = 4-BrC₆H₄) <1996J(P1)1623>;
- the naphtho[1,8-*de*]fused compounds **5a** <1980AXB3140, 1980AXB3142> and **26a** <1984ZNB975>.



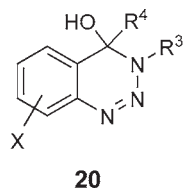
17	$R^4 (X^4)$	$R^5 (X^5)$	$R^6 (X^6)$
a	Me	CONH ₂	Ph
b	OMe	H	PhCHOH
c	Ph	Et ₂ N	Ph
d	4-FC ₆ H ₄	Et ₂ N	4-FC ₆ H ₄
e	Me ₂ N	Me ₂ N	Me ₂ N
f	COOMe	H	Ph



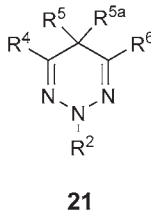
18	R^4	R^5	R^6	X^2
a	Ph	Ph	Ph	O
b	Ar	Ar	Ar	O
c	Ph	H	Me	O
d	Me	H	Me	NH
e	Me	H	Ph	NH



19	$R^3 (X^3)$
a	CONPh ₂
b	CH ₂ SP(S)(OMe) ₂
c	CH ₂ SP(S)(OEt) ₂
d	OH
e	OP(O)(OEt) ₂
f	Me

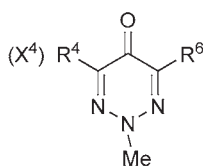


20	R^3	R^4	X
a	Et	H	H
b	Me	Ph	6-Cl
c	Me	Et	H
d	Me	Me	H

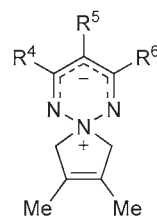
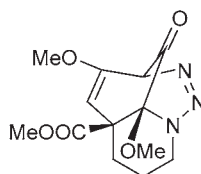


21	R^2	R^4	R^5	R^{5a}	R^6
a	Ph	Ph	H	COOMe	Ph
b	Ph	Ph	PhN=CH	COOMe	Ph
c	4-XC ₆ H ₄	Ph	4-XC ₆ H ₄ N=CH	COOMe	Ph
d	4-XC ₆ H ₄	Ph	4-XC ₆ H ₄ N=CH	COOEt	Ph
e	(see Table 10)				

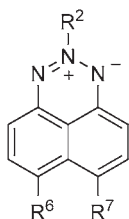
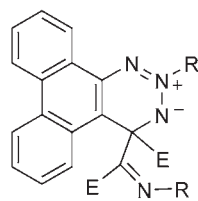
(X = H, OMe, Br, Cl, NO₂).



22	$R^4 (X^4)$	R^6
a	4-ClC ₆ H ₄	4-ClC ₆ H ₄
b	(<i>i</i> -Pr) ₂ N	Ph
c	Bu	Bu
d	Ph	Ph



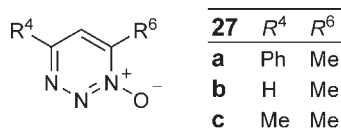
$R^4 = R^5 = R^6 = \text{CF}(\text{CF}_3)_2$



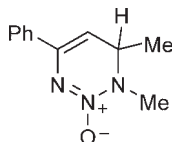
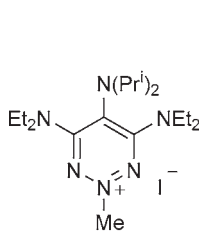
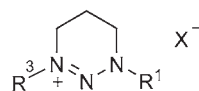
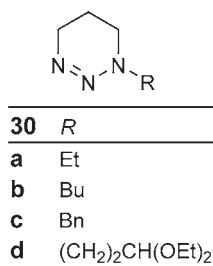
	R^2	R^6	R^7
5a	Me	H	H
5b	Et	H	H
26a	Me	—CH=CH—	
26b	Me	—CH ₂ —CH ₂ —	
26c	Me	—C(E)=C(E)—	

(E = COOMe).

While the structures of several 1,2,3-triazine 2-oxides have been published, only one structure of a 1,2,3-triazine 1-oxide became known, namely that of **27a** <1991AXC2193>. As in the case of its isomeric 2-oxide **18c** <1990AXC2177>, the N–O bond of **27a** (1.264(6) Å) is shorter than that of pyridine *N*-oxide (mean value 1.35 Å from 1.33 and 1.37 Å in two crystallographically independent molecules <1971AXB432>) pointing to a donating effect of the oxido function which results in alterations of bond lengths (Å) and angles (°) in the heteroring. For **27a**, the relevant values are: N(1)–N(2) 1.345(6), N(2)–N(3) 1.314(6), N(3)–C(4) 1.335(5), C(4)–C(5) 1.400(7), C(5)–C(6) 1.360(7), C(6)–N(1) 1.373(5); N(1)–N(2)–N(3) 118.8(3), N(2)–N(3)–C(4) 122.0(4), N(3)–C(4)–C(5) 119.4(4), C(4)–C(5)–C(6) 119.6(3), C(5)–C(6)–N(1) 116.9(4), C(6)–N(1)–N(2) 123.0(4). A comparison is now possible with the corresponding data for both the isomeric 2-oxide and the parent 6-methyl-4-phenyl-1,2,3-triazine <1990AXC2177>; see also <1996CHEC-II(6)483>. Most significant is the variation in the following bond angles (°), given in the order parent/1-oxide/2-oxide as follows: N(1)–N(2)–N(3) 122.3(2)/118.8(3)/126.1(1); N(2)–N(3)–C(4) 119.9(2)/122.0(4)/117.0(1); C(5)–C(6)–N(1) 121.0(2)/116.9(4)/122.6(1); C(6)–N(1)–N(2) 119.1(2)/123.0(4)/115.6(1). Furthermore, bonds C(4)–C(5) and C(6)–N(1) in **27a** are markedly elongated compared to the values for both the 2-oxide **18c** and 4-phenyl-6-methyl-1,2,3-triazine.

**27**

In CHEC-II(1996), the structure of 1,6-dimethyl-4-phenyl-1,6-dihydro-1,2,3-triazine 2-oxide **28** had been mentioned to be reported in <1986CPB109>, but, in fact, it was published elsewhere <1985YZ1122>.

**28****29**

31a: *R*¹ = *R*³ = 4-MeC₆H₄; X = ClO₄
31b: *R*¹ = Bn; *R*³ = 2-ClC₆H₄; X = Cl

A crystallographic pro-molecule/pro-crystal model has been described that allows identification of valence orbital orientations and occupancies of degenerate or near-degenerate atomic ground states in crystals. A method for extracting this additional information from crystal data has been applied to the experimental data for 1,2,3-triazine and the inferences for its electronic structure in the crystal have been outlined <2001HCA1907>.

9.01.3.2 Dipole Moments

For calculated values and orientation of the dipole moment μ of **1** and 4- and 5-methyl-1,2,3-triazines, see Section 9.01.2. An experimental value for **1** is not known, but values (determined in dioxane solution) for 3-methyl-3,4-dihydro-1,2,3-benzotriazin-4-one (**19f**; μ = 1.69 D) and 2-methyl-1,2,3-benzotriazin-2-ium-4-olate (μ = 4.9 D) have been determined earlier <1968PHA629>.

9.01.3.3 Photoionization

Photoionization and PE spectra of the parent **1**, various methylated derivatives thereof, and 2-methylnaphtho[1,8-*de*]-triazin-2-ium-1-ide **5a** have been treated before in connection with theoretical calculations in Section 9.01.2 and in CHEC-II(1996) <1996CHEC-II(6)483>.

9.01.3.4 UV/Vis Spectroscopy and Fluorescence

UV spectra of representative 1,2,3-triazine systems have been tabulated before <1984CHEC(3)369>. To supplement these compilations, Table 10 also lists hitherto not reviewed earlier and recent representative examples. In most of the sources cited, further examples can be found. For assignments, predictions of energies, and oscillator strengths of the parent compound **1** <1997CPH(221)11>, see Tables 5 and 6 (Section 9.01.2).

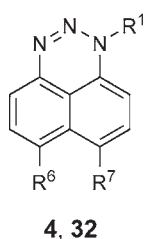
Table 10 Representative UV spectra of 1,2,3-triazines (sh = shoulder)

Compound	Solvent	$\lambda_{\max}$ (nm) ($\log \epsilon$)	Reference
1,2,3-Triazine 1	EtOH	325sh 2.88 (2.93), 232sh	1981CC1174, 1985JOC5520
4-Methyl-1,2,3-triazine	MeOH	290 (2.72), 230sh	1985LA1732
	EtOH	313sh 286 (2.70), 288sh	1981CC1174
	EtOH	286 (2.71), 228sh	1985JOC5520
5-Methyl-1,2,3-triazine	EtOH	288 (2.96), 232sh	1985JOC5520
4-Phenyl-1,2,3-triazine	EtOH	267 (4.08)	1985JOC5520
4,5,6-Trifluoro-1,2,3-triazine		231 (3.32)	1988T2583
4,5,6-Trimethoxy-1,2,3-triazine	CH ₂ Cl ₂	259 (3.37), 270sh	1979CB1529
4,5,6-Tris(diethylamino)-1,2,3-triazine	CH ₂ Cl ₂	350 (3.69), 258 (4.13)	1979CB1514
4-Methyl-6-phenyl-1,2,3-triazine 2-imine 18c	EtOH	380 (3.25), 305 (4.16), 264 (4.23)	1988YZ1056
Triazinium salt 29	CH ₂ Cl ₂	458 (3.80)	1979CB1535
1,6-Dihydro-1,2,3-triazine 2-oxide 28	EtOH	320 (3.41), 240 (4.34)	1985YZ1122
2,5-Dihydrotriazine 21e ^a	<i>c</i> -C ₆ H ₁₂	404 (2.48), 298 (3.72), 244 (3.78)	1990J(P1)2379
Methyl 4-diisopropylamino-5-oxo-6-phenyl-2,5-dihydro-1,2,3-triazine-2-carboxylate	CH ₂ Cl ₂	402 (3.86)	1979CB1535
1-Ethyl-1,4,5,6-tetrahydrotriazine 30a	MeCN	243 (3.90)	1997JOC8660
3,4,5,6-Tetrahydrotriazinium salt 31a	MeOH	348 (4.20), 248 (3.79)	1979CB445
4-Methyl-1,2,3-benzotriazine (36 : R ⁴ = Me)	EtOH	275 (2.83), 227 (4.0), 207 (3.58)	1975J(P1)31
4-Methyl-1,2,3-benzotriazine 2-oxide	EtOH	350sh, 290 (3.9), 260 (4.4), 213 (4.3)	1988J(P1)1509
3-Hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one 19d	MeCN	315 (3.65), 295 (3.77)	2001NJC1281
Same, deprotonated	MeCN	390 (3.70), 340 (3.80)	2001NJC1281
Same, as Fe(III) complex	MeCN	430 (broad, 3.80) ^b , 345 (4.06) ^b	2001NJC1281

^aCompound **21e**: R² = CH(Me)-C(Me)=CH₂; R⁴ = R⁵ = R⁶ = CF(CF₃)₂; R^{5a} = H.

^bLigand-to-metal charge-transfer (LMCT) transitions.

UV/Vis spectral properties of naphtho[1,8-*de*]triazines **4**, **32**, and related systems have been listed in Table 11. Highly structured spectra of **5a** have been obtained in 2-Me-THF solution at 298 and 10 K <1986AGE828>.



	R ¹	R ⁶	R ⁷
4	H	H	H
32a	Me	H	H
b	Et	H	H
c	H	—CH ₂ —CH ₂ —	
d	Me	—CH ₂ —CH ₂ —	
e	Me	—CH=CH—	
f	MeCO	H	H
g	PhCO	H	H

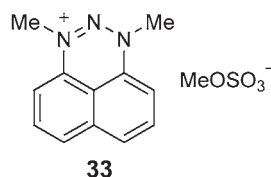


Table 11 UV/Vis spectra of naphtho[1,8-*de*]-1,2,3-triazines and related compounds (sh = shoulder)

<i>Compound</i>	<i>Solvent</i>	$\lambda_{\max}(\text{nm})$ ($\log \epsilon$)	<i>Reference</i> ^a
1 <i>H</i> -Naphtho[1,8- <i>de</i>]-1,2,3-triazine 4	EtOH	452 (2.87), 338.5 (4.00), 232.5 (4.49)	A
	MeOH/HCl	505 (2.99), 332 (3.83), 318 (3.79), 305sh, 224 (4.79)	B
	CH ₂ Cl ₂	438 (2.82), 336 (3.93), 287 (3.45), 376 (3.54), 267 (3.54)	C
1-Methyl-1 <i>H</i> -naphtho[1,8- <i>de</i>]-1,2,3-triazine 32a (red solution)	EtOH	451 (2.98), 338 (4.01), 231.5 (4.51)	A
	MeOH	454 (2.99), 337 (4.07), 276 (3.59), 230 (4.63)	B
1-Ethyl-1 <i>H</i> -naphtho[1,8- <i>de</i>]-1,2,3-triazine 32b	MeOH	Vis only: 453 (3.04)	C
6,7-Dihydro-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]-1,2,3-triazine 32c	MeOH	468 (2.83), 360 (3.92), 352 (3.95), 345 (3.96), 279 (3.61), 226 (4.55), 205 (4.57)	
1-Methyl-6,7-dihydro-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]-1,2,3-triazine 32d	MeOH	Vis only: 470 (2.97)	C
1-Methyl-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]-1,2,3-triazine 32e	EtOH	435 (3.48), 316 (4.24), 303 (4.33), 282 (4.24), 243 (4.29)	D
2-Methyl-1 <i>H</i> -naphtho[1,8- <i>de</i>]-1,2,3-triazin-2-ium-1-ide 5a (blue solution)	EtOH	655 (2.76), 603 (2.91), 559 (2.91), 335 (4.11), 231.5 (4.52)	A
	MeOH	Vis only: 700 (2.53), 602 (2.94), 556 (2.94)	C
2-Ethyl-1 <i>H</i> -naphtho[1,8- <i>de</i>]-1,2,3-triazin-2-ium-1-ide 5b	MeOH	Vis only: 720 (2.39), 652 (2.81), 598 (2.97), 556 (2.96)	C
2-Methyl-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]- 1,2,3-triazin-2-ium-1-ide 26a	EtOH	464 (3.17), 337 (4.55), 330 (4.40), 322.5 (4.39), 248 (4.27)	D
2-Methyl-6,7-dihydro-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]- 1,2,3-triazin-2-ium-1-ide 26b	MeOH	Vis only: 715 (2.66), 648 (2.74), 597 (2.74)	C
6,7-Di(methoxycarbonyl)-2-methyl-1 <i>H</i> -acenaphtho[5,6- <i>de</i>]- 1,2,3-triazin-2-ium-1-ide 26c	EtOH	504 (3.79), 352 (4.71), 340sh (4.58), 276 (4.12), 247 (4.27)	E
1 <i>H</i> -1,3-Dimethylnaphtho[1,8- <i>de</i>]-1,2,3-triazinium methylsulfate 33	MeOH	503 (3.13), 332 (3.86), 318 (3.85), 306 (3.77), 227 (4.89)	B

^aReferences A <1964JCS3005>, B <1967AGE360>, C <1967LA150>, D <1970JC290>, E <1972CC1281>.

2,5-Dihydrotriazines **21a**, **21c**, and **21d** (including **21c** and **21d** with X = NO₂) show a green fluorescence. For **21c**, with X = H, OMe, Br, and Cl, both absorption (band 1: $\lambda_{\max}$ 307–310 nm, band 2: $\lambda_{\max}$ 391 nm) and emission (upon 317 nm excitation, band 1: $\lambda_{\max}$ ca. 483 nm, band 2: $\lambda_{\max}$ ca. 528 nm) were found to be dual. The normalized excitation spectrum (emission recorded at 500 nm) and emission spectrum (at 317 nm excitation) have been depicted for **21a**, with X = H, and the normalized emission spectra at 317 and 400 nm excitation for 10^{−6} M solutions of **21a** (X = H, Cl) show the emission to be dependent on excitation wavelength. It has been concluded that the 528 nm emission correlates with the 310 nm absorption (Stokes shift > 200 nm!) and the 480 nm emission with the 391 nm absorption. Thus, a system of two ground states and two excited states is probably involved. In conclusion, compounds **21a–c** show potential for fluorescence labeling <2006TL1721, 2006JOC5679>.

9.01.3.5 Vibrational Spectroscopy

For experimental IR and Raman spectral data for the parent triazine **1** and band assignments based on theoretical predictions of frequencies and intensities, see **Table 7** (Section 9.01.2). IR spectral data of 1,2,3-triazines and -benzotriazines from the earlier literature have been reviewed <1984CHEC(3)369>. Empirical band assignments for **1** have been given <1985LA1732> and IR frequencies and relative intensities for various methylated and phenylated 1,2,3-triazines have been compiled <1985JOC5520>. The IR spectra of some 1,2,3-triazines bearing alkyl or phenyl groups and one amine donor group have been reported <2003H(59)477, 1979CB1514, 2005AXE93>.

Gas-phase IR spectra of 4,5,6-trifluoro- and 5-bromo-4,6-difluoro-1,2,3-triazine have been recorded, while KBr as matrix was used for 4,6-difluoro-5-iodo-, 4,5,6-trichloro-, and tribromo-1,2,3-triazine <1998TH1>. Slightly different frequencies had been reported earlier for the trichloro compound <1979CB1529>. IR data from KBr disks or liquid films of 1,2,3-triazines with various dialkylamino substituents have been reported <1979CB1529>, and IR frequencies of the following compound types are also available: 2-oxides of alkylated and arylated 1,2,3-triazines

<1986CPB109, 1991CPB2117>, 1-oxides <1986CPB109>, and 2-dicyanomethylides <2004EJO4234>. The imino NH frequency of four 1,2,3-triazine 2-imines has been reported as 3200–3250 cm⁻¹ <1988YZ1056>. IR data for various 1,2,3-triazinium salts can be found as well <1979CB1535, 2003S413>.

IR spectra of 2,5-dihydro-1,2,3-triazines <1990J(P1)2379, 1990J(P1)3321, 1993JCM78, 2003S413>, 2,5-dihydro-1,2,3-triazine-5-ones <1979CB1535, 1990CPB2108, 2003H(59)477>, 2,3,4,5-tetrahydro-1,2,3-triazines (in mineral oil) <1995RJO1005, 1993RJO1928>, 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides <1982H(17)317>, and 3,4,5,6-tetrahydro-1,2,3-triazinium salts <1979CB445> have been published.

IR frequencies of 1,2,3-benzotriazines, recorded from KBr disks <1975J(P1)31, 1970JC765>, from CHCl₃ solutions <1990H(31)895>, and from Nujol mulls <1972J(P1)1315, 1975J(P1)31>, are available.

In the IR spectroscopy of 3,4-dihydro-1,2,3-benzotriazin-4-ones (parent: **3**), interest is focused on the NH and C=O frequencies; the following are for the crystalline solid **3**: (Nujol or hexachlorobutadiene mulls) NH 3140, C=O 1695 <1962JOC4083>, (KBr) NH 3077, C=O 1685 <1979AP842>, (KBr) C=O 1681 cm⁻¹ <1972JOC196>. IR data of 3-alkyl-3,4-dihydro-1,2,3-benzotriazin-4-ones from Nujol mulls or KBr disks have been published <1968PHA629, 1974JOC2710, 1981JOC856, 1973J(P1)868> besides for two corresponding thiones <1968PHA629>. A sharp C=O band at 1723 cm⁻¹ is reported for Ar-matrix-isolated (10 K) 3-methoxy-3,4-dihydro-1,2,3-benzotriazin-4-one <1992CL361>. In addition, selected IR frequencies of 3-acyl- <1962JOC4083, 1991T8917, 2000T4079>, 3-hydroxy- <1977CJC630, 1990S1008>, 3-methoxy- <1977CJC630, 1989J(P1)543>, and 3-methylamino-3,4-dihydro-1,2,3-benzotriazin-4-one <1980JCM246> have been reported. IR data for various benzotriazinone 1-oxides (in CHBr₃ mulls) <1989J(P1)543> and 2-oxides <1988J(P1)1509, 1988S517> as well as for 2-alkyl- and 2-aryl-1,2,3-benzotriazin-4-ones <1972JOC1587, 1974JOC2710> are available.

Some information is also available for the following naphtho[1,8-*de*]triazines: compound **4** (KBr) <2002TH1, 2005T10507>, 1-methyl-1*H*-naphtho[1,8-*de*]-1,2,3-triazine (**32a**, in Nujol) <1964JCS3005>, compounds **32f** and **32g** <2005T10507>, 5,8-dinitro-1*H*-naphtho[1,8-*de*]-1,2,3-triazine <1994RJO487>, and 2-methyl-1*H*-naphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide **5a** <1964JCS3005>.

9.01.3.6 NMR Spectroscopy

Selected ¹H, ¹³C, and ¹⁵N nuclear magnetic resonance (NMR) data, mostly of monocyclic 1,2,3-triazines, have been reviewed in CHEC(1984) and CHEC-II(1996). However, so far, not much information on hydrogenated and fused 1,2,3-triazines has been reviewed; therefore such information from publications prior to 1996 also is included in this chapter. For reasons of space restriction, some information is not given in tables but rather by listing the sources of such information. ¹⁹F data are also included.

9.01.3.6.1 ¹H NMR data

For representative examples, see Table 12. In the outer right column ('additional examples'), the information is given as to how many analogous compounds, beyond the examples selected for inclusion in the table, are described with their ¹H NMR data in that reference. The small ³J_{HH} value of 2 Hz given earlier for the parent compound **1** <1985LA1732> has been questioned and 5.6 Hz has been reported instead <1998CPH(228)39>; other workers had earlier given a value of 6 Hz <1981CC1174, 1985JOC5520>.

Beyond the cases listed, ¹H NMR spectra of numerous 2,5-dihydro-1,2,3-triazines **21** with R² = H <1980CC1182, 1985YZ1122, 1985CC1370, 1992H(33)631>, R² = Me <1985CC1370, 1985YZ1122, 1992CPB2283, 1994CPB1768>, R² = Ph and 4-O₂NC₆H₄ <1990J(P1)3321>, and R² = (1-chlorethoxy)carbonyl <1996J(P1)2511> have been published as well as those of N-alkylated 2,5-dihydrotriazines **21** with perfluorinated side chains (R^{5a} = H; R⁴ = R⁵ = R⁶ = CF(CF₃)₂) <1990J(P1)2379>.

¹H NMR spectra are also available for

- various 1,2,3-benzotriazines **36** <1975J(P1)31, 1981JRM3786, 1989J(P1)543> and 2-oxides thereof <1988J(P1)1509>;
- several 1,2,3-benzotriazinones **19** <1977CJC630, 1981JOC856, 1984OMS641, 1989J(P1)543, 1990S1008, 1991T8917, 1996JOC210, 1999EJM1043> and 2-oxides thereof <1988S517>;
- 3,4-dihydrobenzo-1,2,3-triazines **37** <1975JHC1155, 1975CJC3714, 1983CJC179, 1986CJC250, 1987CJC292>;
- camphortriazine **38** <1977H(8)319> and oxides thereof <2000JHC1663>;
- compounds **39** (*n* = 1,2) <1986H(24)907>;
- 3-methyl-3,4,5,6,7,8-hexahydro-1,2,3-benzotriazin-4-one **40** <1976S717>;
- eight 2,3,4,4a-tetrahydro-1,2,3-benzotriazine derivatives <2002AGE484>;

Table 12 Selected ^1H NMR data of 1,2,3-triazines and related compounds (in CDCl_3 if not stated otherwise)^a

Compound	Freq. (MHz)	Selected chemical shifts δ_{H} (ppm), J (Hz)	Reference	Addnl. expts. ^b
1,2,3-Triazine 1		9.04 (d, 4-H, 6-H), 7.45 (t, 5-H), $^3J_{\text{HH}}$ 5.60	1998CPH(228)39	
1,2,3-Triazines 17 $\text{R}^4 = \text{R}^6 = \text{H}$; $\text{R}^5 = \text{Ph}$				
	300	9.31 (s, 4-H, 6-H)	1992H(33)631	
	300	9.25 (s, 4-H, 6-H)	2003S413	>3
	300	9.34 (s, 4-H, 6-H)	2003TH1	2
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{X}^5 = \text{Br}$	300	9.16 (s, 4-H, 6-H)	2003TH1	
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{X}^5 = \text{OEt}$	300	8.72 (s, 4-H, 6-H)	1998MI119	
$\text{R}^4 = \text{Ph}$; $\text{R}^5 = \text{R}^6 = \text{H}$	300	7.50–7.58 (3H, Ph), 7.73 (d, ^3J 4, 5-H), 8.16–8.21 (2H, Ph), 9.02 (d, ^3J 4, 6-H)	2003TH1	
$\text{R}^4 = \text{COOMe}$; $\text{R}^5 = \text{R}^6 = \text{H}$	60	8.06 (d, ^3J 6.0, 5-H), 9.35 (d, ^3J 6.0, 6-H)	1993LA367	9
$\text{R}^4 = \text{CONEt}_2$; $\text{R}^5 = \text{R}^6 = \text{H}$	60	7.75 (d, ^3J 6.0, 5-H), 9.25 (d, ^3J 6.0, 6-H)	1998MI119	
$\text{X}^4 = \text{OMe}$; $\text{R}^5 = \text{R}^6 = \text{H}$	300	6.92 and 8.79 (two d, J 2.9, 5-H and 6-H)	1998MI119	
$\text{R}^4 = \text{PhCO}$; $\text{R}^5 = \text{OEt}$; $\text{R}^6 = \text{H}$	300	8.96 (s, 6-H)	1998MI119	>14
1,2,3-Triazinium-ylides 34 $\text{R}^4 = \text{R}^5 = \text{R}^6 = \text{H}$ (DMSO- d_6)		8.39 (d, ^3J 5, 4-H, 6-H), 7.48 (t, ^3J 5, 5-H)	1992H(33)631	
$\text{R}^4 = \text{Ph}$; $\text{R}^5 = \text{R}^6 = \text{H}$ (acetone- d_6)	300	7.55 (d, ^3J 6.2, 5-H), 8.88 (d, ^3J 6.2, 6-H)	2004EJO4234	3
$\text{R}^4 = \text{Me}$; $\text{R}^5 = \text{H}$; $\text{R}^6 = \text{Ph}$		6.86 (s, 5-H)	1991H(32)2015	3
Dihydrotriazines: 35 : $\text{R}^1 = \text{Pr}^i$; $\text{R}^4 = \text{R}^6 = \text{Ph}$		5.64 (d, ^3J 5.4, 5-H), 5.21 (d, ^3J 5.4, 6-H)	1996H(43)1759	10
Compound 21f		2.80 (2H, 5-H, 5a-H), 9.02 (N(2)–H)	1985YZ1122	2
Compound 21g	400	3.45 (s, 5a-H), 8.32 (broad, N(2)–H)	1996J(P1)2511	>2
Compound 21h	300	4.56 (dd, $^3J_{5,6}$ 4.5, $^3J_{5,\alpha}$ 9.5, 5a-H), 6.78 (d, J 4.5, 6-H)	2003S413	1
Compound 21i	300	3.51 (d, ^3J 2.2, 5a-H), 6.80 (d, ^3J 2.2, 6-H)	2003S413	2
Compound 21j	300	9.29 (s, 6-H)	2003S413	5
1,2,3-Triazinium salts 87 ^c (CD_3CN): $\text{R}^2 = \text{R}^4 = \text{H}$; $\text{R}^5 = \text{Ph}$; $\text{X} = \text{BF}_4$	300	8.12–8.15 (m, 4-H, 6-H), 12.60 (br, N(2)–H)	2003S413	3
$\text{R}^2 = \text{Et}$; $\text{R}^4 = \text{H}$; $\text{R}^5 = \text{Me}$; $\text{X} = \text{PF}_6$	300	9.60 (s, 4-H, 6-H)	2003S413	6
$\text{R}^2 = \text{Ph}$; $\text{R}^4 = \text{Me}$; $\text{R}^5 = \text{H}$; $\text{X} = \text{PF}_6$	300	8.34 (d, ^3J 5.8, 5-H), 9.67 (d, ^3J 5.8, 6-H)	2003S413	7
Compound 36 : $\text{X}^4 = \text{NH}_2$ (DMSO- d_6)		8.00 (m, 6-H), 8.15 (m, 7-H, 8-H), 8.50 (m, 5-H), 9.10 (broad, NH_2)	2001CHE567	10
Compound 4 (DMSO- d_6)	400	6.13, 6.89, 7.03, 7.13, 7.26; 13.29 (NH)	2005T10507	
Compound 11 (unstable, D_2O)	300	1.82 (m, 2H), 3.16 (t, 2H), 4.18 (t, 2H)	1997SC1569	
Compound 31b (DMSO- d_6)	250	2.28 (quintet, 5-H ₂), 3.95 (t, 4- or 6-H ₂), 4.16 (t, 4- or 6-H ₂)	2002BMC3001	

^aSee also table 4 on p. 486 of <1996CHEC-II(6)483>.^bNumber of additional analogous compounds characterized by ^1H NMR data in the same reference.^cSee Section 9.01.5.2.

- 2,3,4,5-tetrahydro-1,2,3-triazin-4,5-diones **41a** ($\text{R}^1 = \text{Bn}$) <1995RJO1005> and **41b** ($\text{X}^1 = \text{NH}_2$) <1993RJO1928>;
- compounds **30a** and **30b** <1997JOC8660>;
- four 1,3-diaryl-3,4,5,6-tetrahydro-1,2,3-triazinium perchlorates **31** in trifluoroacetic acid (TFA) <1979CB445>; and
- 1,5-diphenyl-3-benzylhexahydro-1,2,3-triazin-4,6-dione **42** <1978CB2173>.

9.01.3.6.2 ^{13}C NMR data

For recent and so far not reviewed data from sources prior to 1996, see Table 13. The chemical shifts for the ring carbon atoms in 1,2,3-triazines and their one-bond coupling constants to hydrogen underline the electron-poor character of the heterocycle. ^{13}C spectra have been published also for

- two 1,6-dihydro-1,2,3-triazinones **43** ($\text{R}^1 = \text{CH}(\text{Me})\text{Ph}$ and CHPh_2) <2006EJO3021>;
- nine substituted 2,5-dihydro-1,2,3-triazines **21** <1992CPB2283, 1994CPB1768, 1996J(P1)2511, 2003S413>; and
- the tetrahydro-1,2,3-triazinium salt **31b** <2002BMC3001>.

Table 13 Selected ^{13}C NMR data of 1,2,3-triazines and related compounds (in CDCl_3 if not stated otherwise)^a

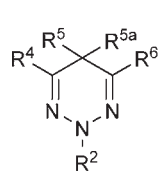
Compound	Freq. (MHz)	δ_{C} (ppm), J (Hz)	Reference	Addnl. expls. ^b
1,2,3-Triazine 1		149.8 (dd, $^1J_{\text{CH}}$ 188.2, $^3J_{\text{CH}}$ 4.0, C-4, C-6) 117.8 (dt, $^1J_{\text{CH}}$ 174.2, $^2J_{\text{CH}}$ 5.4, C-5)	1998CPH(228)39	
1,2,3-Triazines 17				
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{R}^5 = \text{C}\equiv\text{CPh}$	75.45	150.27 (C-4, C-6), 120.59 (C-5)	2003TH1	2
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{R}^5 = \text{Ph}$	75.45	147.38 (C-4, C-6), 130.95 (C-5)	2003TH1	
$\text{X}^4 = \text{X}^6 = \text{Br}$; $\text{R}^6 = \text{H}$	75.45	153.44 (C-4), 127.82 (C-5), 151.66 (C-6)	2003TH1	1
$\text{R}^4 = \text{R}^6 = \text{Bu}$; $\text{X}^5 = \text{NEt}_2$		161.5 (C-4, C-6), 139.4 (C-5)	2003H(59)477	
$\text{R}^4 = \text{R}^6 = \text{Ph}$; $\text{X}^5 = \text{NEt}_2$	54.6	12.7 (Me), 46.0 (CH_2), 128.2, 128.7, 129.5, 136.7, 138.0, 152.6	2005AXE93	
$\text{R}^4 = \text{R}^6 = \text{Me}$; $\text{R}^5 = \text{CH}_2\text{COPh}$		19.58, 37.23, 124.87, 128.20, 129.07, 134.31, 135.70, 158.83, 193.14	1996J(P1)2511	3
$\text{R}^4 = \text{R}^6 = \text{Et}$; $\text{R}^5 = \text{CH}_2\text{SO}_2\text{Ph}$		12.08, 25.63, 53.58, 117.17, 128.21, 129.81, 134.85, 138.16, 163.11	1993CPB1644	3
$\text{X}^4 = \text{X}^5 = \text{X}^6 = \text{F}$. (ext. C_6D_6)		158.15 (dq, $^1J_{\text{CF}}$ 266.35, $^3J_{\text{CF}}$ 6.24, C-4, C-6)	1998TH1 ^c	2 ^d
$\text{X}^4 = \text{X}^6 = \text{F}$; $\text{X}^5 = \text{Cl}$ (ext. C_6D_6)		133.46 (dt, $^1J_{\text{CF}}$ 296.84, $^2J_{\text{CF}}$ 19.57, C-5) 164.74 (dd, $^1J_{\text{CF}}$ 262.55, $^3J_{\text{CF}}$ 8.33, C-4, C-6) 107.38 (t, $^2J_{\text{CF}}$ 25.59, C-5)	1998TH1	
1,2,3-Triazine 2-oxides 18 ($\text{X} = \text{O}$)				
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{R}^5 = \text{Me}$		157.8 (C-4, C-6), 118.4 (5), 14.7 (Me)	1986CPB109	
$\text{R}^4 = \text{Me}$; $\text{R}^5 = \text{R}^6 = \text{H}$		168.7 (C-4), 107.9 (C-5), 156.0 (C-6), 21.7 (Me)	1986CPB109	
$\text{R}^4 = \text{R}^6 = \text{Me}$; $\text{R}^5 = \text{CONH}_2$ (CD_3OD)		168.22, 166.08, 132.02, 19.38 (Me)	1991H(32)2015	2
1,2,3-Triazine 1-oxides 27				
$\text{R}^4 = \text{H}$; $\text{R}^6 = \text{Me}$ (27b)		137.4 (C-4), 123.5 (C-5), 146.9 (C-6)	1986CPB109	
$\text{R}^4 = \text{R}^6 = \text{Me}$ (27c)		146.1 (C-4), 123.9 (C-5), 148.1 (C-6)	1986CPB109	
Dicyanomethylides 34				
$\text{R}^4 = \text{R}^6 = \text{H}$; $\text{R}^5 = \text{Me}$ (acetone- d_6)	125	156.91 (C-4, C-6), 130.66 (C-5), 114.01 (CN)	2004EJO4234	1
$\text{R}^4 = \text{Me}$; $\text{R}^5 = \text{H}$ (acetone- d_6)	75.7	167.83 (C-4), 109.95 (C-5), 155.40 (C-6), 113.59	2004EJO4234	1
$\text{R}^4 = \text{R}^6 = \text{Ph}$; $\text{R}^5 = \text{H}$		99.65, 112.65, 127.43, 129.58, 131.10, 133.53, 162.71	1991H(32)2015	4
$\text{R}^4 = \text{R}^6 = \text{Et}$, $\text{R}^5 = \text{CH}_2\text{SO}_2\text{Ph}$ (DMSO- d_6)		10.65, 25.28, 52.48, 74.49, 109.95, 113.56, 128.66, 129.89, 134.92, 138.52, 169.25	1993CPB1644	4
1,6-Dihydrotriazine 35 ($\text{R}^1 = \text{Pr}^i$; $\text{R}^4 = \text{R}^6 = \text{Ph}$)		21.4 (Me_2), 56.5 (CHMe_2), 55.0 (C-6), 104.0 (C-5), 143.4 (C-4)	1996H(43)1759	10
2,5-Dihydrotriazine 21a	100	134.8 (C-4), 38.4 (5), 134.7 (C-6), 167.8 (C=O)	2006JOC5679 ^c	
21b	100	135.3 (C-4), 53.7 (C-5), 134.9 (C-6), 160.5 ($-\text{N}=\text{CH}-$), 170.2 (ester C=O)	2006JOC5679 ^c	
Tetrahydro-1,2,3-triazine 30a		13.0, 15.7, 43.3, 47.0, 50.9	1997JOC8660	2

^aSee also Table 5 on p. 487 of <1996CHEC-II(6)483>.^bNumber of analogous compounds characterized by ^{13}C NMR data in the same reference.^cSee also <1988T2583>.^dCompound **17** with $\text{X}^4 = \text{X}^6 = \text{F}$; $\text{X}^5 = \text{Br}$, I.^eSee also <2006TL1721>.

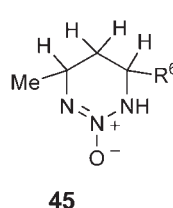
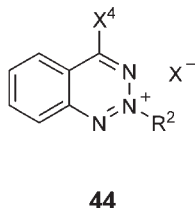
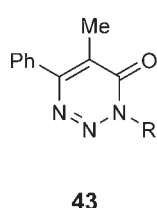
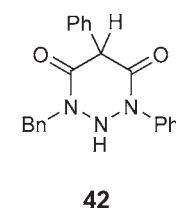
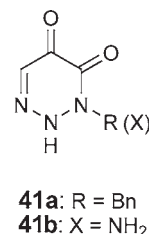
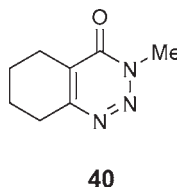
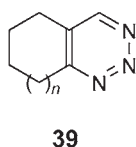
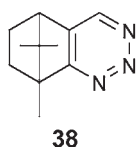
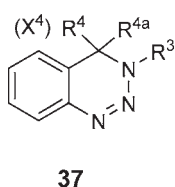
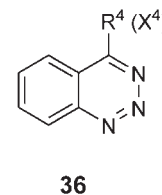
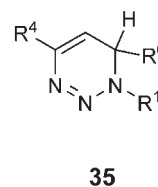
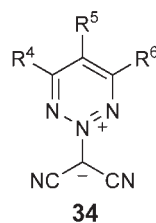
The carbonyl chemical shifts δ_{C4} (ppm) in various 3,4-dihydro-1,2,3-benzotriazin-4-ones **19** demonstrate a high shielding of this carbon atom as follows:

- $\text{R}^3 = (\text{CH}_2)_4\text{Cl}$ (CDCl_3): 155.37 <1994JME2552>;
- $\text{R}^3 = \text{CH}_2\text{COOMe}$ and related groups (CDCl_3): 154.9–156.0 <2004JCO38>;

- $R^3 = \text{CH}_2\text{CONH}_2$ (dimethyl sulfoxide- d_6 , DMSO- d_6): 154.9 (C-4), 168.1 (amide) <1996JOC210>;
- R^3 = various alkyl groups (CDCl_3 , 125.77 MHz): ca. 155.5 <2006JHC731>;
- $R^3 = 4\text{-MeC}_6\text{H}_4\text{CO}$ (CDCl_3 , 50 MHz): 155.0 <2000T4079>;
- $X^3 = \text{OH}$ (DMSO- d_6 , in various examples substituted in the benzo ring): 149.7–151.3 <1990S1008>.

 21	21	R^2	R^4	R^5	R^{5a}	R^6
	f	H	Me	H	H	Ph
	g	H	Me	CMe_2COOMe	H	Me
	h	Et	Ph	$\text{CH}(\text{COMe})_2$	H	H
	i	Et	Me	Indol-3-yl	H	H
	j	Et	Me	$=\text{C}(\text{COMe})_2$	H	H
	k	R^F	R^F	$=\text{C}(\text{CF}_3)_2$	R^F	R^F
	l	R^F	R^F	R^F	H	R^F

$\text{R}^F = \text{CF}(\text{CF}_3)_2$



9.01.3.6.3 ^{15}N NMR data

In addition to the ^{15}N chemical shifts reported in the previous edition, so far unreviewed data from the literature prior to 1996, as well as δ_{N} values from the recent literature, have been compiled in [Table 14](#). For the parent compound **1** in the first publication <1985LA1732>, the upfield resonance (13.71 ppm, d) had been assigned to N-1 and N-3, and the downfield resonance at 80.76 (t) to N-2. This assignment had been confirmed later <1998CPH(228)39> on the basis of the couplings observed for the upfield signal ($^2J_{\text{NH}}$ 12.5 Hz, $^3J_{\text{NH}}$ 0.7 Hz). More recently, the downfield signal was assigned to N-1 and N-3 and the upfield signal to N-2 in 4- and 5-phenyl-1,2,3-triazine <2003S413> (see [Table 14](#)). In 1,2,3-triazinium salts such as **87** (see [Section 9.01.5.2](#)), all ^{15}N shifts are found at higher field than those observed for the corresponding 1,2,3-triazines. ^{15}N data are also available for compound **21k** in $\text{CF}_2\text{Cl}-\text{CFCl}_2$ /acetone- d_6 , δ_{N} (rel. to MeNO_2): -46.4 (s, N-1, N-3), 40.2 (d, $J = 14$ Hz, N-2) <1988T2583>.

9.01.3.6.4 ^{19}F NMR data

Fluorine chemical shifts for four fluorinated 1,2,3-triazines have been collected in [Table 15](#). ^{19}F spectra of 1,2,3-triazines bearing perfluoroalkyl side chains ($\text{R}^4 = \text{R}^5 = \text{R}^6 = \text{CF}(\text{CF}_3)_2$ and $\text{R}^4 = \text{R}^6 = \text{CF}(\text{CF}_3)_2$, $\text{R}^5 = \text{F}$) <1988T2583> and of three related 2,5-dihydrotriazines of type **21** ($\text{R}^4 = \text{R}^5 = \text{R}^6 = \text{CF}(\text{CF}_3)_2$, $\text{R}^{5a} = \text{H}$, $\text{R}^2 = \text{CH}(\text{Me})\text{C}(\text{Me})=\text{CH}_2$ or $\text{C}(\text{Me})_2\text{C}(\text{Me})=\text{CH}_2$, and $\text{R}^2 = \text{Ph}$, $\text{R}^4 = \text{R}^6 = \text{CF}(\text{CF}_3)_2$, $\text{R}^{5,5a} = =\text{C}(\text{CF}_3)_2$) <1990J(P1)2379> have also been published.

Table 14 ¹⁵N chemical shifts of 1,2,3-triazines and related compounds^a

Compound	Freq. (MHz)	δ_N (ppm), J (Hz)				Reference
1,2,3-Triazine 1 (CDCl ₃)		81.01 (N-2), 13.096 (² J _{NH} 12.5, ³ J _{NH} 0.7, N-1, N-3)				1998CPH(228)39
1,2,3-Triazines 17						
R ⁴ = R ⁶ = H; R ⁵ = Ph (DMSO- <i>d</i> ₆) ^b	50.7	71.48 (N-1, N-3), 10.62 (N-2)				2003S413
R ⁴ = Ph; R ⁵ = R ⁶ = H (acetone- <i>d</i> ₆) ^b	50.7	83.14 (N-1, N-3), 8.32 (N-2)				2003S413
1,2,3-Triazinium salts 87 ^c (acetone- <i>d</i> ₆)						
R ² = Et; R ⁴ = H; R ⁵ = Ph; X = BF ₄ ^b	50.7	−17.49 (N-1, N-3), −81.46 (N-2) ^d				2003S413
R ² = Et; R ⁴ = Ph; R ⁵ = H; X = BF ₄ ^b	50.7	−21.46 (N-1, N-3), −69.93 (N-2) ^d				2003S413
Compound	Freq. (MHz)	N-1 or N-3	N-2	N-1 or N-3	Other resonances	Reference
1,2,3-Benzotriazines 36						
R ⁴ = Me	36.51	16.8	68.5	−14.6		1984JCM62
R ⁴ = Ph	36.51	16.5	66.5	−14.9		1984JCM62
X ⁴ = butylamino	36.51	−15.4	67.3	−67.7	−292 (4-NHBu)	1984JCM62 ^c
X ⁴ = (2-methoxyethyl)amino	36.51	−13.7	67.6	−67.3	−295.9 (4-NHR)	1984JCM62 ^c
X ⁴ = (4-methylphenyl)amino	36.51	−7.6	66.3	−65.1	−278.7 (4-NHAr)	1984JCM62 ^c
1,2,3-Benzotriazinium salts 44						
R ² = Pr; X ⁴ = butylamino; X = I	36.51	−40.5	−84.6	−91.8	−269.3 (4-NHBu)	1984JCM64
R ² = Pr; X ⁴ = (2-MeO-ethyl)amino; X = I	36.51	−39.6	−84.4	−91.6	−272.6 (4-NHR)	1984JCM64
R ² = Pr; X ⁴ = 4-Me-anilino; X = I	36.51	−36.6	−85.5	−90.4	−261.4 (4-NHAr)	1984JCM64
R ² = Me; X ⁴ = 4-Me-anilino; X = MeSO ₃	36.51	−35.8	−88.6	−93.5	−269.1 (4-NHAr)	1984JCM64
Compound	Freq. (MHz)	N-1	N-2	N-3	Other resonances	
3,4-Dihydro-1,2,3-benzotriazin-4-one 3	25.36	−16.5	29.3	−152.5 ^f		2002MRC300
3,4-Dihydro-1,2,3-benzotriazinones 19						
R ³ = Me	25.36	−16.0	32.8	−153.8		2002MRC300
R ³ = Bn	25.36	−13.5	32.4	−143.8		2002MRC300
R ³ = 2-chloroethyl	25.36	−14.0	31.8	−150.3		2002MRC300
R ³ = 1-ethoxyethyl	18.25	−14.3	26.6	−140.6		1989J(P1)543
R ³ = aminocarbonylmethyl	25.36	−14.7	33.1	−151.3	−274.6 (CONH ₂) ^f	2002MRC300 ^g
X ³ = OH	25.36	−23.8	24.7	−113.4		2002MRC300
X ³ = O-CO-Ph	25.36	−17.1	25.2	−104.1		2002MRC300
6-Chloro-3,4-dihydro-1,2,3-benzotriazin-4-one	25.36	−18.8	30.0	−152.5 ^f		2002MRC300
3-(Aminocarbonylmethyl)-3,4-dihydro-1,2,3-benzotriazin-4-imine	25.36	−29.0	31.0	−168.4	−177.8 (=NH) ^f −275.2 (NH ₂) ^f	2002MRC300 ^g

^aSee also Table 6 on p. 487 of <1996CHEC-II(6)483>. If not stated otherwise, solvent DMSO-*d*₆ with added chromium tris(acetylacetonate), nitromethane as an external standard.

^bNitromethane as internal standard.

^cSee Section 9.01.5.2.

^dThree bond couplings between N-2 and Me and 6-H have been observed.

^eSee also <1984JCM64>.

^fAssignment confirmed by heteronuclear gated decoupling giving ¹H decoupled spectra with full NOE for this signal.

^gSee also <1996JOC210>.

Table 15 ¹⁹F NMR data of fluorinated 1,2,3-triazines **17**

X ⁴	X ⁵	X ⁶	Solvent	δ_F (ppm), J (Hz)	Reference
F	F	F	(ext. C ₆ D ₆)	−168.7 (t, ³ J _{FF} 21, 5-F), −96.3 (d, ³ J _{FF} 21, 4-F, 6-F)	1998TH1
			CDCl ₃	−166 (t, ³ J _{FF} 23, 5-F), −96.0 (d, ³ J _{FF} 23, 4-F, 6-F)	1988T2583
F	Cl	F	(ext. C ₆ D ₆)	−82.5 (s, 4-F, 6-F)	1998TH1
			CDCl ₃	−80.0 (s, 4-F, 6-F)	1988T2583
F	Br	F	CDCl ₃	−72.2 (s, 4-F, 6-F)	1998TH1
Cl	Cl	F	CDCl ₃	−79.5 (s, 6-F)	1988T2583
F	I	F	CDCl ₃	−61.68 (s, 4-F, 6-F)	1998TH1

9.01.3.7 Mass Spectrometry

The large majority of investigations, either for routine characterization or investigations aimed at elucidating fragmentation patterns, uses electron impact (EI) ionization at 70 eV. Basic fragmentation patterns and routine results published prior to the mid-1990s have been treated in CHEC(1984) and CHEC-II(1996) <1984CHEC(3)369, 1996CHEC-II(6)483>. Occasionally, fragmentation of substituents competes with the well-known fragmentation of 1,2,3-triazines into N₂, an alkyne, and a nitrile <1972CB3695>; this fragmentation pattern matches that of thermolysis and photolysis (see Section 9.01.5.1). Beyond the cases reviewed previously, EI mass spectrometry (MS) data became available for 1,2,3-triazines bearing one or more alkyl, aryl, alkynyl, amino, and halogen substituents <1985LA1732, 1988CPB3838, 2003TH1, 2003S413, 2005AXE93>, alkoxy, amino, acyl, and α -hydroxyalkyl groups <1998MI119>, alkyl and ester groups <1993LA367>, and either three halogen atoms (F, Cl, Br) or three perfluoroisopropyl groups or one halogen and two such perfluoro substituents <1988T2583>.

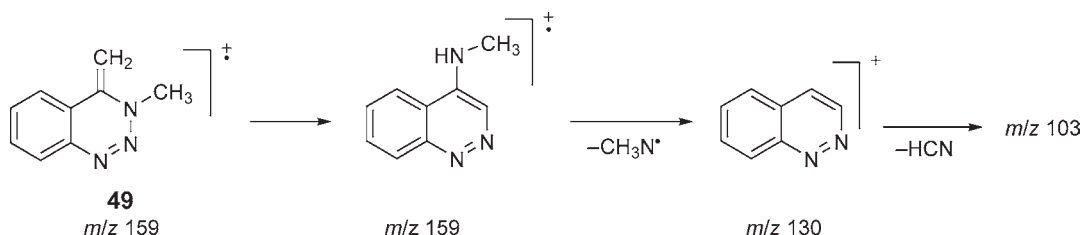
Mass spectra of 1,2,3-triazine 2- and 1-oxides have been published with emphasis on the fragmentation pattern (which deviates from that of 1,2,3-triazines) <1986CPB109>, and, in each case, such data have been reported for a limited number of compounds <1980CC1182, 1985LA1732, 1991CPB2117>. Various 1,2,3-triazine 2-dicyanomethylides <2004EJO4234, 1993CPB1644> and 2-(*N*-acylimines) <1988YZ1056> have also been investigated.

Besides conventional EI MS, low-energy fragmentation methods have also been applied. A series of C-monomethylated or monophenylated, N-2-protonated, -ethylated, or -phenylated 1,2,3-triazinium tetrafluoroborates or hexafluorophosphates (87; see Section 9.01.5.2) have been analyzed by field desorption (FD) MS at 15–20 mA. The following ions (T^+ = substituted triazinium, $M = T^+$ with attached anion) have been observed: T^+ , $[T^+ - 1]$, $[T^+ + 1]$, $[M + T^+]$ <2003S413>. Chemical ionization (CI) using methane as reagent gas was applied to four halogen-substituted 1,2,3-triazines so that $[M + 1]^+$ ions could be observed where M^+ ions were absent in the EI mode <1988CPB3838>. The 3,4-dihydro-1,2,3-triazine derivatives **43**, with $R = \text{CH}(\text{Me})\text{Ph}$ and CHPh_2 , giving M^+ ions of very low intensity upon EI have been investigated by EI high-resolution mass spectrometry (HRMS), and, for $R = \text{C}(\text{Me})\text{Ph}$, also by fast atom bombardment (FAB) to allow the observation of the $[M + H]^+$ ion (100% rel. int.) and five major fragments. Compound **43**, with $R = \text{CHPh}_2$, on electrospray ionization (ESI) showed positive ions $[2M + Na]^+$, $[M + K]^+$, and $[M + Na]^+$ <2006EJO3021>.

EI MS data are also available for 2,5-dihydrotriazines **21** ($R^2 = \text{Et}$, $R^4 = \text{Me}$ or Ph , $R^{5a} = \text{various diacylmethyl or hetaryl (indol-3-yl, pyrrol-2-yl or -3-yl) residues}$) <2003S413>, as well as for **21e** ($R^4 = R^5 = R^6 = \text{CF}(\text{CF}_3)_2$, $R^{5a} = \text{H}$, $R^2 = \text{CH}(\text{Me})\text{C}(\text{Me})=\text{CH}_2$) <1990J(P1)2379>. The tetrahydrotriazin-4,5-dione **41** ($X = \text{NH-CO-CO-CH}_2\text{-CO-C}_6\text{H}_4\text{Br(4)}$) experiences fragmentation of the N(2)–N(3) and C(4)–C(5) bonds to generate the ion $[M - \text{COCHN}_2]^+$ <1995RJO1109>. M^+ ions are absent in the EI MS of 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides **45** ($R^6 = \text{Me}$ or Ph), but CI allows detection of $[M + 1]^+$ and $[(M + 1) - 16]^+$ ions, demonstrating N–O bond fission <1982H(17)317>.

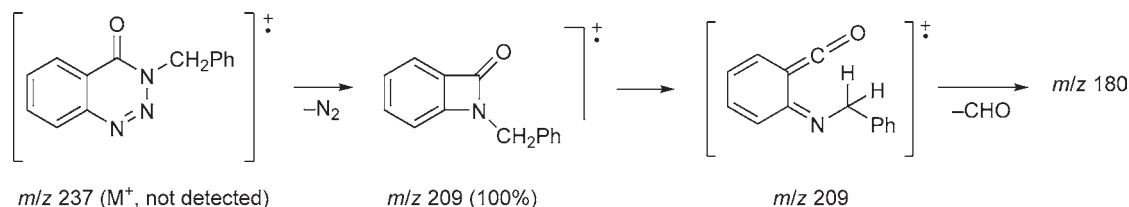
1,2,3-Triazines **30** (being in fact cyclic aliphatic triazenes) undergo facile N₂ extrusions, so that M^+ may be weak in the EI MS. While M^+ is detectable (18%) for $R = \text{Et}$ (**30a**), it is quite weak for $R = \text{Bn}$ (**30c**). Correct masses have been found for the $[M + 1]^+$ ion by FAB for **30b** ($R = \text{Bu}$) and **30d** ($R = 3,3\text{-diethoxyprop-1-yl}$) <1997JOC8660>.

1,2,3-Benzotriazines show intense parent and fragment ions corresponding to losses of N₂ and RCN <1975J(P1)31>, but M^+ and $[M - \text{N}_2]^+$ may be of medium to low intensity when a 4-(arylmethyl) group is present <1981JCM324, 1981JRM3786>. 3-Methyl-4-methylene-3,4-dihydro-1,2,3-benzotriazine is exceptional since it does not show a fragment ion corresponding to direct loss of N₂ since the base peak at m/z 130 is best explained as arising instead from the more stable 4-methylaminocinnoline ion formed from M^+ by rearrangement (Scheme 3) <1975CJC3714>.



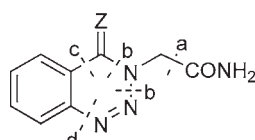
Scheme 3 Fragmentation of 3-methyl-4-methylene-3,4-dihydro-1,2,3-benzotriazine **49** in the mass spectrometer <1975CJC3714>.

As early as 1968, 3-methyl-3,4-dihydro-1,2,3-benzotriazin-4-one **19f** (and the corresponding 4-thione), as well as the isomeric 2-methyl-1,2,3-benzotriazin-4-olate (and the corresponding 4-thiolate), have been subjected to low-energy (2–4 eV) EI and electron-attachment MS (the (+)- and (–)-spectra being shown) <1968PHA629>. Subsequently, 3,4-dihydrobenzo-1,2,3-triazin-4-ones have received considerable interest. Compounds **19**, with $R^3 = \text{Me}$, Et, allyl, Pr, Pr^i , and Bn, show loss of N_2 and CHO which is explained through a ring contraction to a benzazetinone cation, followed by electrocyclic ring opening of the latter to a ketene and intramolecular transfer of hydrogen to the ketene $\text{C}=\text{O}$ group <1984OMS641>, as exemplified for $R^3 = \text{Bn}$ in **Scheme 4**.



Scheme 4 Fragmentation of 3-benzyl-3,4-dihydro-1,2,3-benzotriazin-4-one <1984OMS641>.

Positive (10–16 eV) and negative (2–4 eV) ion fragmentations have also been investigated for 4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-ylalkanoic acids of type **19** ($R^3 = \text{CH}_2\text{COOH}$, $\text{CH}(\text{Me})\text{COOH}$) <1985OMS184>. A fragmentation pattern avoiding early loss of N_2 has been suggested for 3-carbamoylmethyl-3,4-dihydro-1,2,3-benzotriazin-4-one and the corresponding imine <1996JOC210>; see **Scheme 5**.



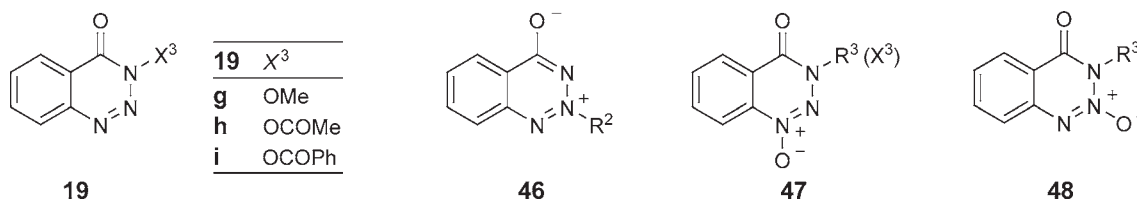
	Z = O	Z = NH	
	<i>m/z</i> (%)	<i>m/z</i> (%)	Assignment
	204 (12)	203 (10)	M^+
a	160 (100)	159 (100)	$[\text{M} - \text{CONH}_2]^+$
b	132 (57)	131 (8)	$[\text{N}_2\text{C}_6\text{H}_4\text{C}=\text{Z}]^+$
c	104 (40)	104 (60)	$[\text{C}_6\text{H}_4\text{N}_2]^+$
d	77 (100)	77 (80)	$[\text{C}_6\text{H}_5]^+$

Scheme 5 Fragmentation of 3-carbamoylmethyl-3,4-dihydro-1,2,3-benzotriazin-4-one ($\text{Z} = \text{O}$) and its corresponding imine ($\text{Z} = \text{NH}$) <1996JOC210>.

The molecular ion M^+ , $[\text{M}-28]^+$, and base peaks only, for a series of 3-alkyl-, aryl-, and methoxycarbonylalkyl-3,4-dihydro-1,2,3-benzotriazin-4-ones of type **19** (including benzo-ring-halogenated derivatives), have been published <2004JCO38>. For 6-(1-piperidinyl)-3-phenyl-3,4-dihydro-1,2,3-benzotriazin-4-one, the 12-peak EI-MS has been assigned and corroborated by HRMS determination of all exact masses <1976LA946>. (3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)benzoic acids (including benzo-ring-halogenated derivatives) show medium abundant molecular and $[\text{M}-28]^+$ ions <1986ZC166>; for similar 3-yl cyclohexane-4-carboxylic acids see <1986ZC250>.

The organophosphate pesticides Azinphos methyl and ethyl (**19b** and **19c**) have been characterized by tandem quadrupole MS/MS, aimed at developing standardized analytical techniques of high sensitivity. Daughter ion spectra of $[\text{M}+1]^+$ (reagent gas methane) and $[\text{M}-\text{R}]^-$ (negative CI with NH_3 as reagent gas) were presented <1986OMS785>.

3-Oxy-substituted 3,4-dihydro-1,2,3-benzotriazin-4-ones **19g-i** show a diversified fragmentation behavior in medium-resolution EI MS. While for **19g** the major pathway is the ring cleavage route releasing $[\text{HN}_2\text{-C}_6\text{H}_4\text{-CHO}]^+$ and competing with loss of CH_2O (from OCH_3) to generate the parent benzotriazinone with no loss of N_2 , **19h** prefers release of acetyl to generate 3-hydroxybenzo-1,2,3-triazinone **19d**, while **19i** does release N_2 , benzyloxy, benzoyl, and even CO_2 <1977CJC630>. The fragmentation pattern of **19g** has been confirmed independently <1989J(P1)543>. Reluctance to N_2 loss is evident from the MS of four 1,2,3-benzotriazin-4-one 1-oxides **47** ($R^3 = \text{Me}$, Bn, Ph, and $\text{X}^3 = \text{OCH}_3$) <1989J(P1)543> and five corresponding 2-oxides **48** <1988S517, 1988J(P1)1509>. Fragmentations of 2-aryl-1,2,3-benzotriazin-4-olates **46** have also been interpreted <1972JOC1587, 1974JOC2710>.



The triazines **38** and **39** (with annelation of the 1,2,3-triazine ring to a saturated ring) lose N_2 upon ionization <1977H(8)319, 1986H(24)907>, whereas the 2-oxide and the 1,2-dioxide of **38** are characterized by $[M-NO]^+$ and $[M-NO-N_2]^+$ ions <2000JHC1663>.

1*H*-naphtho[1,8-*de*]-1,2,3-triazines **4** and **32a** tend to form both $[M-N_2]^+$ and $[M-N_2R^1]^+$ fragment ions upon EI. This behavior resembles the fragmentation pattern of 1,2,3-benzotriazoles <1970OMS367>. A series of 2-(ethoxycarbonylalkyl)-1*H*-naphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ides **5** show some reluctance toward fragmentation since M^+ is almost invariably observed as the base peak <2000TL6665>.

9.01.4 Thermodynamic Aspects

9.01.4.1 Melting Points, Purification, Stability

Most of the compounds treated in this chapter are stable solids melting between 30 and 240 °C. Methyl- and phenyl-substituted 1,2,3-triazines are stable at room temperature, and the parent compound **1** is stable for several months under vacuum at -20 °C <1993JSP388, 1995JPH135> (see also <1997CPH(221)11>), but decomposes in strongly acidic or alkaline solution <1985JOC5520>. Most dihydro- and tetrahydro-1,2,3-triazines are oils at room temperature. Some 1,2,3-triazine 2-imines (e.g., **18d** and **18e** <1988YZ1056>) and 1,2,3-triazinium dicyanomethylides **34** decompose on melting <1992H(33)631, 1993CPB1644, 2004EJO4234>. Usually crystallization from hydrocarbon or chlorocarbon solvents, also from ethers and alcohols and mixed solvents, is successful in purification.

Volatility is sufficient for

- sublimation under reduced pressure, as in the cases of parent **1** (m.p. 69.5–71 °C <1981CC1174>, 70–71 °C <1985JOC5520>), 4-methyl-1,2,3-triazine (m.p. 31 °C <1980CC1182>, 30–31 °C <1985JOC5520>), 5-methyl-1,2,3-triazine (m.p. 67–68 °C <1985JOC5520>, 68–70 °C <1985LA1732>), all at $<10^{-4}$ Torr at room temperature; compound **43** (R = CH(Me)Ph, m.p. 88–90 °C), sublimed *in vacuo* <2006EJO3021>; 4-methyl-1,2,3-benzotriazine 2-oxide (m.p. 176–178 °C), sublimed at 0.15 Torr at 147–155 °C <1988J(P1)1509>;
- distillation at 10^{-2} Torr (2,5-dihydro-1,2,3-triazines **21m** and **21n**) <1990J(P1)2379>;
- preparative gas/liquid chromatography (G/LC) <1988T2583> for 1,2,3-triazines **17g** (b.p. 163–165 °C), **17h** (m.p. 52–53 °C), **17i** (m.p. 43–46 °C), **17k** (colorless liquid), and the 2,5-dihydro-1,2,3-triazine **21l** (yellow liquid, b.p. 195–197 °C).

Column chromatography on silica gel or neutral (or preferentially basic) alumina using all common organic solvents and solvent mixtures has proven to be successful in general, but 1,4,5,6-tetrahydro-1,2,3-triazines **11** and **30** are delicate. While the oily compounds **30** (R ≠ H) may be chromatographed on neutral or basic alumina using pentane/Et₂O/isopropylamine mixtures <1997JOC8660>, compound **11** (colorless oil) is too unstable for such treatment <1997SC1569>. Contact of 3,4-dimethyl-3,4-dihydro-1,2,3-benzotriazin-4-ol **20d** with alumina results in dehydration to 3-methyl-4-methylene-3,4-dihydro-1,2,3-benzotriazine (**49**; see Scheme 7) <1985CJC2455>. 1,2,3-Triazinium salts may be hygroscopic and not suitable for elemental analysis <2003S413>.

9.01.4.2 Protonation and Deprotonation Equilibria

For 1,2,3-triazine **1** and 1,2,3-benzotriazine **2**, N-2 as the preferred site of protonation has been predicted from theoretical investigations (see Section 9.01.2.12). The preparation of stable 4- and 5-phenyl-1,2,3-triazin-2-ium tetrafluoroborates and their spectral characterization have been described <2003S413>. Regarding the protonation of the acid-sensitive 1,4,5,6-tetrahydro-1,2,3-triazine **11**, see Section 9.01.2.15.

1-Methyl-1,4-dihydro-1,2,3-benzotriazin-4-one is a stronger base (3-protonated benzotriazinium ion: pK_a ca. 0.8) than 3-methyl-3,4-dihydro-1,2,3-benzotriazin-4-one (1-protonated benzotriazinium ion: pK_a ca. -2.7) <1988CC631>. pK_a Values have also been determined for

- 3,4-dihydro-1,2,3-benzotriazin-4-one **3**: 8.23 <1988J(P1)1509>;
- 4-oxo-3,4-dihydro-1,2,3-benzotriazine 2-oxide: 1.64; this compound is N-3-methylated by diazomethane, and the 6-nitro analogue is even more acidic (0.86) <1988J(P1)1509>;
- 4-oxo-3,4-dihydro-1,2,3-benzotriazine 1-oxide: 5.3 <1989J(P1)543>;
- 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one **19d**: 4.23 <1988J(P1)1509>; this cyclic hydroxamic acid is thus markedly more acidic than benzhydroxamic acid (8.81) <1967JIC820>.

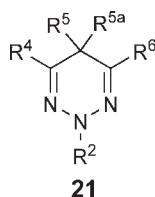
A value of 4.3 had earlier been reported for **19d** <1970CB2024>.

The acidity of **19d** and the O-nucleophilic character of its anion are regarded as crucial for active ester formation and suppression of racemization of acylated α -amino acids in peptide synthesis <1970CB2024>; see Section 9.01.12.3.

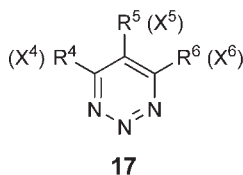
9.01.4.3 Electroreduction of 1,2,3-Triazines

Cyclic voltammograms (CVs, Hg-electrode, Ar-atmosphere, MeCN, 0.1 M Et₄NClO₄) of **17l,n,p,r,t** were scanned reductively and revealed two irreversible reduction waves, the second one being almost identical with the (single) reduction wave of the corresponding dehalogenated 1,2,3-triazines **17m,o,q,s,u**; $E_{1/2}$ (V) versus SCE are given as follows: **17l** -1.48, -1.93; **17m** -1.95; **17n** -1.55, -1.96; **17o** -1.96; **17p** -1.56, -2.01; **17q** -2.03; **17r** -1.27, -1.80; **17s** -1.82; **17t** -1.26, -1.68; **17u** -1.64. This finding is interpreted by fast dehalogenation forming the 1,2,3-triazin-5-yl-radical, which in turn picks up a hydrogen atom from the solvent. In the backward positive scans of **17l,n,p,r**, the oxidation of bromide was noted, which supports the rationale given <1991T4317>.

The CVs (Pt-electrode, MeCN, Bu₄NBF₄) of 3,4,5,6-tetrahydrotriazin-2-yl salts **31a** and **31c-e** show a partly irreversible reduction wave at 20 mV s⁻¹ - 2.0 V s⁻¹ scan speed and turn into a reversible reduction to the radicals at 20 V s⁻¹, $E_{1/2}$ (V) versus Ag/AgCl = -0.826 **31a**, -0.788 **31c**, -0.844 **31d**, -0.561 **31e**. A plot of the sums of the Hammett σ_p constants versus the reduction potentials shows a linear correlation <1980LA285>.

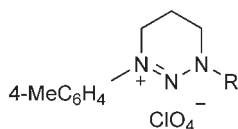


	R^2	R^4, R^5, R^6	R^{5a}
m	CH(Me)-C(Me)=CH ₂	CF(CF ₃) ₂	H
n	C(Me) ₂ -C(Me)=CH ₂	CF(CF ₃) ₂	H



	R^4 (X^4)	R^5 (X^5)	R^6 (X^6)
g	CF(CF ₃) ₂	CF(CF ₃) ₂	CF(CF ₃) ₂
h	CF(CF ₃) ₂	F	CF(CF ₃) ₂
i	F	Cl	F
k	F	F	F
l	Me	Br	Me
m	Me	H	Me
n	Et	Br	Me

	R^4	R^5 (X^5)	R^6
o	Et	H	Me
p	Et	Br	Et
q	Et	H	Et
r	Me	Br	Ph
s	Me	H	Ph
t	Ph	Cl	Ph
u	Ph	H	Ph

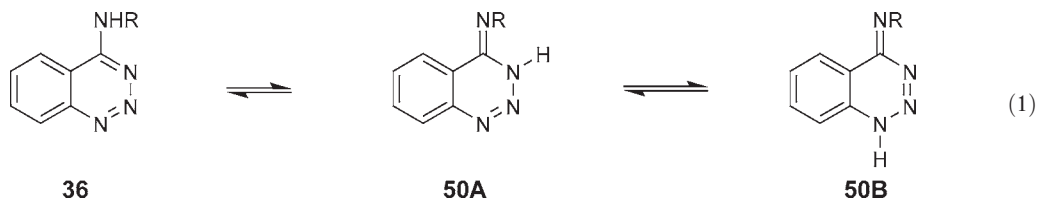


31	R
a	4-Me-C ₆ H ₄
c	Ph
d	4-MeOC ₆ H ₄
e	4-O ₂ N-C ₆ H ₄

9.01.4.4 Prototropy

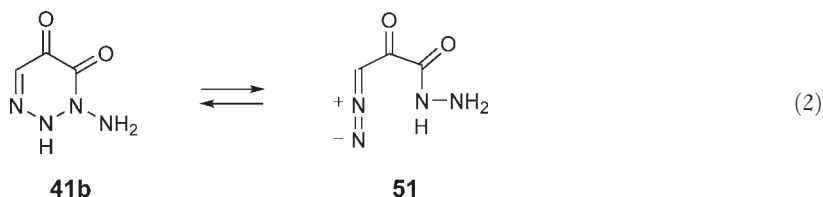
Similar to the case of compound **3**, which exists solely as the oxo tautomer <B-1976MI141>, 5-hydroxy-1,2,3-triazines <1991T4317> are in fact 2,5-dihydro-1,2,3-triazin-5-ones, as derived from their ^1H and ^{13}C NMR data.

4-Alkylamino- and 4-arylamino-1,2,3-benzotriazines may exist in any of the tautomeric forms **36**, **50A**, and **50B** (Equation 1) <1984JCM62>. The IR spectra show that in the solid state the 4-methoxybenzyl compound exists in the amino form **36** and compounds with $\text{R} = n\text{-Bu}$, $(\text{CH}_2)_2\text{NEt}_2$, and 4-chlorobenzyl in the imine form **50A**; in solution, all the UV spectra are nearly identical <1969JHC779>. Examination of the ^1H and ^{15}N NMR spectra shows that in solution the compounds with $\text{R} = n\text{-Bu}$, $(\text{CH}_2)_2\text{OMe}$, pyrid-2- (or-3-)ylmethyl, and 4-tolyl exist in the amino form **36** <1984JCM62>. Isomers of type **36** and **50A** may be distinguished by their UV, IR, and ^1H NMR spectra <1970JC765>.

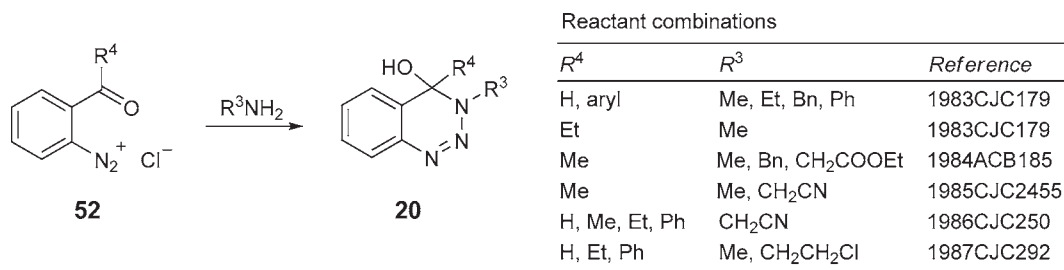


9.01.4.5 Ring-Chain Tautomerism

While the IR spectrum of crystalline dione **41b** does not show any absorption of a diazo group, but the IR spectrum of a solution of **41b** in dioxane indicates the presence of such a group, an equilibrium with **51** (Equation 2) must exist in solution. A ^1H NMR investigation (in $\text{DMSO}-d_6$) reveals the initial presence of both forms, giving way to the sole existence of the open form **51** upon prolonged storage of the solution <1993RJO1928>. Compound **41a** ($\text{R} = \text{Bn}$) does not undergo this ring opening <1995RJO1005>.



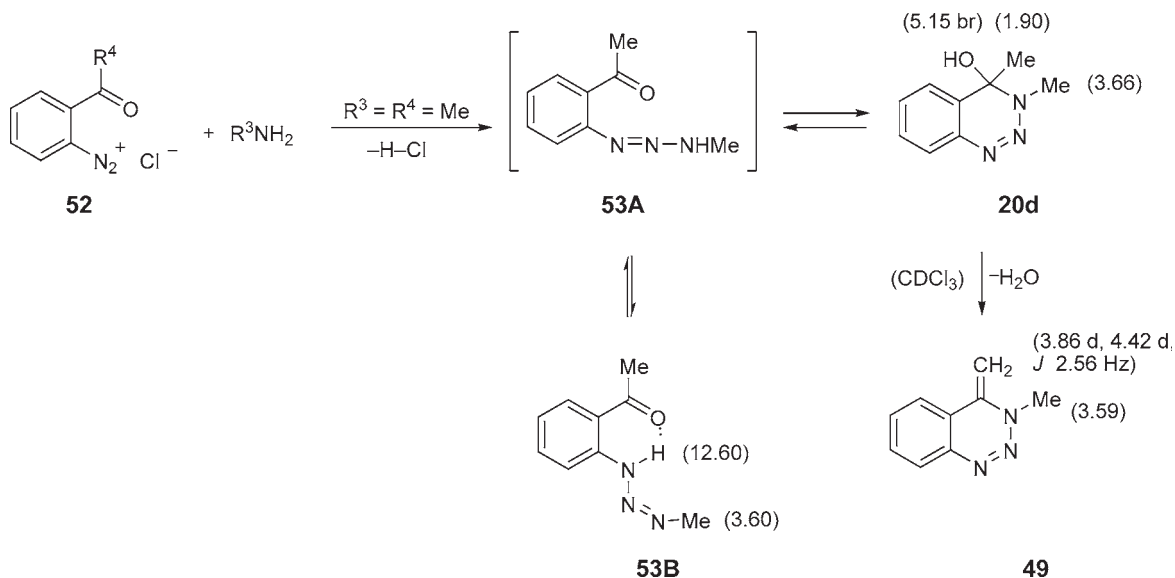
3,4-Dihydro-1,2,3-benzotriazin-4-ols **20** are formed from 2-acylbenzenediazonium chlorides **52** and primary aliphatic amines; see Scheme 6 for the scope of this transformation and relevant references.



Scheme 6 Formation of 3-substituted-3,4-dihydro-1,2,3-benzotriazin-4-ols **20**.

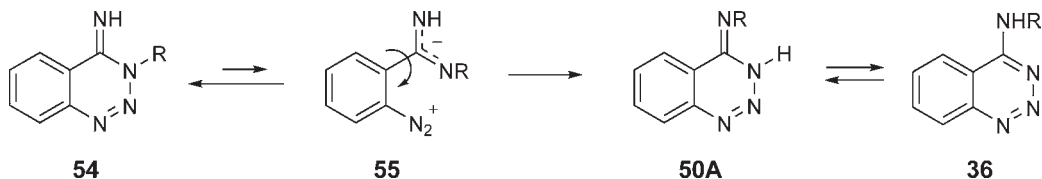
Compounds **20** are in equilibrium with the isomeric 1-(2-acylphenyl)-3-alkyltriazenes **53A** and **53B**, as outlined in Scheme 7 for compound **20d**. The triazene **53** is assumed to be formed first, followed by its reversible ring closure to **20d**. The latter represents an interesting class of moderately stable carbinolamines, which are stable in the solid state and in $\text{DMSO}-d_6$ <1984ACB185, 1986CJC250, 1987CJC292>, while the open triazene **53** is present together with

the ring-closed tautomer **20d** in CDCl_3 . From ^1H NMR data, the 3-aryl tautomer **53B**, favored by an intramolecular hydrogen bond, is regarded as the preferred triazene tautomer in CDCl_3 solution <1985CJC2455>. Facile dehydration of **20d**, which does not require special acidification, to the methylene compound (here **49**) is a complication <1975CJC3714, 1984ACB185, 1985CJC2455, 1987CJC292>. Structure **20** may be fixed by replacement of 4-OH by 4-OMe <1987CJC292>.



Scheme 7 Formation, ring-chain tautomerism, and dehydration of 3,4-dimethyl-3,4-dihydro-1,2,3-benzotriazin-4-ol **20d**. Characteristic ^1H chemical shifts δ_{H} (ppm) in CDCl_3 are given in parentheses.

3-Substituted-3,4-dihydro-1,2,3-benzotriazin-4-imines **54** ($\text{R} = \text{Bn}, \text{Ar}$), prepared by spontaneous cyclization of 3-aryl- (or benzyl-) 1-(2-cyanophenyl)-triazenes in boiling ethanol, rearrange in boiling acetic acid to the isomeric 4-amino-1,2,3-benzotriazines **36** (Scheme 8) <1974J(P1)609, 1995JME3482>. Rearrangement of 3-aryl-3,4-dihydro-1,2,3-benzotriazin-4-imines to the corresponding 4-anilino-1,2,3-benzotriazines in ethanol or 2 N HCl is facilitated by electron-withdrawing substituents in the aryl group <1970JC765>, but 3-(carbamoylmethyl)-3,4-dihydro-1,2,3-benzotriazin-4-imine does not rearrange in refluxing ethanol or on contact with alumina to the corresponding 4-alkylaminobenzotriazine **36** <1996JOC210>.



Scheme 8 Isomerization of 3-substituted-3,4-dihydro-1,2,3-benzotriazin-4-imines **54** to 4-(substituted amino)-1,2,3-benzotriazines **36** ($\text{R} = \text{Bn}, \text{Ar}$) in boiling acetic acid.

The successful transformations are best explained by ring opening of **54** to a diazonium-amidine zwitterion **55** <1974J(P1)609>, which undergoes recyclization at the (ambident) amidine anion moiety to generate compounds **36** via **50A** and prototropy. Support for this rationale comes from experiments to trap **55** by azo coupling with 2-naphthol <1970JC765>.

9.01.4.6 Energetic Aspects, Aromaticity Criteria

Because of intense theoretical work in this area, dynamic aspects of structure such as rotational barriers of methyl substituents and deviations from planarity have been treated in [Section 9.01.2.1](#). For the same reason, calculated heats of formation, total energies, resonance energies, aspects of delocalization and conjugation, homodesmotic stabilization energies, electron distribution, polarizability and magnetic and bond-order-based aromaticity indexes have been discussed in [Section 9.01.2.8](#). Complexation of the parent **1** by water has also been considered ([Section 9.01.2.12](#)).

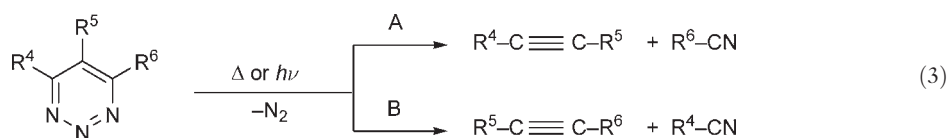
9.01.5 Reactivity of Fully Conjugated Rings

For the reasons given in the introduction, 3,4-dihydro-1,2,3-benzotriazin-4-ones, named also 1,2,3-benzotriazin-4(3*H*)-ones in the literature, and analogous compounds have been included in this section.

9.01.5.1 Unimolecular Thermal and Photochemical Reactions

In thermal degradations, product distributions and degradation pathways depend on the way thermal activation is applied. While at low pressures and elevated temperatures in the vapor phase relatively clean unimolecular decompositions dominate, heating a solid or a liquid, either neat or in the presence of a mediator or trapping reagents for any intermediates expected, may lead to a plethora of products, including some being formed from more than one molecule of starting material.

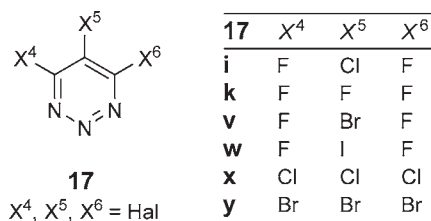
Work prior to 1995, predominately treating 1,2,3-benzotriazines and 3,4-dihydro-1,2,3-benzotriazin-4-ones and only to a smaller extent monocyclic 1,2,3-triazines, has been reviewed amply in CHEC(1984) and CHEC-II(1996) <1984CHEC(3)369 and 1996CHEC-II(6)483>. Investigation of both thermolysis and photolysis of 1,2,3-triazines has been intriguing because of their inherent capability for nitrogen extrusion whereby stable or elusive four-membered ring systems (azetes, azetines, azetinones, and their benzo analogues) could be expected or at least follow-up products thereof could be isolated. From the earlier reviews in CHEC(1984) and CHEC-II(1996) it could be taken that 1,2,3-triazines **17**, both in vapor-phase pyrolysis and in solution photolysis, may be fragmented into alkynes, nitriles, and N₂ ([Equation 3](#)); see also [Sections 9.01.2.10 and 9.01.3.7](#). In pyrolysis, the preferred mode of fragmentation (A or B) in the case of unsymmetrical substitution (R⁴ ≠ R⁶) is dependent on the nature of substituents R⁴, R⁵, and R⁶, and, thus, on the relative stability of the products, whereas in photolysis an almost equal partitioning between the two modes seems to prevail <1977H(8)319>.



Azetes may occur as intermediates in these fragmentations, but only one sufficiently stable azete has been isolated from a 1,2,3-triazine flash vacuum pyrolysis (FVP), namely from that of 4,5,6-tris(dimethylamino)-1,2,3-triazine **17e** <1973AGE847>, while two other stable azetes have been obtained from the attempted preparation of 1,2,3-triazines by pyrolysis of azidocyclopropanes <1986AGE842, 1988AGE1559>. While 2-phenylbenzazete is stable up to −40 °C <1975J(P1)45>, but dimerizes on warming <1973CC19>, 2-phenylnaphth[2,3-*b*]azete is stable at room temperature <1975J(P1)45>. 3-(1-Adamantyl)-3,4-dihydro-1,2,3-benzotriazin-4-one gave the isolable 1-(1-adamantyl)-benzazetine-2-one and minor amounts of biphenylene and 1-adamantylisocyanate upon FVP <1973J(P1)868>. Analogous benzazetinones, however, could not be detected in the thermolyses of other 3,4-dihydro-1,2,3-benzotriazin-4-ones but were detected spectroscopically in photolysates in some cases <1966TL93, 1968CB3079>. In general, 3,4-dihydro-1,2,3-benzotriazin-4-ones do release N₂ in both thermolysis and photolysis, but the structure of the products depends much on the nature of the 3-substituents <1984CHEC(3)369>. The aforementioned comprehensive treatments will here be supplemented with a few remarks on earlier work, including cases hitherto not reviewed, together with reports on the progress made since 1995.

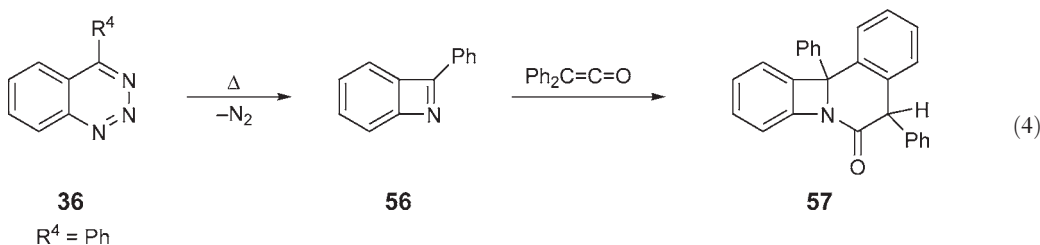
The vapor-phase pyrolysis of 4,5,6-triphenyl-1,2,3-triazine (**17z**, see Equation 10) is hampered by its very low volatility. The sublimation temperature required at 10^{-3} Torr is 240 °C, which causes marked decomposition during the sublimation. Pyrolysis of the vapor below 400 °C led to a recovery of 70% of the starting material, at 420 °C to 16% of the starting material and 40% of diphenylacetylene, while at 460 °C the alkyne was the only product isolated <1975J(P1)45>. The more volatile 4,5,6-tri-*tert*-butyl-1,2,3-triazine is more readily subjected to simple thermolysis (130 °C) and FVP (700 °C, 10^{-6} mbar), generating di-*tert*-butylethyne and pivalonitrile <1986AGE842>. 4,6-Diphenyl-5-(4-methoxyphenyl)-1,2,3-triazine has been converted to (4-methoxyphenyl)phenylethyne at 625 °C/ 10^{-2} Torr <1981JCM162>. Beyond the preparation of two perfluoroalkynes, namely perfluoro-3-methyl-1-butyne from perfluoro-4,6-diisopropyl-1,2,3-triazine (600 °C, 10^{-2} Torr) <1989CC1657> and difluoroethyne from 4,5,6-trifluoro-1,2,3-triazine (**17k**, 700 °C, 0.02–0.1 mbar) <1991CC456>, application of 700 °C at 10^{-3} mbar on the triazines **17i**, **k**, **v**–**y** shows the preparative utility of this fragmentation as follows:

- **17i** → Cl–C≡C–F + FCN + N₂ <1995MI282>,
- **17k** → F–C≡C–F + FCN + N₂ <1998TH1>,
- **17v** → Br–C≡C–F + FCN + N₂ <1999SAA695, 1998TH1>,
- **17w** → N≡C–C≡C–F + N₂ (IF not detected) <1998TH1>,
- **17x** → Cl–C≡C–Cl + ClCN + N₂ <1998TH1>,
- **17y** → N≡C–C≡C–Br + Br₂ + N₂ <1998TH1>.

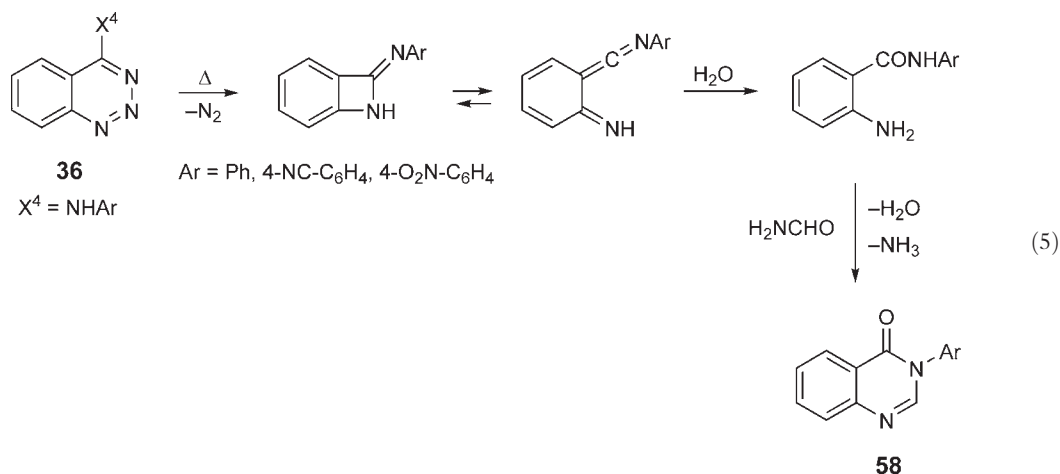


Cases **17w** and **17y** demonstrate that (probably at lower C–Hal bond energies) another fragmentation option may take place, leaving all three carbon atoms of the triazine nucleus in one chain under additional elimination of halogen (e.g., Br₂).

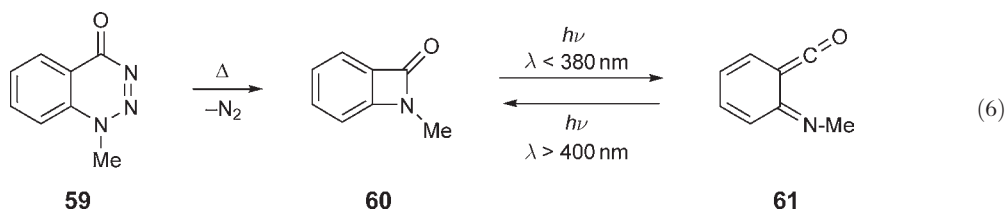
In addition to the examples of 1,2,3-benzotriazine thermolysis reviewed earlier, the following cases are noteworthy: ring contraction by loss of N₂ transforms 4-phenyl-1,2,3-benzotriazine (**36**; R⁴ = Ph) into 2-phenylbenzazete **56**, which is allowed to react with diphenylketene in a formal [4+2] cycloaddition (probably stepwise) followed by a hydrogen shift to generate the tetracyclic lactam **57** (Equation 4) <1976CC125>.



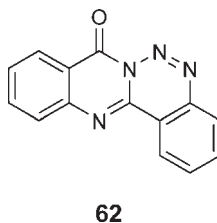
4-Arylamino-1,2,3-benzotriazines **36** (R⁴ = NHAr) (and their potential precursors of type **54** analogous to those shown in Scheme 8; see Section 9.01.4.5) have been heated in moist formamide to form 3-aryl-3,4-dihydroquinazolin-4-ones **58**. The latter are rationalized to occur via a benzazetiminine and a ketenimine, which hydrolyzes to an anthranilamide. The latter reacts with formamide to undergo ring closure to **58** (Equation 5) <1984J(P1)2765>.

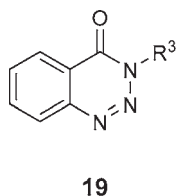


The thermal decomposition of solid 1-methyl-1,4-dihydro-1,2,3-benzotriazin-4-one **59** at $>120^\circ\text{C}$ in a stream of argon results in ready loss of N_2 with ring contraction to the benzazetinone **60** (Equation 6), which was identified by matrix isolation at 15 K (IR: $\text{C}=\text{O}$ at 1843 cm^{-1}). Irradiation of **60** results in photoreversible ring opening to the iminoketene **61**, characterized by an IR band at 2125 cm^{-1} and a UV absorption centered at 420 nm <1989CC1777>.

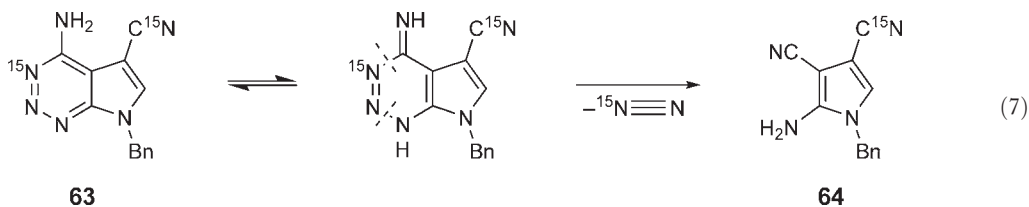


The triazine polar reactivity of 3,4-dihydro-1,2,3-benzotriazin-4-ones (i.e., cleavage of the N(2)–N(3) bond, generating a diazonium function and an anionic center at the former N-3 position) has been demonstrated by many examples, among them early reports of azo couplings with functionalized 2-naphthols <1966AGE675> and Japp–Klingemann-type reactions of **3**, several 3-aryl-3,4-dihydro-1,2,3-benzotriazin-4-ones, and the tetracyclic benzotriazine derivative **62** with methylene-active esters. For example, 3-(4-cyanophenyl)-3,4-dihydro-1,2,3-benzotriazin-4-one **19m** reacts with ethyl cyanoacetate to give 2-[2-(4-cyanophenylaminocarbonyl)phenylhydrazono]cyanoacetate <1974J(P1)2482>. There may, however, be exceptions to this commonly accepted rationale. Pyrolysis of the benzotriazine-analogous 4-amino-7-benzylpyrrolo[2,3-*d*]-1,2,3-triazin-5-carbonitrile **63** (neat at 250°C under Ar) releases N_2 with formation of 2-amino-1-benzylpyrrole-3,5-dicarbonitrile **64**. ^{15}N labeling confirmed the loss of N-2 and N-3 (not N-1 and N-2; Equation (7) <1999OL537>).

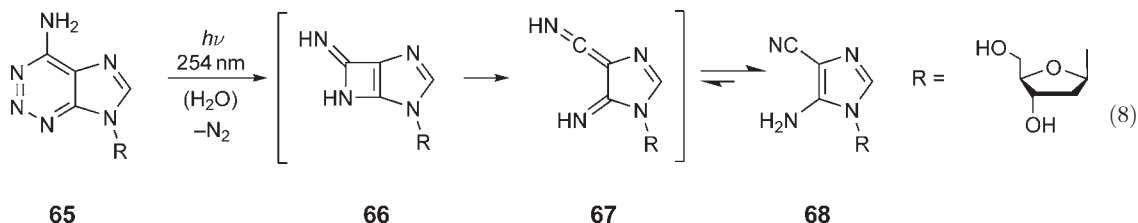




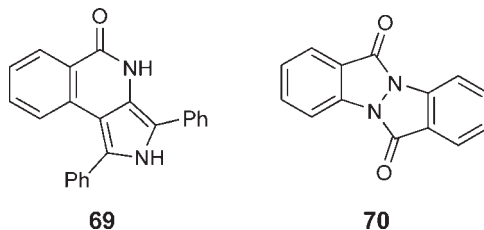
19	R^3
j	2,5-Diphenylpyrrol-3-yl
k	2-Azidobenzoyl
l	4-(Dimethylamino)phenyl
m	4-NC-C ₆ H ₄
n	Ph



A photochemical equivalent of this type of fragmentation may be seen in the photolysis of 2-aza-2'-deoxyadenosine **65**, generating 5-amino-4-cyano-1-imidazolyl-2-deoxy-β-D-ribofuranoside **68**. The authors consider two plausible intermediates, namely **66** and **67** (Equation 8). The structure of **68** was confirmed by independent synthesis <1991LA695>.

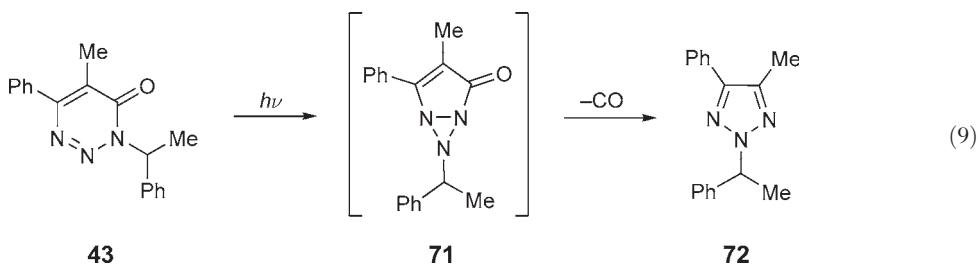


Pyrolysis of suitably 3-substituted benzotriazinones **19** provides access to various fused heterocycles. Thus, pyrolysis of **19j** at 250 °C gives 1,3-diphenyl-2*H*-pyrrolo[3,4-*c*]isoquinolin-5-one **69** <1992JHC1309>, and a multistep sequence transforms **19k** into the dione **70** <1982JCM295>.



In addition to the examples of photochemical reactivity reviewed in CHEC(1984) and CHEC-II(1996), the following cases deserve attention.

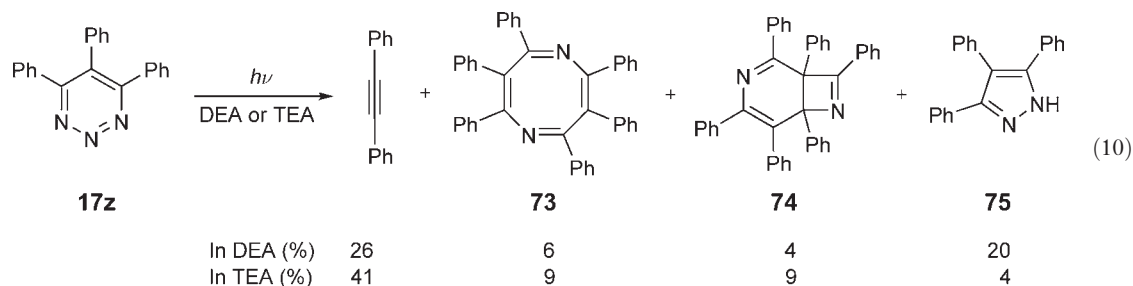
Irradiation (254 nm, Et₂O) of **43** (R = Ph(Me)CH) does not effect loss of N₂ but extrusion of CO from a proposed intermediate **71**, giving rise to the 1,2,3-triazole **72** (Equation 9) <2006EJO3021>. This behavior is completely different from that of the analogous benzo-fused dihydro-1,2,3-triazinones.



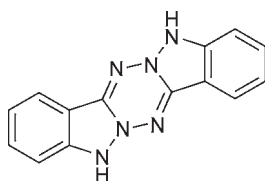
Earlier investigations showed that the photolysis of trimethyl-1,2,3-triazine in benzene and dichloromethane gave an almost quantitative yield of acetonitrile and 2-butyne <1972JOC1051> and that triphenyl-1,2,3-triazine **17z** was fragmented to diphenylethyne and benzonitrile, with some 2,3-diphenylquinoline and hexaphenyl-1,5-diazocine, indicating the intermediacy of triphenylazete <1974JOC940>. Azete intermediates have also been proposed in the photolyses of trifluoro-1,2,3-triazine **17k** and perfluoro-4,6-diisopropyl-1,2,3-triazine **17h** <1990J(P1)983>. This pattern may, however, not be general, as demonstrated by a detailed study of the photoreactivity of the parent compound **1** <1995JPH135>. Its photolysis was investigated in methanol and hexane solution (both degassed and undegassed) within the wavelength range 230–390 nm at 20 nm intervals at a 6 nm band pass and at 295 ± 2 K. The progress was followed by monitoring the UV absorption of the solution under irradiation; products were identified by freezing the photolysate in liquid nitrogen, degassing, warming to -80°C , and the gases evolving at that temperature were identified by Fourier transform infrared (FTIR) spectroscopy. Vapor-phase photolysis was carried out at a constant pressure of the vapor in equilibrium with the solid at a constant wavelength of 288 nm, and both ethyne and HCN were identified by IR. A plot of ethyne concentration versus irradiation time was linear. From solution photolyses, however, only ethyne could be identified as a product but not quantitatively determined. Lack of detection of HCN may be due to its low vapor pressure (<1 Torr) at -80°C . In general, the photolyses were not much influenced by either the choice of solvent or degassing, but the water content of moist hexane caused the simultaneous presence of both anhydrous and hydrogen-bonded **1** with different spectral properties (see Section 9.01.2.5) and photoreactivity. Thus, the quantum yield of degradation of **1** at 290 nm was 1.91 for the hydrogen-bonded species and 0.70 for the anhydrous form.

At least for the vapor-phase photolysis of **1**, the results are consistent with the fragmentation of **1** generating N_2 and leading to either a 1,4-diradical or azete, the latter in turn decomposing to ethyne and HCN, while azete could also be formed from the valence isomer **14** (see Section 9.01.2.16) obtained from **1** initially. In solution photolyses, the lack of effect of degassing contradicts the importance of a 1,4-diradical, and the absence of any products attributable to transformation of azete in the photolysates does not give support to its intermediacy <1995JPH135>. Accordingly, most likely there may be more pathways of 1,2,3-triazine photodecomposition beyond the generally accepted one (generating alkynes, nitriles, and N_2), which is also operative in FVT and MS (see Section 9.01.2.10).

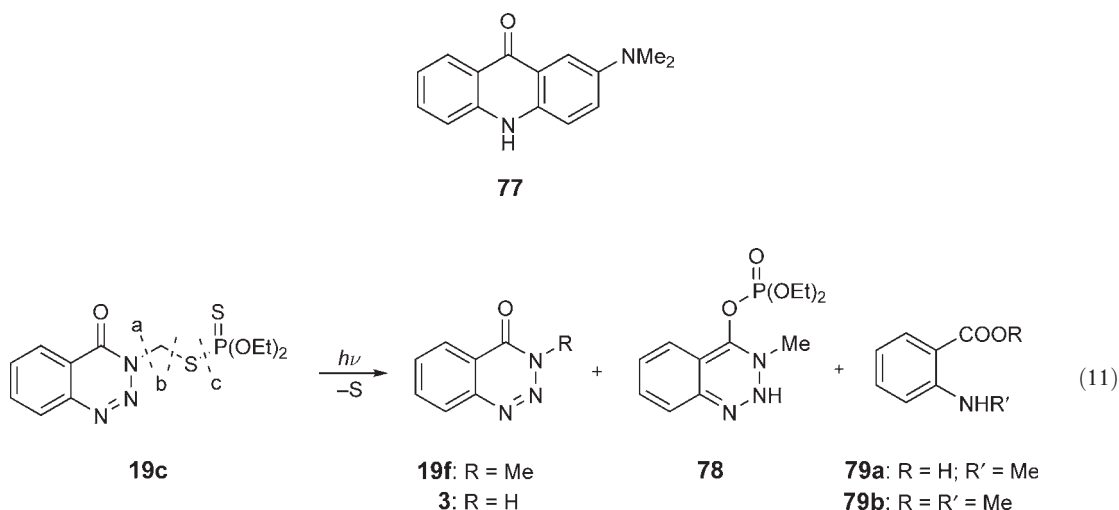
Photolysis of triphenyl-1,2,3-triazine **17z** in diethylamine (DEA) and triethylamine (TEA) as solvents gives diphenylethyne as the main product and the diazocine **73**, its valence isomer 1,2,4,5,6,8-hexaphenyl-3,7-diazabicyclo[4.2.0]octa-2,4,7-triene **74**, and a product of reductive ring contraction of **17z**, namely the 3,4,5-triphenylpyrazole **75**, as minor products (Equation 10). To generate **75**, the amine has to act as a sacrificial donor on the excited triazine and it is proposed that, after a series of consecutive electron and proton transfers (totalling four reduction equivalents), contraction of the six- to the five-membered ring occurs with release of ammonia <2002TH1>.



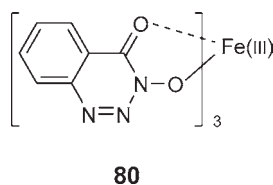
Irradiation of matrix isolated (Ar, 10 K) 1,2,3-benzotriazine **2** generated a single product which was assigned as benzazete on the basis of its IR absorptions in comparison with a calculated spectrum <1999JA10563>. From the older literature, the finding that 3-azido-1,2,3-benzotriazine forms 1,2,4,5-tetrazino[2,3-*b*:5,6-*b'*]diindazole **76** upon irradiation should be mentioned <1971JHC785>.

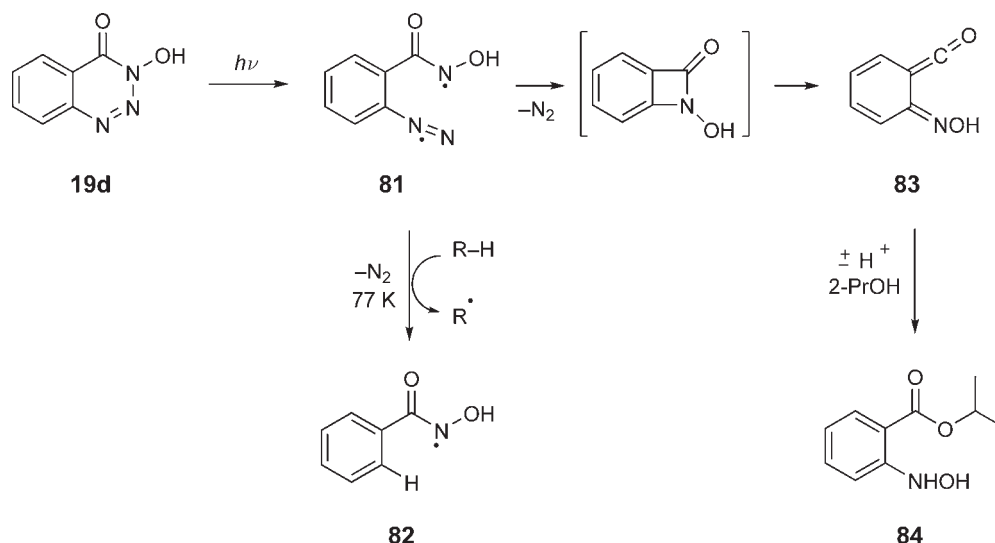


The loss of N-1 and N-2 as N₂ in the photolysis of 3-phenyl-3,4-dihydro-1,2,3-benzotriazin-4-one **19n** has been documented earlier in an N-3-¹⁵N labeling experiment <1968CB3089>, and the results of photolysis of 3-(lithio-*p*-tosylamino)-3,4-dihydro-1,2,3-benzotriazin-4-one <1969CC220> have been revised and reinterpreted. It was suggested that the usual N(2)–N(3) bond heterolysis is followed by release of N₂, and the resultant intermediacy of a benzazetinone in equilibrium with a ketene accounts well for the products observed <1988JOC208>. In addition to the cases reviewed previously, the photodegradation of 2-dimethylaminoacridone **77** from **19l** should be mentioned <1982CPB1980>. In view of the noted stability of 3-alkyl-1,2,3-benzotriazin-4-ones against UV light <1971JC2317, 1973J(P1)868>, the photodegradation of azinphos ethyl **19c** in chloroform (77% conversion) and methanol (85% conversion) is of interest. Both the benzotriazine ring and the side-chain function are involved in several modes of degradation (Equation 11), giving (yields (%)) for chloroform/methanol in brackets) products **3** (28/33), **19f** (17/22), **78** (8/11), **79a** (5/–), **79b** (–/7), and sulfur (–/38). Compounds **3**, **19f**, **79a** and **79b** were identified by comparison with authentic samples. The following may be proposed: compound **3** originates from N(3)–C cleavage (a) and H-abstraction from a donor R–H, **19f** from C–S fission (b) and H-abstraction, **78** from sulfur release (c), hydrolysis of the thiophosphate group to a phosphate group, and transfer of the diethylphosphoryl group to the triazinone oxygen, and **79** by degradation of the benzotriazinone moiety to the corresponding benzazetinone (and/or iminoketene) followed by hydrolysis or methanolysis of the latter <1987ZNB907>. For a similar investigation on the photodegradation of azinphos methyl **19b**, see <2007MI99>.



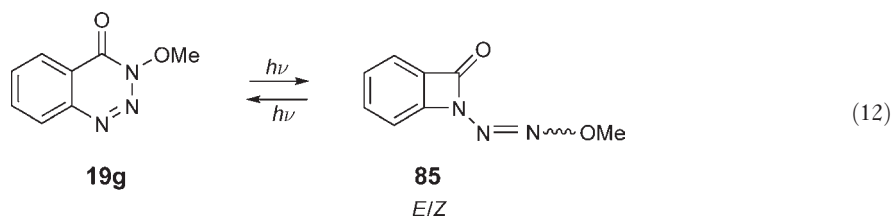
Tris[3-oxy-3,4-dihydro-1,2,3-benzotriazin-4-one]iron(III) **80** may undergo a ligand-centered excitation at 300 nm and two LMCT transitions at 340 and 425 nm (see also Table 10, Section 9.01.3). The ligand-centered state is also reached by direct irradiation (≥ 345 nm) of free **19d**. Irradiation (≥ 345 nm) of 0.1 M solutions of **80** in acetonitrile under anaerobic conditions results in a rapid first-order photobleaching with partial recovery of the complex when air is admitted to the photolysate, showing release of Fe(II) into the solution. Irradiation at 455 nm shows the same effect but with a rate reduced by a factor of 20. As determined by head-space GC–MS, at the latter wavelength less than 10% of the nitrogen is released compared to the amount liberated at 345 nm excitation. The ligand radical species produced upon LMCT excitation is of interest as an effective DNA-cleaving agent <2000CC69>. Upon 345 nm excitation of **19d** in an ethanol glass at 4 K, electron paramagnetic resonance (EPR) reveals the formation of a diradical **81** ($S=1$) which releases N₂ and partitions between pickup of a H-atom from the matrix to generate species **82** and building up the hydroxylimino ketene **83**, which in solution photolysis at 355 nm may add a solvent molecule to generate, for example, the ester **84** (Scheme 9) <2001NJC1281>.





Scheme 9 Proposed photoreaction of **19d** both in a glassy matrix (≤ 77 K) and in solution (298 K).

Under matrix isolation, liberation of N_2 from 3,4-dihydro-1,2,3-benzotriazin-4-ones is not the only process that may be observed. Irradiation of 3-methoxy-3,4-dihydro-1,2,3-benzotriazin-4-one **19g** (Ar matrix, 10 K, ≥ 300 nm) resulted in photoreversible formation of (*E/Z*)-benzazetines **85** (photo-interconvertible), while there was no firm indication of a ketene intermediate. Thus, a 1,3-sigmatropic shift of the $C=O$ group from N-3 to N-1 was proposed (Equation 12). A similar reaction was observed for the 3-butoxy- but not for the 3-methylbenzotriazinone **19f** <1992CL361>.

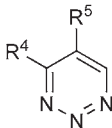
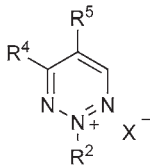


9.01.5.2 Reactions with Electrophiles at Nitrogen

In general, protonation of 1,2,3-triazines is hampered by their electron-poor nature and thus low basicity. Electron-donating substituents such as dialkylamino groups support protonation at ring nitrogens, usually at N-2. Thus, the tetrafluoroborate salt of 5-chloro-4,6-bis(dimethylamino)-1,2,3-triazine was isolated ca. 30 years ago <1979CB1535>. A point of concern is the limited stability of some 1,2,3-triazinium salts under the conditions of their preparation. Any potent nucleophile present may add to the ring and thus initiate ring opening. Steric reasons also play a role; thus, while 5-chloro 4,6-bis(dimethylamino)-1,2,3-triazinium is stable, tris(diisopropylamino)-1,2,3-triazine experiences rearrangement to an imidazolium structure upon reaction with tetrafluoroboric acid <1979CB1535>.

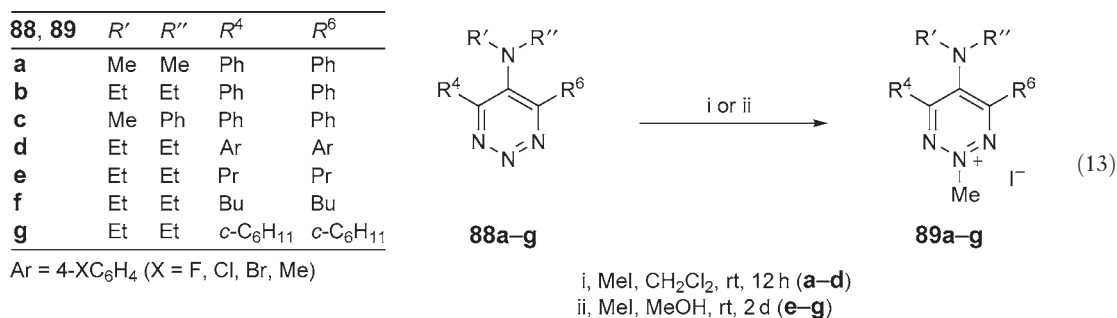
Previously, it had been surmised that protonation of ring N-atoms in alkyl- and/or aryl-substituted monocyclic 1,2,3-triazines did not occur due to their presumed low basicity. However, recently it was shown that treatment of 4- and 5-phenyl-1,2,3-triazine (**86a** and **86b**), with tetrafluoroboric acid in ether solution at 0 °C gave stable triazinium tetrafluoroborates **87a** and **87b**, while 4- and 5-methyl-1,2,3-triazine (**86c** and **86d**) decomposed under the same conditions <2003S413>. The site of protonation was assumed to be N-2 by analogy to ethylation and by

identification of the N-2-protonated species as the thermodynamically most stable example by *ab initio* calculations (see Section 9.01.2.12). However, it should be noted that in the case of **86a** the N-1-protonated species is predicted to be of comparable energy <2003S413>.

86	R^4	R^5		<i>Triazine 86</i>	<i>Reagents, conditions</i>	<i>Product 87</i>	R^2	R^4	R^5	X	<i>Yield (%)</i>	
a	Ph	H		a	HB F_4 , Et $_2$ O, CHCl $_3$	a	H	Ph	H	BF $_4$	92	
b	H	Ph		b	0 °C	b	H	H	Ph	BF $_4$	88	
c	Me	H		a	Et $_3$ O $^+$ BF $_4^-$, CHCl $_3$	c	Et	Ph	H	BF $_4$	95	
d	H	Me		b	0 °C $\rightarrow$ -20 °C, 3 d	d	Et	H	Ph	BF $_4$	98	
				c	Et $_3$ O $^+$ PF $_6^-$, CH $_2$ Cl $_2$	e	Et	Me	H	PF $_6$	56	
				d	0 °C $\rightarrow$ -20 °C, 3 d	f	Et	H	Me	PF $_6$	57	
				a	Ph $_2$ I $^+$ PF $_6^-$, CH $_2$ Cl $_2$	g	Ph	Ph	H	PF $_6$	68	
				b	10 mol% CuI,	h	Ph	H	Ph	PF $_6$	29	
				c	Ambient temp., 3 d	i	Ph	Me	H	PF $_6$	43	
87a-j				d		j	Ph	H	Me	PF $_6$	26	

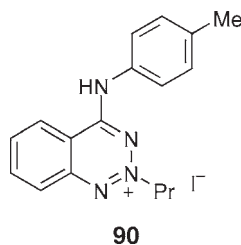
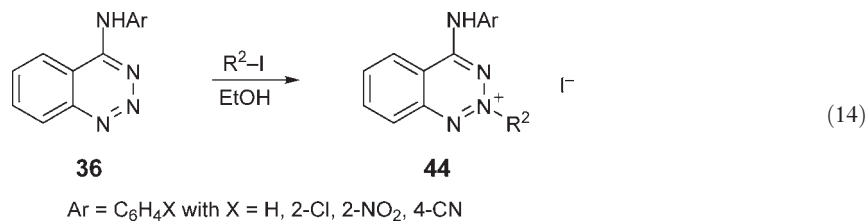
Besides the ring-substitution pattern in the triazine, in alkylations using reagents R-X, the nature of the leaving group X may be critical. Both ethyl iodide and 1-chloroethyl chloroformate failed to alkylate the monosubstituted 1,2,3-triazines **86a-d**, even though the former had been successful in the N-2 methylation of 4,6-dimethyl-1,2,3-triazine. Dimethyl sulfate did not methylate the parent 1,2,3-triazine **1** <1992H(33)631> though both methylation and ethylation worked well with the corresponding trialkyloxonium tetrafluoroborates or hexafluorophosphates <2003S413>. Triethyloxonium tetrafluoroborate had been used previously with 1,2,3-benzotriazin-4(3H)-one to give a 3:1 ratio of N-3 versus O-ethylation <1971JHC785>. 2-Ethyl-1,2,3-triazinium salts **87c-f** (structures supported by { ^{15}N , ^1H }HMBC (heteronuclear multiple bond correlation) NMR and a lack of dinitrogen liberation in EI (MS) are stable under argon at 0 °C for only a few days. N-2-Phenylated 1,2,3-triazinium hexafluorophosphates **87g-j**, obtained by treatment of **86a-d** with diphenyliodonium hexafluorophosphate, are stable under argon for several months <2003S413>.

In contrast, when the triazine is electron rich, as in **88a-g**, stable 2-methyltriazinium iodides **89a-c** <1985BCJ1073>, **89d** <2002HCO325>, and **89e-g** <2003H(59)477> (Equation 13) are formed.

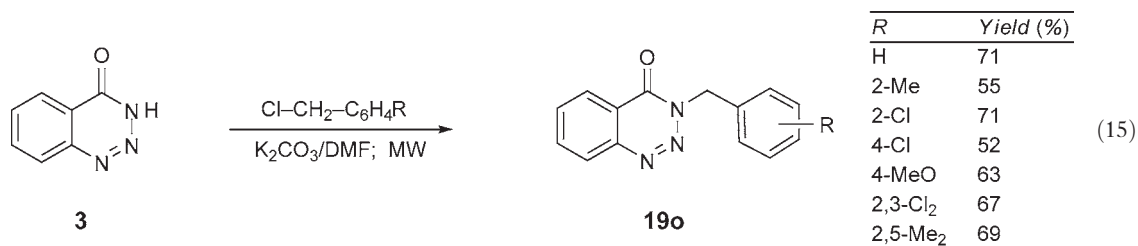


It had become known as early as 1970 that alkylation of 4-anilino-1,2,3-benzotriazines **36** ($X^4 = \text{NHAr}$) with alkyl iodides in refluxing ethanol affords 2-alkyl-4-anilino-1,2,3-benzotriazinium iodides **44** ($X^4 = \text{NHAr}$) <1970JC2289>. Related N-2 quaternary salts like **90** became of interest because of their quinidine like antiarrhythmic activity (Equation 14) <1980MI154, 1986EJM87>. Thus, the anilino group at C-4 fosters successful alkylation at N-2.

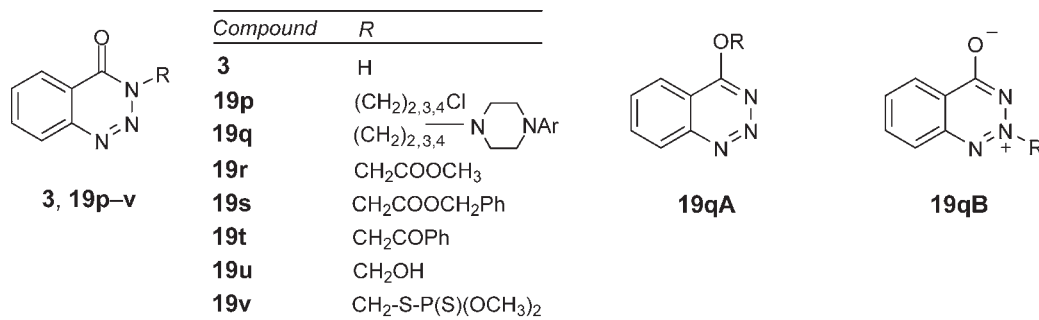
However, 1,2,3-benzotriazines bearing various benzyl groups <1981JCM324, 1981JRM3786> or various hydroxylated branched alkyl groups at C-4 could not be quaternized by propyl iodide in ethanol or 1-butanol at reflux temperature <1986EJM87>.



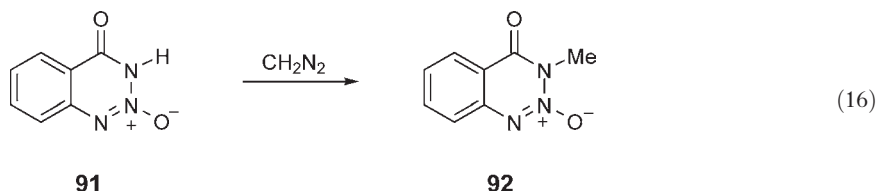
In contrast, alkylations of 3,4-dihydro-1,2,3-benzotriazin-4-ones occur almost exclusively at N-3, and, in recent years, several examples of this finding have been presented, increasingly with microwave activation. 3-Benzylated benzotriazinones **19o** were prepared from **3** with the corresponding benzyl chlorides in dimethylformamide (DMF) (Equation 15) <1997JHC1391>.



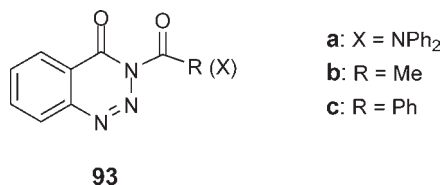
3-(ω -Chloroalkyl)-3,4-dihydrobenzo-1,2,3-triazin-4-ones **19p** were obtained from **3** with Br(CH₂)_nCl ($n = 2-4$) in DMF in the presence of potassium carbonate <2001EJM873>, and numerous 3-(4-arylpiperazinoalkyl)-3,4-dihydrobenzo-1,2,3-triazin-4-ones **19q**, and analogues thereof bearing various substituents in the benzene ring, have been prepared by N-3 alkylation <1987EJM337>. In the latter case, minor amounts of by-products formed pointed to the competing formation of O-alkylated products **19qA**; however, the authors claimed that their spectral data did not rule out betaines **19qB** completely.



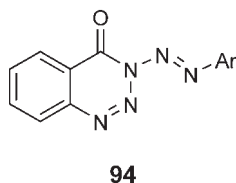
Other successful N-3 alkylations of **3** include the preparation of **19r** from ethyl bromoacetate in the presence of potassium carbonate using butan-2-one as solvent <1999EJM1043>, of **19s** (62%) from benzyl bromoacetate/Et₃N in refluxing THF overnight <1999JFA1276>, of **19t** <1968CB3079>, **19u** <1956USP2758115>, and **19b** (Azinphos methyl) from paraformaldehyde and potassium *O,O*-dimethyldithiophosphate in cooled concentrated sulfuric acid <1974HCA1658>, demonstrating the stability of **3** to acid. The sodium and potassium salts of 6,8-dichloro-3,4-dihydrobenzo-1,2,3-triazin-4-one were methylated, ethylated, butylated, and allylated at N-3 <1969JHC809>. The 3-H of 3,4-dihydro-1,2,3-benzotriazin-4-one 2-oxide **91** is sufficiently acidic to be abstracted by diazomethane, leading to methylation and formation of **92** (Equation 16) <1988JP11509>.



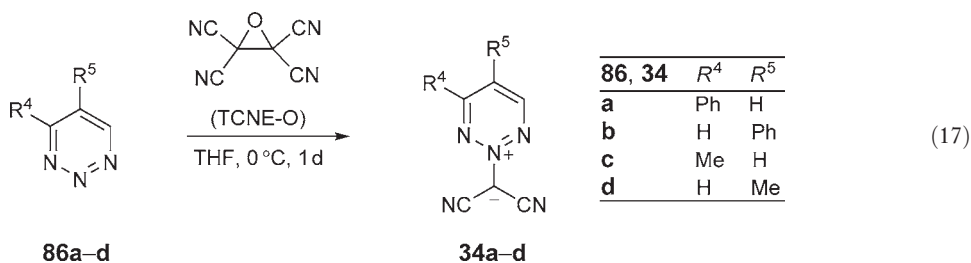
Few N-acylations of **3** have been reported; however, it has been shown earlier that *N,N*-diphenylaminocarbonyl chloride transforms **3** into the protected benzotriazinone **93a** in the presence of *N*-ethyl-*N*-diisopropylamine <1991T8917> and the N-acylated species **93b** and **93c** are formed from the reactions of the silver salt of **3** with acetyl chloride and benzoyl chloride, respectively <1962JOC4083>.



Little is known about the reaction of **3** with electrophiles other than alkylating and acylating agents, but attack of arene (or hetarene) diazonium ions (as BF₄[−] salts) on N-3 of **3** or its sodium salt, to generate 3-aryl (or 3-hetaryl)azo-3,4-dihydro-1,2,3-benzotriazin-4-ones **94**, has been reported <1984JIC65>.

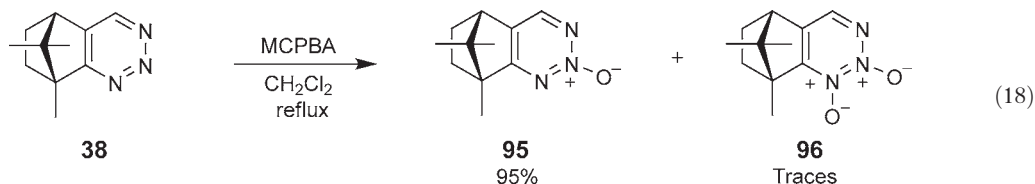


Earlier work on dicyanomethylenation <1991H(32)2015, 1993CPB1644, 1993H(35)581> has been recently supplemented <2004EJO4234>. Thus, reaction of 1,2,3-triazines **86a–d** with oxiranetetracarbonitrile (TCNE-O) (Equation 17) gave the ylides **34a–d**, which behave similarly to the corresponding pyridinium <1987CL807> and pyrimidinium <1986H(24)3473> dicyanomethylides. In addition, the parent representative of **34** (R⁴ = R⁵ = H) has been described <1992H(33)631>. See also Section 9.01.2.14 for statements based on theoretical calculations on ylidation and *N*-oxide and *N*-imine formation.

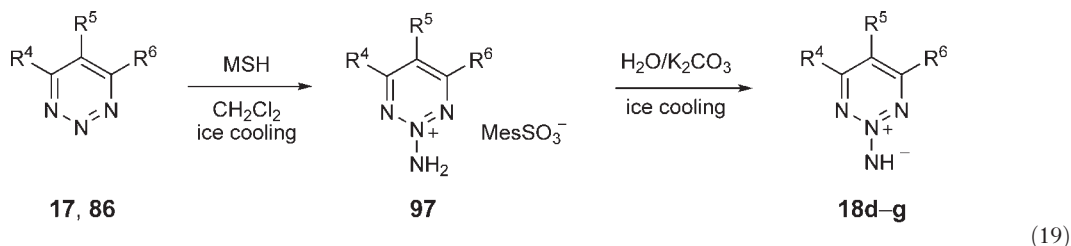


While the parent 1,2,3-triazine **1** is reported not to react with *m*-chloroperbenzoic acid (MCPBA) even after 3 days <1992H(33)631>, 4-methyl-1,2,3-triazine **86c**, 4,6-dimethyl-1,2,3-triazine **17m**, and 4-methyl-6-phenyl-1,2,3-triazine **17s** gave mixtures of 1-oxides (minor) and 2-oxides (major) when treated with MCPBA or AcOH/H₂O₂. In contrast, 4,5,6-triphenyl- and 4,6-diphenyl-1,2,3-triazine gave solely the 2-oxides <1996CHEC-II(6)483>.

8,9,9-Trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,3-benzotriazine **38** (camphortriazine, resembling a 4,5-dialkyl-1,2,3-triazine) <1977H(8)319> is oxidized by MCPBA in refluxing dichloromethane to form the 2-oxide **95** accompanied by a trace of the 1,2-dioxide **96** (Equation 18) <2000JHC1663>.

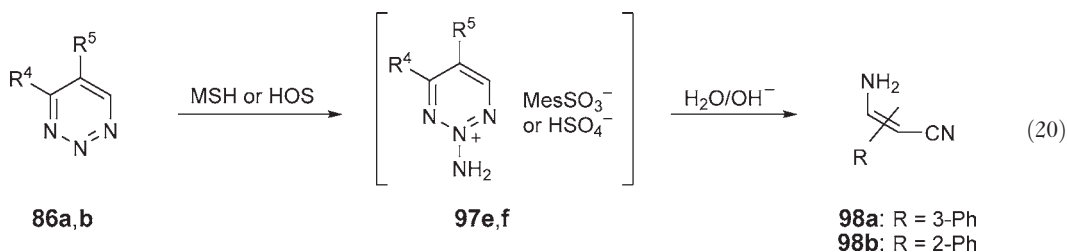


1,2,3-Triazine 2-imines **18d–g** are available from 4,6-disubstituted-1,2,3-triazines with *O*-(mesitylenesulfonyl)hydroxylamine (MSH) followed by treatment with potassium carbonate solution (Equation 19) <1988YZ1056>. N-2 Amination failed for monosubstituted 1,2,3-triazines **86a** and **86b** using both MSH and hydroxylamine-*O*-sulfonic acid (HOS). In the latter two cases, ring degradation by base occurred and only the 3-amino-2(3)-phenylacrylonitriles **98a** and **98b** were isolated as products, presumably via action of base on the intermediates **97**. Lack of a substituent at C-6 of **86a** and **86b** was regarded as responsible for this failure <2004EJO4234> (Equation 20).

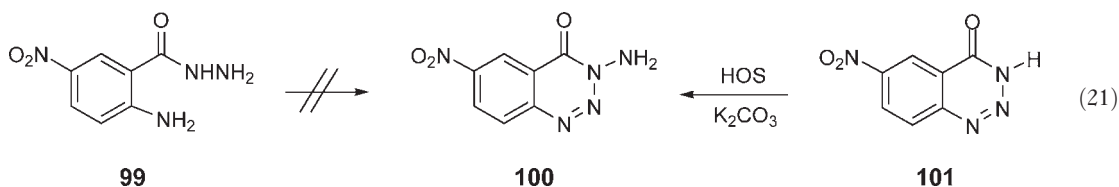


17, 86	<i>R</i> ⁴	<i>R</i> ⁵	<i>R</i> ⁶	97	%
17m	Me	H	Me	a	82
17s	Me	H	Ph	b	76
17u	Ph	H	Ph	c	91
86e	Me	Me	Me	d	78
86a	Ph	H	H	e	
86b	H	Ph	H	f	

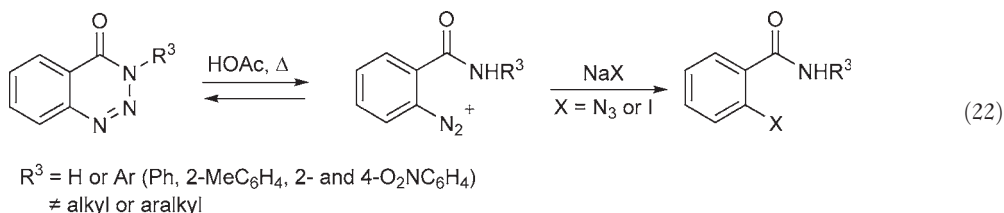
18	<i>R</i> ⁴	<i>R</i> ⁵	<i>R</i> ⁶	%
d	Me	H	Me	78
e	Me	H	Ph	92
f	Ph	H	Ph	92
g	Me	Me	Me	97



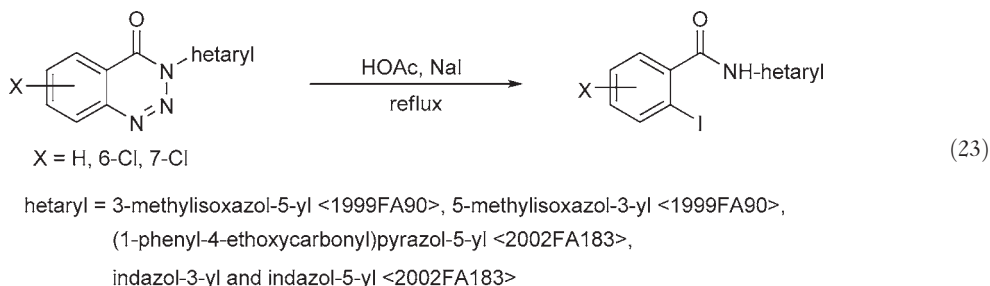
Since the usual method of preparation for 3-amino-6-nitro-3,4-dihydro-1,2,3-benzotriazin-4-one **100** by diazotization of 2-amino-5-nitrobenzohydrazide **99** had failed, giving only the corresponding benzazide, N-3 amination of **101** was carried out with HOS in aqueous potassium carbonate solution to yield 47% of **100** <1971JC981> (Equation 21).



So far, all electrophilic attacks on nitrogen in this section have occurred at ring N-atoms with maintenance of the 1,2,3-triazine or -benzotriazine basic structures. One should be aware, though, that there is a long-known diazonium ion chemistry of 3,4-dihydro-1,2,3-benzotriazin-4-ones caused by reaction with mineral acid under warming <1978HC(33)3, 1984CHEC(3)369>. The attack of H^+ in these cases may well not be on a N-atom but on the carbonyl oxygen, even if N-3 eventually ends up protonated. Nevertheless, a considerable number of reactions ensuing are reminiscent of uncatalyzed Sandmeyer reactions, leading to displacement of the diazonium function by azide or nucleophilic halogen. This reaction can also be realized by warming the benzotriazinone in acetic acid in the presence of the nucleophile as a salt; see Equation (22) for an example <1977J(P1)103>. Weaker nucleophiles (Br^- , Cl^- , CN^- , AcO^- , HSO_3^-) do not react.



This method for the introduction of iodine into a position *ortho* to a carboxamide function is still of preparative interest (Equation 23) <1999FA90, 2002FA183>. In addition, examples of intramolecular arylation <1984CHEC(3)369, 1964JCS3663> and displacement of N_2^+ by OH <1971JC2317> have been known for some time.



9.01.5.3 Reactions with Electrophiles on Carbon

Electrophilic attack on carbon is unknown for 1,2,3-triazines and this lack of reactivity is attributed to the marked π -electron deficiency of the ring system. 5-Halogenated products may be obtained, though, from action of halogen or interhalogen compounds on 4,6-dimethyl-1,2,3-triazine <1986CPB4432>. This reaction is interpreted in terms of an electrophilic addition/elimination mechanism (attack of halogen on the lone pair at N-2 enhances the tendency for addition of halide ions at C-5, and release of hydrogen halide from the Hal_2 adduct affords the 5-halogenated product). The scope and limitations of this process have been discussed <1996CHEC-II(6)483>.

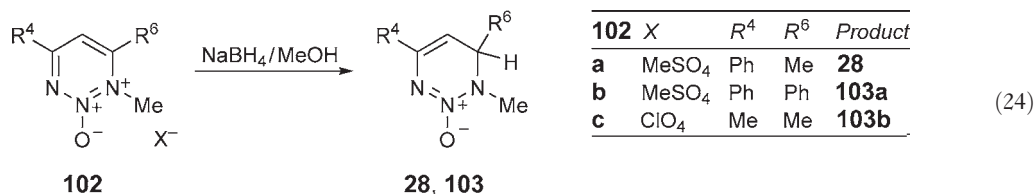
It should be noted, however, that the lack of electron density in the π -system may be bypassed by creating local σ -electron density by lithiation and reaction with suitable electrophiles. Quenching of lithiated alkoxy-1,2,3-triazines with aromatic aldehydes generates (α -hydroxybenzyl)-1,2,3-triazines, products of an electrophilic attack on carbon. Dehydrogenation of their alcohol function with manganese dioxide affords formal Friedel–Crafts acylation products <1998MI119>. Lithiation has been discussed from a theoretical point of view in Section 9.01.2.13, and practical implications are presented in Section 9.01.5.5.

9.01.5.4 Reactions with Nucleophiles

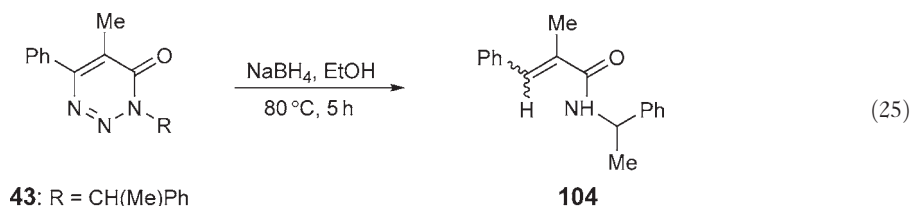
Nucleophiles relevant for this chapter are hydride ion, O-atom- and N-atom-centered nucleophiles and C-nucleophiles like organometallic compounds, ketene acetals, and ester enolates as well as electron-rich heterocycles. Reductions of 1,2,3-triazines and 2-methyl-1,2,3-triazin-2-ium salts by sodium borohydride in methanol and lithium alanate in ether to yield 2,5-dihydro-1,2,3-triazines have been reviewed in CHEC(1984) and CHEC-II(1996). The reaction is explained by nucleophilic attack of the hydride ion at C-5. Borohydride reductions of 1,2,3-triazine

N-oxides may lead to diversified results. While 6-methyl-4-phenyl-1,2,3-triazine 1-oxide **27a** is deoxygenated by NaBH₄ in MeOH presumably via release of H₂O from the elusive intermediate 1,2-, 1,4-, or 1,6-dihydro-1-hydroxy-1,2,3-triazine, the main products from analogous treatment of 4,6-dimethyl- and 4-methyl-6-phenyl-1,2,3-triazine 2-oxide are the 1,4,5,6-tetrahydro-1,2,3-triazine 2-oxides **45** (R⁶ = Me: 63:20 mixture of two diastereomers; R⁶ = Ph: one diastereomer) <1996CHEC-II(6)483>. The following supplementary cases are noteworthy.

1-Methyl-1,2,3-triazinium 2-oxides **102** are reduced to 1,6-dihydro-1,2,3-triazine 2-oxides **28** and **103** (Equation 24) <1985YZ1122>. Again, the *N*-oxide function has been retained in this reduction.

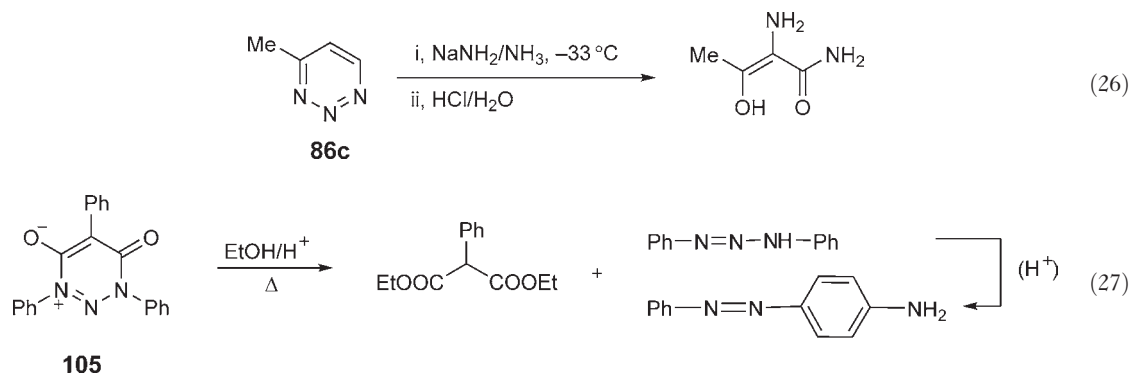


The 3,4-dihydro-1,2,3-triazin-4-one **43** (R = 1-phenylethyl) is reductively ring-opened to a 4:1 (*Z/E*)-mixture of the unsaturated amide **104** by treatment with sodium borohydride (Equation 25) <2006EJO3021>.

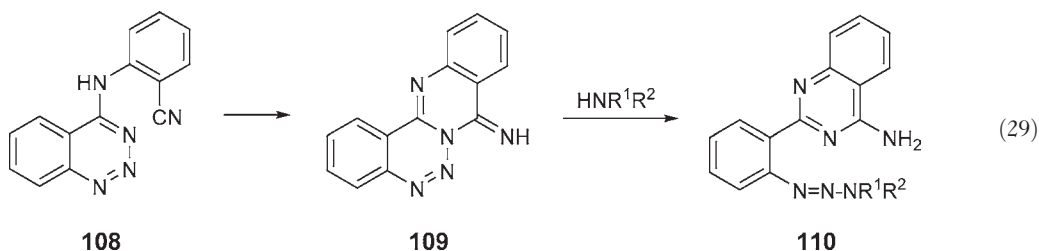
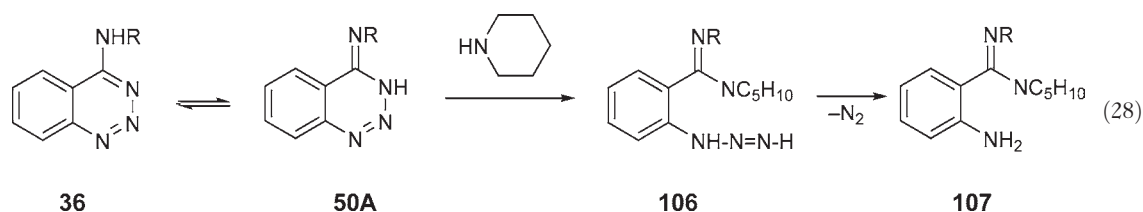


The C-4 and C-6 positions of 1,2,3-triazines and the C-4 position of 1,2,3-benzotriazines may be regarded as carbonyl-*C* analogues; thus hydrolytic ring cleavage of 1,2,3-triazines to generate 1,3-dicarbonyl compounds is a logical consequence. A number of protic heteroatom nucleophiles capable of undergoing condensations (H₂O, OH[−] from aqueous or alcoholic NaOH or KOH, alcohols with or without added mineral acids, phenyl hydrazine, and hydroxylamine hydrochloride) have been reacted with 1,2,3-triazines, 1,2,3-benzotriazines, and 3,4-dihydro-1,2,3-benzotriazin-4-ones. For the latter, with C-4 at the oxidation stage of a carboxyl group, generally N(3)–C(4) bond cleavage with generation of benzoic acids or derivatives thereof has been observed, while 2-functionalized benzaldehydes or phenyl ketones have been formed from various 1,2,3-benzotriazines <1984CHEC(3)369>. Attention is drawn to the following cases hitherto not reviewed.

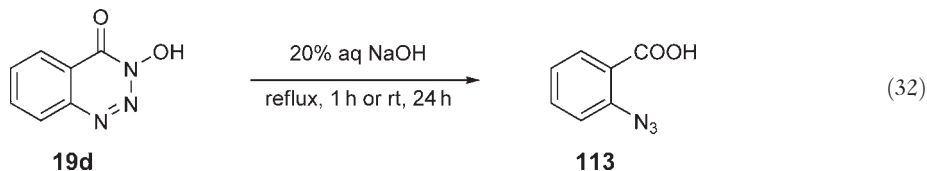
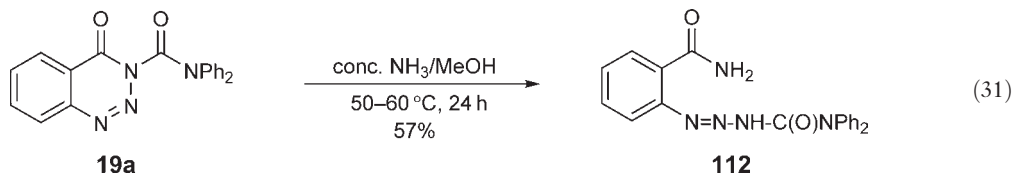
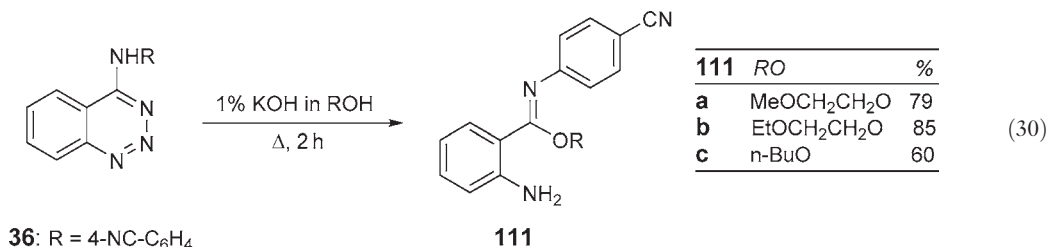
Reaction of 4-methyl-1,2,3-triazine **86c** with sodium amide in liquid ammonia followed by acidification gives 2-amino-3-hydroxycrotonamide (Equation 26) <1985LA1732>, and the mesoionic compound **105** is cleaved by acidified ethanol into diethyl phenylmalonate and 1,3-diphenyltriazene (accompanied by a small amount of its follow-up product 4-aminoazobenzene) (Equation 27) <1978CB2173>.



As in the cleavage of **3** by piperidine to afford 2-aminobenzpiperidine <1974J(P1)611>, the amidine-like C-4 position of **36** (in equilibrium with **50A**; R = Ph, 4-NC₆H₄, 2-, 3-, and 4-O₂NC₆H₄, 2-, 3-, and 4-H₂NC₆H₄, 4-MeC₆H₄) is attacked by piperidine to afford the triazene **106**. The latter releases N₂ to form the 2-aminobenzamidine **107** (Equation 28), while compound **108** gives the triazene **110** via **109** by attack of various secondary amines on the masked diazonium group (Equation 29) <1974J(P1)615>.

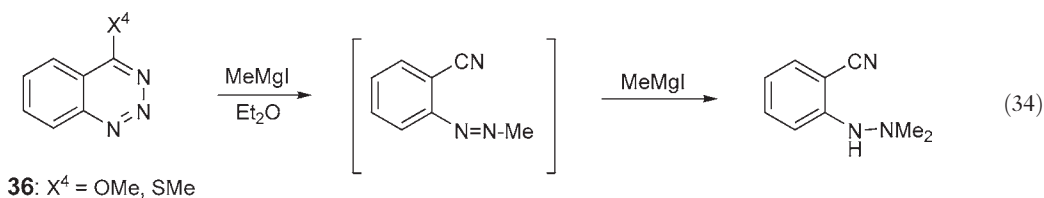
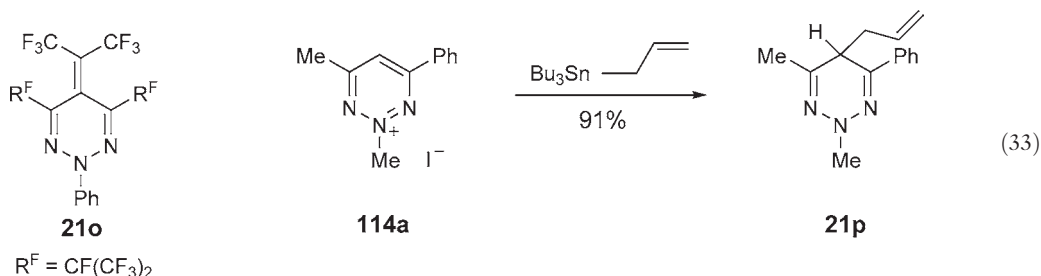


Under conditions of attempted quaternization with Pr-I in EtOH or BuOH under reflux, 4-arylmethyl-1,2,3-benzotriazines are transformed into 2-aminophenylarylmethylketones [\[1981JCM324, 1981JRM3786\]](#). 4-(4-Cyanophenyl)amino-1,2,3-benzotriazine (**36**; $\text{R} = 4\text{-NC}_6\text{H}_4$) may be transformed into 2-aminobenzimidates **111a–c** by treating **36** with KOH in high-boiling alcohols (Equation 30) [\[1972J\(P1\)295, 1974J\(P1\)615\]](#). 3,4-Dihydro-1,2,3-benzotriazin-4-ones **19a** and **19d** undergo ‘normal’ N(3)–C(4) cleavage with ammonia or NaOH, preserving the contiguous N_3 chain (Equations 31 and 32, products **112** and **113**) [\[1991T8917, 1960JCS2157\]](#).

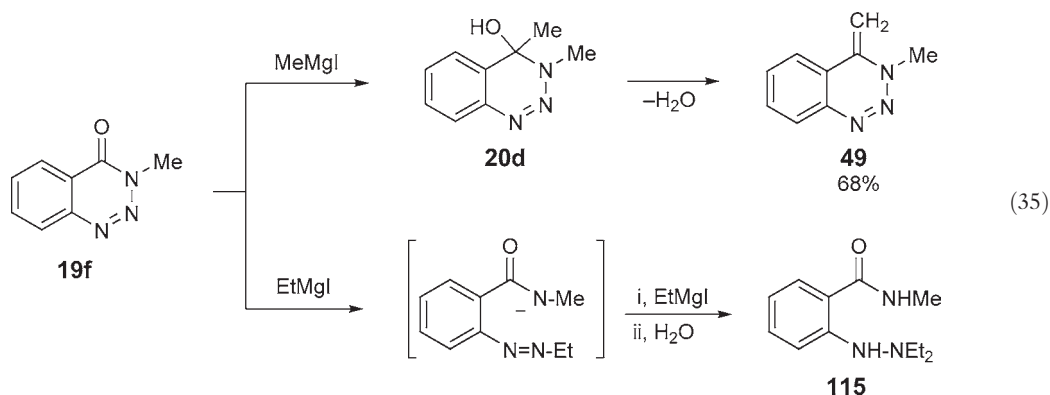


Addition of carbon nucleophiles is a major topic. The addition of Grignard reagents to 1,2,3-benzotriazine 3-oxides ($\text{R}^4 = \text{Me}$ or Ph) and 3-aryl-3,4-dihydro-1,2,3-benzotriazin-4-ones takes place at the C-4 position with N(3)–C(4) bond heterolysis. This process generates a tertiary alcohol or related function and a triazene moiety or follow-up function thereof in an *o*-position on a benzene ring [\[1984CHEC\(3\)369\]](#). The parent 1,2,3-triazine **1** gives 4-methyl-2,5-dihydro-1,2,3-triazine in 42% yield from reaction with MeMgI but only 13% of the analogous product from reaction with PhMgBr . The main product from reaction of **1** with PhMgBr or PhLi is cinnamaldehyde, pointing to an attack of the carbanionoid at C-4. With both reagents mentioned, 4,6-dimethyl-1,2,3-triazine experiences attack at both C-5 (minor) and N-2 (major) to give 2,5-dihydrotriazines and a ring-contracted product, 1,3,5-trimethylpyrazole (or 3,5-dimethyl-1-phenylpyrazole). 4,5,6-Tris(perfluoroisopropyl)-1,2,3-triazine adds PhMgBr solely at N-2, affording eventually the dihydrotriazine **21o** by loss of F^- from the 5-(CF_3)₂CF group. While 4,6-disubstituted-2-methyl-1,2,3-triazinim iodides add Grignard reagents at the C-5 position in medium to good yields, 1,2,3-benzotriazines experience attack of RMgX at N-2, concomitant with either ring opening or ring contraction [\[1996CHEC-II\(6\)483\]](#).

5-Allyl-2,4-dimethyl-6-phenyl-2,5-dihydro-1,2,3-triazine (**21p**) is obtained in 91% yield from the triazinium iodide **114a** and allyltributylstannane (Equation 33) <1994CPB1768>. 4-Heterosubstituted-1,2,3-benzotriazines **36** ($X^4 = \text{OMe}, \text{SMe}$) undergo attack of MeMgI at N-2 and, since X^4 acts as a leaving group, form 2-methyldiazenyl- and finally (with excess of MeMgI) 2-(N^2, N^2 -dimethylhydrazino)benzonitriles (Equation 34) <1983CC1344>.

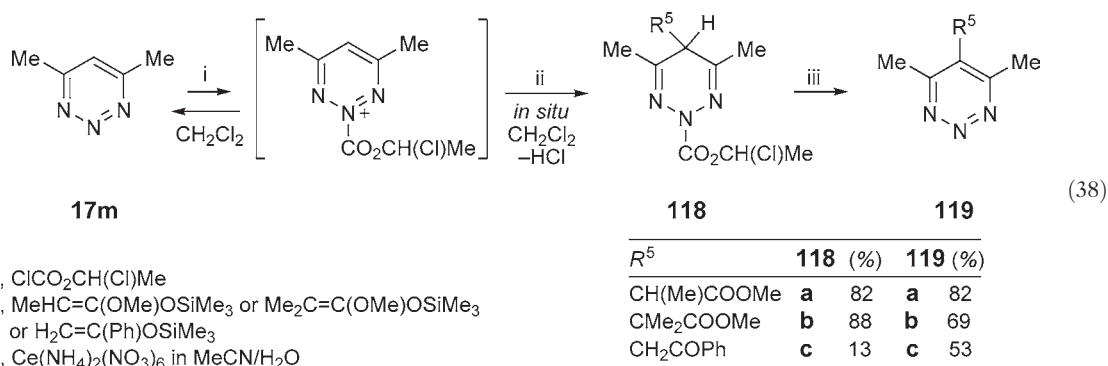
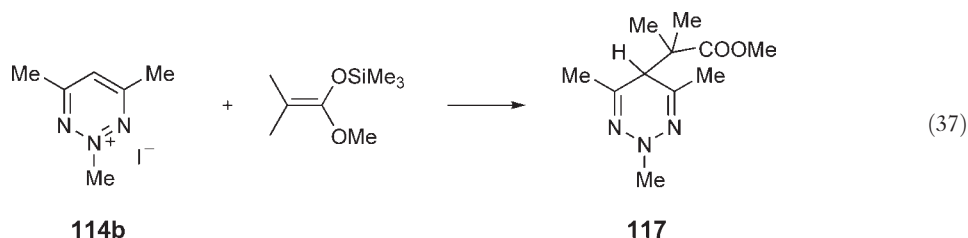
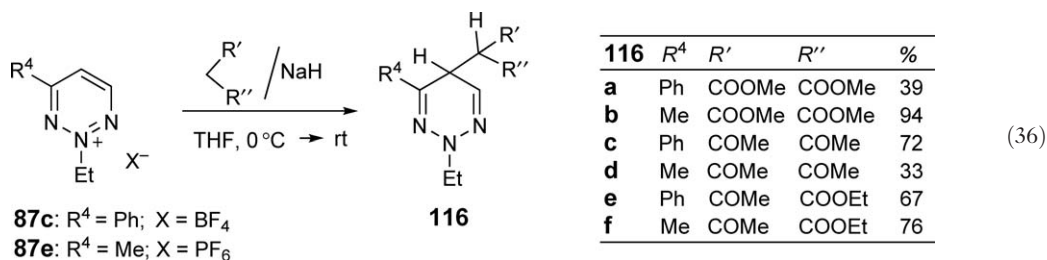


With **19f**, MeMgI and EtMgI react differently. While the former attacks the C-4 position to give **20d** and eventually **49**, the latter attacks twice at the N-2 position (Equation 35) with formation of 2-(N^2, N^2 -diethylhydrazino)-benz-*N*-methanamide **115** <1983CC1344>.



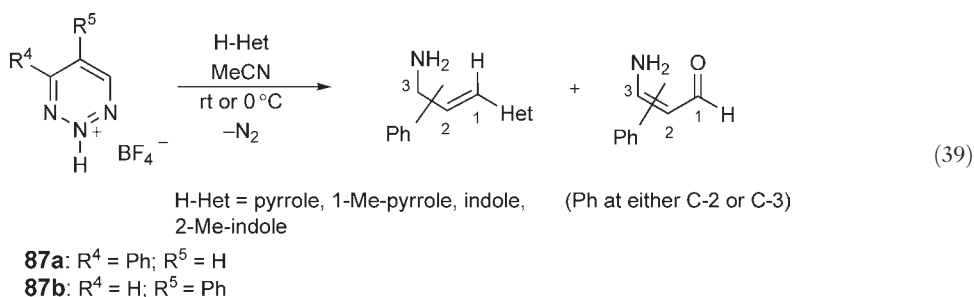
Anions of methylene-active compounds (1,3-dione enolates and ester enolates), ketene acetals, and even electron-rich five-membered heterocycles comprise another group of nucleophiles that attack triazine rings, preferably in the form of 1,2,3-triazin-2-ium salts. 4,6-Disubstituted-2-methyl-1,2,3-triazin-2-ium iodides add malonic ester anion at the C-5 position to form 4,6-disubstituted-2-methyl-5-bis(ethoxy-carbonyl)methyl-2,5-dihydro-1,2,3-triazines in 57–76% yield <1992CPB2283, 1996CHEC-II(6)483>. The following cases have been published more recently.

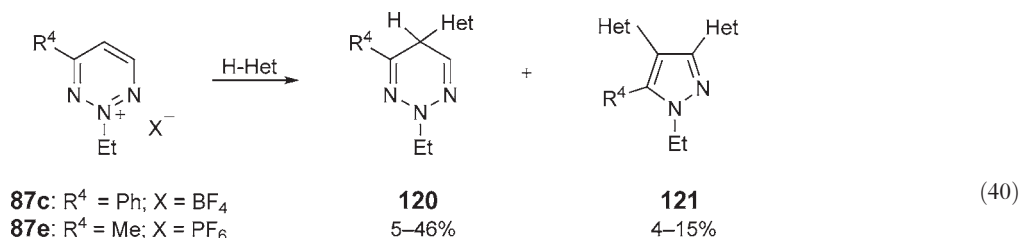
Triazin-2-ium salts **87c** and **87e**, when added to a mixture of dimethyl malonate (or acetylacetone or ethyl acetoacetate) and NaH in THF at 0°C and the mixture allowed to warm up to room temperature, give the 2,5-dihydro-1,2,3-triazines **116** (Equation 36) <2003S413>. While 2,4,6-trimethyl-1,2,3-triazin-2-ium iodide **114b** reacts with the trimethylsilyl enol ether of methyl 2-methylpropanoate in dichloromethane at room temperature to afford **117** (Equation 37) <1996J(P1)2511>, 1,2,3-triazine **17m** may be converted with analogous reagents to the dihydrotriazines **118** only in the presence of 1-chloroethyl chloroformate as acylating agent. The dihydrotriazines **118** may be oxidized to the 4,5,6-trisubstituted-1,2,3-triazines **119** (Equation 38) <1995CPB881, 1996J(P1)2511>. Similarly, and with comparable yields, this sequence has been carried through with the three analogous 1,2,3-triazines **17s**, **17u**, and **17** ($R^4 = R^6 = \text{Et}$).



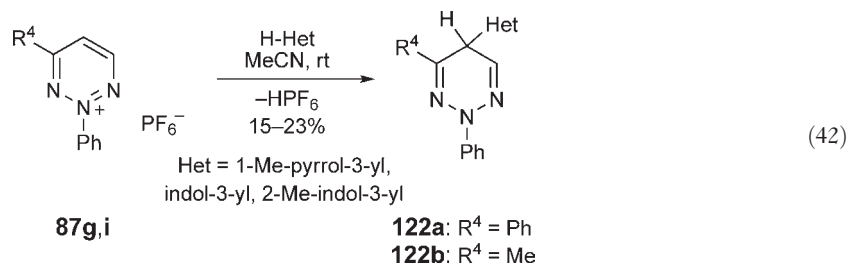
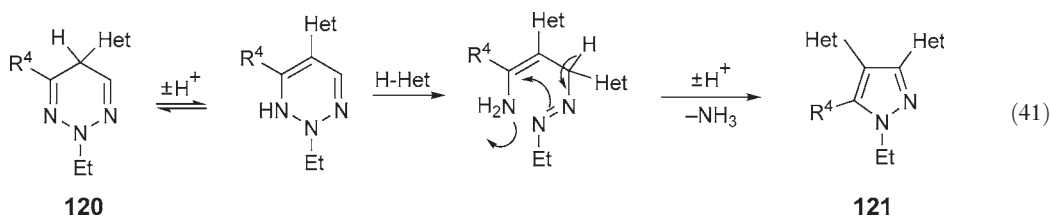
Electron-rich heterocycles (e.g., pyrroles and indoles) may be regarded as enamine-like and thereby represent electron-rich olefins. The following typical additions to 1,2,3-triazin-2-ium ions have been observed [<2003S413>](#):

- Heterocycles, as specified, are added to 2-protonated 1,2,3-triazinium tetrafluoroborates **87a** and **87b** with N_2 evolution and ring opening, generating positionally isomeric allylamines and β -aminopropenals (Equation 39).
- 4-Substituted 2-ethyl-1,2,3-triazinium salts **87c** and **87e** give poor yields of 2-ethyl-2,5-dihydro-1,2,3-triazines **120** ($R^4 = \text{Ph}$ or Me) and, additionally, in two cases, a pyrazole **121** bearing two identical heterocyclic substituents (Equation 40). The ring contraction generating **121** is rationalized in Equation (41).
- 2-Phenyl-1,2,3-triazinium hexafluorophosphates **87g** and **87i** in MeCN at room temperature are transformed into 2,5-dihydro-1,2,3-triazines **122** (Equation 42).





120: $R^4 = \text{Ph}$ or Me ; $\text{Het} = 2,5\text{-Me}_2\text{-pyrrol-3-yl}$, $2,4\text{-Me}_2\text{-pyrrol-3-yl}$, indol-3-yl , 2-Me-indol-3-yl
 $R^4 = \text{Ph}$; $\text{Het} = \text{pyrrol-2-yl}$ and 3-yl , 1-Me-pyrrol-3-yl
 $R^4 = \text{Me}$; $\text{Het} = \text{pyrrol-2-yl}$, 1-Me-pyrrol-2-yl , $3,5\text{-Me}_2\text{-pyrrol-2-yl}$
121: $R^4 = \text{Ph}$ or Me ; $\text{Het} = \text{pyrrol-2-yl}$, indol-3-yl



The following two nucleophilic reactions have also been reviewed in CHEC-II(1996) <1996CHEC-II(6)483>:

- the addition of branched alkenes to the N-2 position of the especially electron-demanding 4,5,6-tris(perfluoroisopropyl)-1,2,3-triazine **17g** generating 2-(1,1,2-trimethyl-2-propenyl)- and 2-(1,2-dimethyl-2-propenyl)-2,5-dihydro-1,2,3-triazines and the spiro-zwitterion **24**; and
- the treatment of 4,6-disubstituted-1,2,3-triazin-2-ium dicyanomethylides with chloromethyl phenylsulfone and a strong base (*t*-BuOK or NaH) in DMSO or THF at room temperature, whereby, in a so-called vicarious nucleophilic substitution <2004CRV2631>, a phenylsulfonylmethyl group is introduced at the C-5 position of the triazine ring.

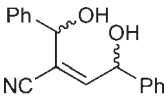
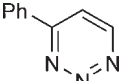
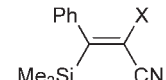
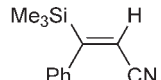
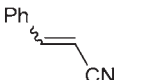
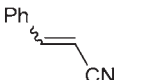
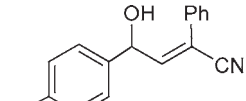
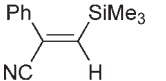
9.01.5.5 Nucleophilic Attack on Hydrogen Attached to Carbon

This section treats the lithiation of 1,2,3-triazines by lithium 2,2,6,6-tetramethylpiperidide (LTMP). The theoretical aspects of H/Li-exchange, especially for alkoxytriazines, have been discussed in Section 9.01.2.13, and the option to bypass the reluctance of 1,2,3-triazines to undergo electrophilic substitution by lithiation, followed by quenching with electrophiles, has been pointed out in Section 9.01.5.3.

It had been expected that triazines **1**, **86a**, and **86b**, having no special acidifying or *ortho*-directing groups, could be lithiated successfully with a strongly basic lithiating reagent followed by reaction with suitable electrophiles, either by accumulating the lithiated species with time or by shifting the equilibrium between the triazine and its lithio derivative using an excess of lithiating agent. The results summarized in Table 16 for compounds **1**, **86a**, and **86b** have been obtained by applying either one of the following two conditions:

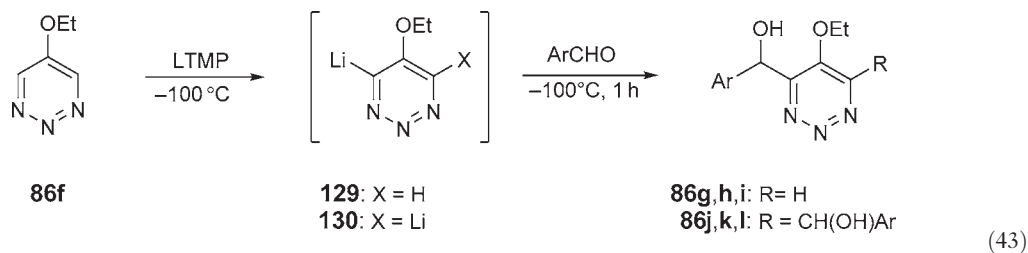
- Method A (accumulation of lithiated triazine attempted).** The triazine was treated with 4 equiv of LTMP in THF at -100°C for 20 min, followed by reaction with an arenealdehyde at -100°C for 1 h and subsequent aqueous acidic workup.
- Method B (shift of equilibrium to the lithio derivative attempted).** The triazine was treated with a mixture of LTMP and TMSCl at -100°C for 2 h and subsequent aqueous acidic workup.

Table 16 Products from lithiation of triazines **1**, **86a**, and **86b** followed by trapping with electrophiles

Starting triazine	Method applied	Electrophile	Products and yields (%)
 1	A	PhCHO	 123 (main product: <i>R</i> [*] , <i>S</i> [*] , 10%)
	B	TMSCl	Many silylated products (from GC–MS); none isolated or identified
 86a	A	PhCHO	No triazines; products not identified
	B	TMSCl	 124a : X = SiMe ₃  124b : X = H  125  126
 86b	A	4-MeC ₆ H ₄ CHO	 127 (27%)
	B	TMSCl	 128 (60%)

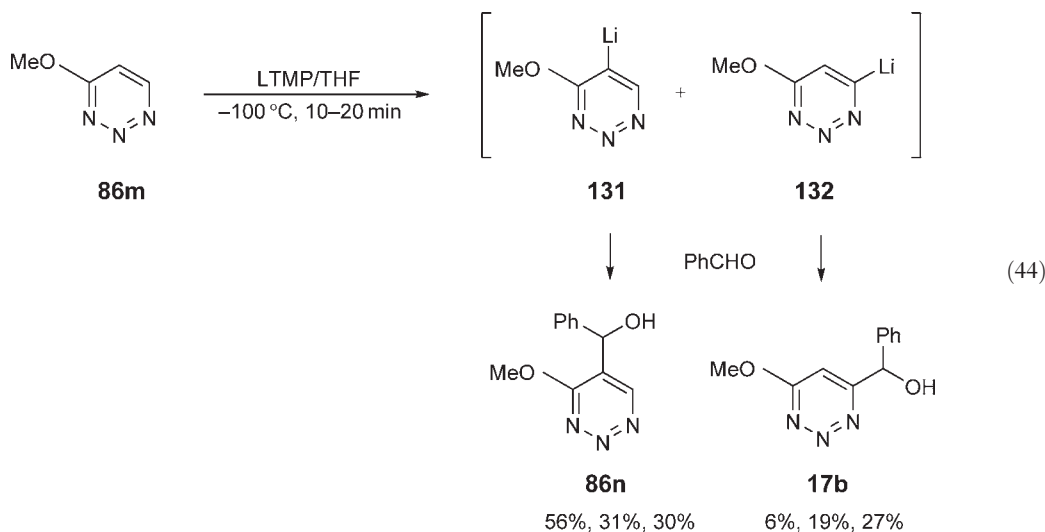
All of the products, **123–128**, were characterized fully spectroscopically and, in the case of (*R*^{*},*S*^{*})-**123**, also by a single crystal X-ray structure analysis. It was demonstrated that the starting triazines had been degraded with the loss of two N-atoms and that, from the number of residues introduced by reaction with electrophiles, 2 equiv of LTMP had been used. N-atoms alone may support lithiation but do not stabilize the lithiated species satisfactorily <2003TH1>.

Using the adapted method A, 5-ethoxy-1,2,3-triazine **86f** can be mono- or dilithiated depending on reaction time. Quenching by arenaldehydes gives various product distributions **86g–l** derived from the mixture of the mono- **129** and the dilithiated **130** triazine as outlined in Equation (43) for five out of twelve examples <1998MI119>.



LTMP equiv	Time (min)	ArCHO (equiv)	Ar	Products and yields (%)
2	10	2	Ph	86g (9)
2	20	2	Ph	86g (30), <i>meso</i> - 86j (3), <i>rac</i> - 86j (3)
2	20	2	4-MeC ₆ H ₄	86h (22), <i>meso</i> - 86k (19), <i>rac</i> - 86k (19)
4	20	4	4-MeC ₆ H ₄	86h (10), <i>meso</i> - 86k (26), <i>rac</i> - 86k (18)
4	20	2	4-ClC ₆ H ₄	86i (18), <i>meso</i> - 86l (12), <i>rac</i> - 86l (13)

4-Methoxy-1,2,3-triazine **86m** has been metalated by LTMP at -100°C for 10, 15, and 20 min, and the mixture of lithiotriazines **131** and **132** has been reacted with benzaldehyde at -100°C to afford products **86n** and **17b** in the yields given for the three time spans used in the lithiation step (Equation 44) <1998MI119>.



All attempts to lithiate 5-bromo-1,2,3-triazine and *N,N*-diethyl-1,2,3-triazine-4-carboxamide with LTMP at -100°C , followed by reaction with electrophiles, were unsuccessful <1998MI119>.

9.01.5.6 Radical Reactions, Catalytic Hydrogenation, Reductions

No new material relevant to this topic has appeared since CHEC-II(1996), but a few cases of interest have not been reviewed previously. These will be included here after a brief synopsis of the material treated in CHEC(1984) and CHEC-II(1996).

Attack of the 1,2,3-triazine system by an organic radical is used in the introduction of a carboxamide function at C-5 by the treatment of 4,6-disubstituted 1,2,3-triazin-2-ium 2-dicyanomethylides **34** ($\text{R}^5 = \text{H}$; $\text{R}^4, \text{R}^6 = \text{Me, Ph, Et}$) with formamide in the presence of ammonium persulfate at 80°C . Under these conditions, the 1,2,3-triazine is restored by loss of dicyanomethyl radical. The corresponding 2-methyl-1,2,3-triazin-2-ium iodides gave the demethylated 5-aminocarbonyl-1,2,3-triazines in good yields <1991H(32)855, 1991H(32)2015>. Aside from this case, mostly catalytic hydrogenations, dissolving metal reductions, and a few electroreductions have been carried out.

Reductions of monocyclic 1,2,3-triazines under various conditions may lead to reductive ring contractions. The case of 4,5,6-triphenyl-1,2,3-triazine **17z** is typical. Reduction with Zn/HOAc , catalytic hydrogenation (H_2/Pd in HOAc) <1984CHEC(3)369>, and treatment with $\text{Fe}_2(\text{CO})_9$ have afforded 3,4,5-triphenylpyrazole **75** <1996CHEC-II(6)483>. The same product (among others) has been found in the photoreduction of **17z** in di- and triethylamine as solvents <2002TH1> (see Section 9.01.5.1). Also, the one-electron reduction of 4,6-disubstituted-2-methyl-1,2,3-triazinium iodides by potassium superoxide in MeCN in the presence of a crown ether is noteworthy as a true symmetrical radical coupling reaction, forming 5,5'-bis(2-methyl-2,5-dihydrotriazinyl) <1992CPB2283>. Reductive ring contractions and/or ring-opening reductions are also typical for many compounds with 1,2,3-benzotriazine connectivity <1984CHEC(3)369>.

3-Aminoindazoles are formed from

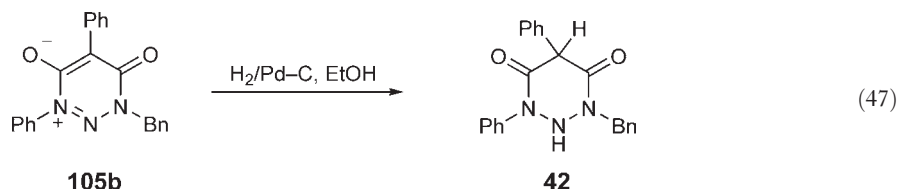
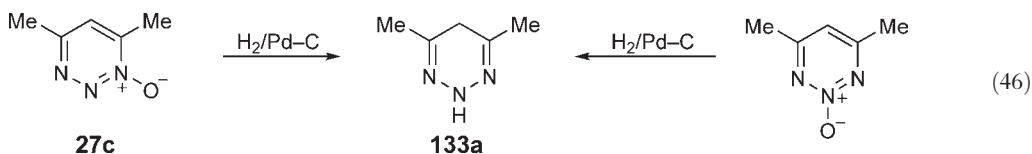
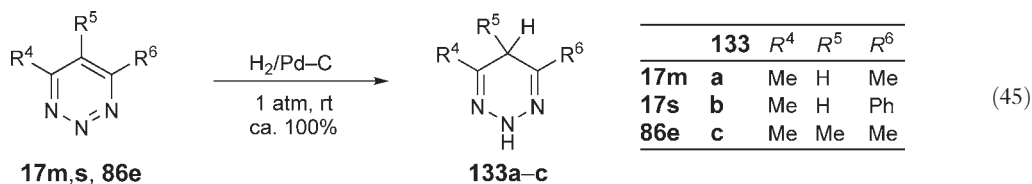
- 3,4-dihydro-1,2,3-benzotriazin-4-imines upon treatment with SnCl_2 in ethanol under reflux <1964JCS3663>,
- 4-imino-2-alkyl-3,4-dihydro-1,2,3-benzotriazin-2-ium-3-ides with hydrazine/Raney-nickel ($\text{N}_2\text{H}_4/\text{Ra-Ni}$) at $60\text{--}65^{\circ}\text{C}$ in ethanol <1970JC2289>,
- 4-amino-1,2,3-benzotriazine 3-oxide with $\text{H}_2/\text{Ra-Ni}$ in MeOH at 60°C and 275 mbar or with $\text{SO}_2/\text{Na}_2\text{SO}_3$ in water <1961JCS4930, 1958CIL1234>, and
- 4-methyl-1,2,3-benzotriazine 3-oxide with Zn/HOAc <1927CB1736>.

2-Aminobenzanilides or 2-aminobenzamidines were formed from

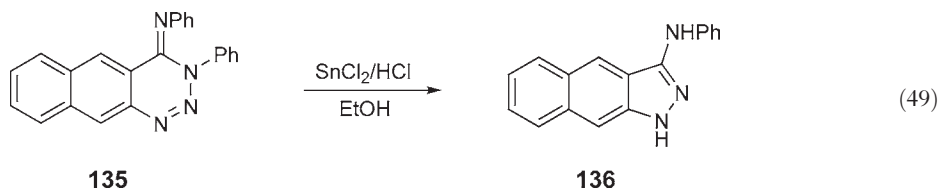
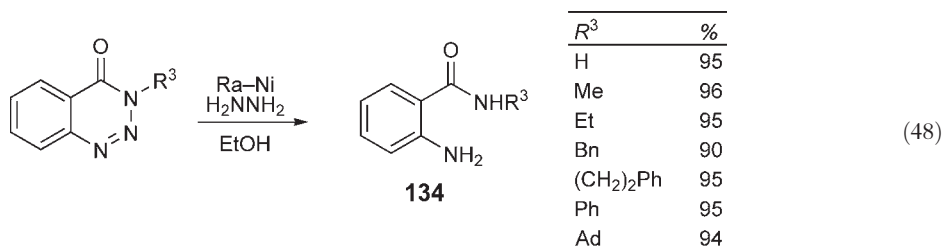
- benzotriazinones **3**, **19f**, **19n** ($R^3 = \text{H, Me, Ph}$) with H_2/Pd in EtOH (87%, 72%, and 61% yield) <1976S717>;
- 3-alkyl-3,4-dihydro-1,2,3-benzotriazin-4-ones ($R^3 = \text{Me, Pr, Bu, } i\text{-C}_6\text{H}_{11}$) by catalytic hydrogenation (H_2/Pd) in AcOH in the presence of HClO_4 <1976S717>; and
- 4-(NHR)-1,2,3-benzotriazines ($R = \text{Ph, Bn}$) and 3-aryl-4-imino-3,4-dihydro-1,2,3-benzotriazines with $\text{N}_2\text{H}_4/\text{Ra-Ni}$ in EtOH <1970JC2308>.

Both 3-amino- (and 3-substituted amino-) indazoles and 2-aminobenzanilides (or 2-aminobenzamidines) have been obtained from 3-benzyl-4-imino- and 3-methyl(or phenyl)-4-phenylimino-3,4-dihydro-1,2,3-benzotriazines upon treatment with $\text{N}_2\text{H}_4/\text{Ra-Ni}$ <1970JC2308>. Electrochemical reduction of **3** in the presence of dilute H_2SO_4 and of **19n** in EtOH/0.5 M HCl gave good yields of indazolin-3-one (**137**; see Equation (50) <1976BSF433>.

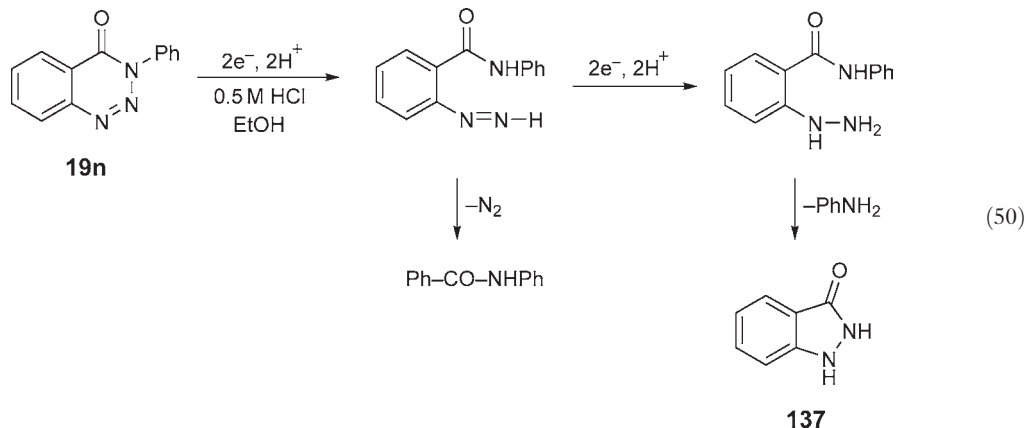
The following cases have not been reviewed in previous editions. Catalytic hydrogenation of 1,2,3-triazines **17m**, **17s**, and **86e** gives quantitative yields of 2,5-dihydro-1,2,3-triazines **133a–c** (Equation 45) and, both 4,6-dimethyl-1,2,3-triazine 1-oxide **27c** and its isomeric 2-oxide undergo catalytic hydrogenation and deoxygenation to form **133a** (Equation 46) <1980CC1182>. The latter result is different from that of NaBH_4 reduction of these *N*-oxides <1996CHEC-II(6)483>. The mesoionic compound **105b** is catalytically hydrogenated to the dione **42** (Equation 47) <1978CB2173>.



A series of 3,4-dihydro-1,2,3-benzotriazin-4-ones were treated with hydrazine and Ra-Ni in EtOH to give good yields of the 2-aminobenzamides **134** (Equation 48) <1971JC2317>; for $R^3 = 1\text{-adamantyl (Ad)}$, see <1975AP161>. 3,4-Dihydro-3-phenyl-4-phenylimino[2',3':5,6]naphtho-1,2,3-triazine **135** was reduced to 3-phenylamino-5,6-benzindazole **136** in 93% yield (Equation 49) <1971JOU2516>.



Electrochemical reduction has been applied occasionally on benzotriazinones. Thus, compound **19n** was reductively degraded to indazolin-3-one **137**, aniline, and benzanilide (Equation 50); the latter was the sole product (90%) upon electroreduction of **19n** in DMF. 3-Phenyl-3,4-dihydro-1,2,3-benzotriazine, when subjected to cathodic reduction, gave only 18% of *N*-benzylaniline along with more than eight minor, unidentified products <1979ACB233>.



Finally, an electroanalytical study based on direct current and differential pulse polarography and coulometry of ‘Azinphos methyl’ (**19b**, also named ‘Guthion’) in 20% (v/v) MeOH/H₂O has been interpreted in terms of two discrete two-electron reduction steps <1988JEC221>.

9.01.5.7 Cycloadditions

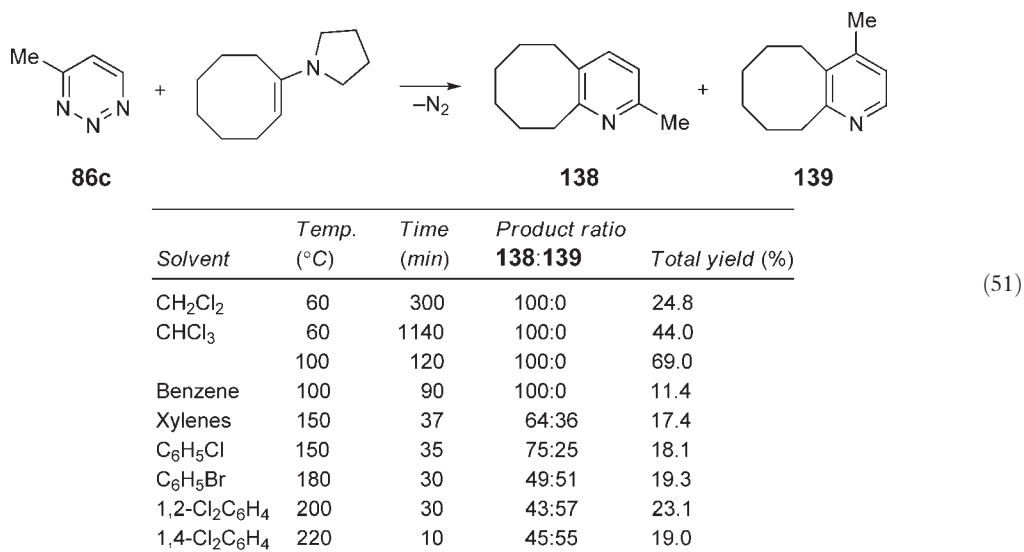
The prototypical [4+2] cycloaddition of ethene to 1,2,3-triazine **1** has been analyzed theoretically in Section 9.01.2.11. Preparative potential lies in the inverse electron demand Diels–Alder additions of 1,2,3-triazines. The review literature of the 1980s, however, while rich in examples of such reactions with other heterocyclic azadienes, is rather terse for 1,2,3-triazines <1983T2869, 1986CRV781, B-1987MI300>; see also <1998HOU(E9c)530>. Indeed, most of the papers describing 1,2,3-triazine cycloadditions appeared after 1986. There are also a few examples of [3+2] cycloadditions, which are described below. A list of dienophiles unreactive toward **1** has been given by Neunhoeffer *et al.* <1985LA1732>.

The following cases were mentioned in CHEC-II(1996) <1996CHEC-II(6)483>.

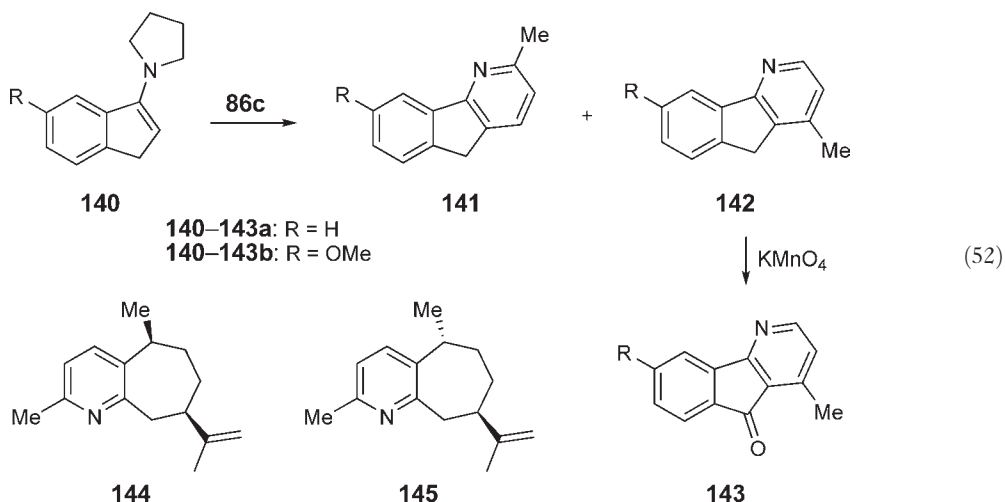
- The addition of 1-diethylaminopropyne and pyrrolidinocyclopentene to **1** and 4-methyl-1,2,3-triazine **86c** gives pyridine derivatives <1985LA1732>.
- [4+2] Cycloadditions of electron-rich and -poor dienophiles (1-diethylaminopropyne, phenylethyne, phenyl vinyl-sulfone, ketene diethylketal) to 4,6-dimethyl-1,2,3-triazine **17m** at 180 °C are mentioned. The product distribution could not be rationalized with the 1,4-addition mechanism (see Section 9.01.2.11) alone but also with a prefragmentation to 2,4-dimethylazete and addition of the dienophiles to opposite faces of that intermediate <1985CPB3050, 1990CPB2108>. This latter option, however, had been given low probability on the basis of a theoretical calculation (see Section 9.01.2.11), rendering azetes as of too high energy to be competitive with the concerted pathway <2002J(P2)1257>.
- The addition of various pyrrolidinocycloalkenes to 4-methyl-1,2,3-triazine **86c** leads to cycloalkane-*b*-annulated pyridines <1985H(23)2789, 1986H(24)29> and the extension of this work to the parent compound **1**, 5-methyl- and higher methylated 1,2,3-triazines <1989H(29)1809>.
- The use of aldehyde-derived enamines, the application of Lewis acid catalysts, and the use of this technique in the preparation of the alkaloid fusaric acid <1994H(38)1595> and other alkaloids <1992CEX321> are also mentioned.
- The regioselective [3+2] cycloaddition of 1-diethylaminopropyne to 4,6-disubstituted 1,2,3-triazine 2-imines, followed by electrocyclic ring opening of the N(1)–N(2) bond of the original triazine ring within the adduct and recyclization accompanied by liberation of diethylamine <1990CPB2108>, are also mentioned. The structures of the final products are supported by a single crystal X-ray structure determination for one representative.

- The analogous [3+2] cycloaddition of dimethyl acetylenedicarboxylate (DMAD) to 4,6-disubstituted 1,2,3-triazine 2-imines, followed by skeletal rearrangement of the adducts accompanied by a conjugate addition of the imino N-atom to the dipolarophile, <1983CPB3759> has also been reported.

The effects of solvent and temperature on the direction of the [4+2] cycloaddition of pyrrolidinocyclooctene to 4-methyl-1,2,3-triazine **86c** have been studied. The ratio of products **138** and **139** changed while the total yields dropped with increasing temperature (Equation 51) <1988H(27)2213>.



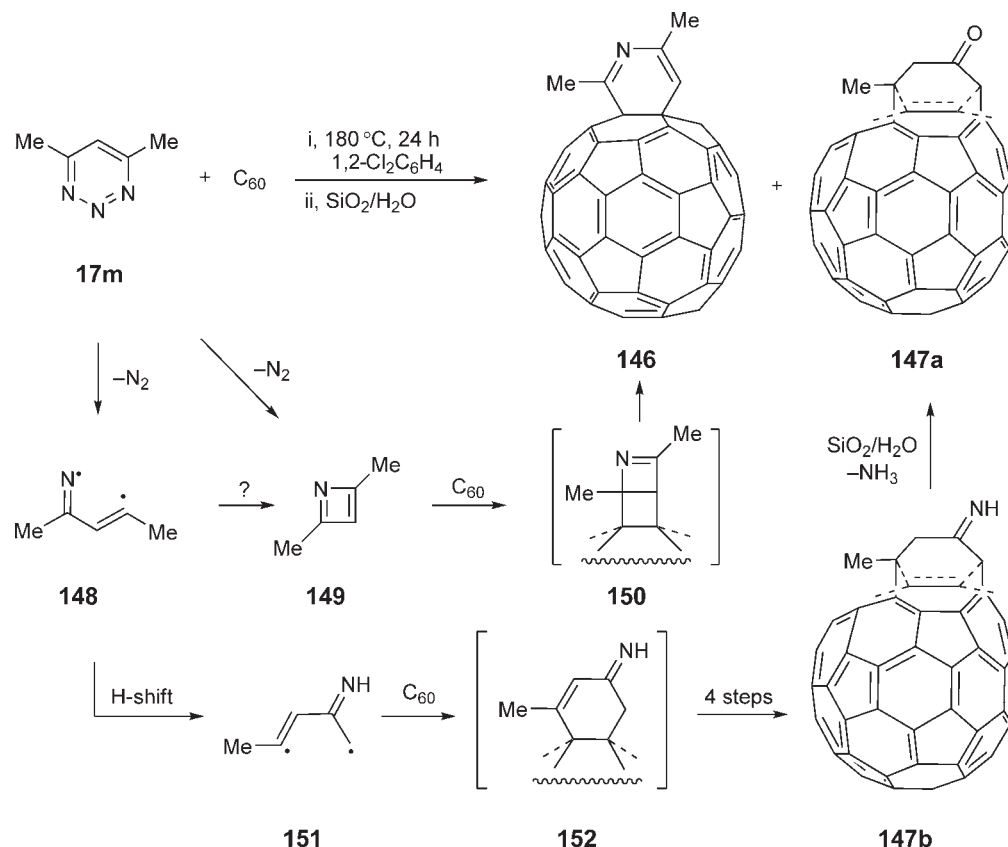
Pyrrolidinoindenes **140** reacted with **86c** to afford **141** and **142**. The latter compound was oxidized with KMnO₄ to give onychine **143a** and 6-methoxyonychine **143b** in 72% and 90% yield, respectively (Equation 52) <1988H(27)2213>. A related approach allowed the synthesis of guaipyridine **144** and epiguaipyridine **145** <1987H(26)595>.



Reaction of preformed enamines (or cyclic ketones and pyrrolidine) with 4,6-dimethyl-1,2,3-triazine **17m** in a focused microwave reactor (atmospheric pressure, 270 W, 20 min, max. temp. 150 °C) allowed the preparation of various annelated pyridines with considerably improved yields <2001SL236> compared to the conventional thermal method (200–220 °C in 1,2-dichlorobenzene) <1989H(29)1809>.

A thermal reaction of the strained diene fullerene C₆₀ with 4,6-dimethyl-1,2,3-triazine **17m** gave the azacyclohexadiene-fused fullerene derivative **146** and another product **147a** after separation of the product mixture by silica gel flash chromatography. Compound **147a** has an eight-membered orifice of the C₆₀ cage (Scheme 10)

<2001JOC8187>. The molecular formulas of both products were determined by HR FAB MS (**146**: $C_{65}H_7N$; **147a**: $C_{65}H_6O$), and the structures were established by ^1H and ^{13}C NMR as well as by comparison of the UV/Vis spectrum of **146** with that of 1,2-dihydrofullerene <1999JOC3483, 1993CB1061>. Compound **147a** also showed a characteristic $C=O$ absorption at 1723 cm^{-1} and its NMR spectra were similar to those of its desmethyl derivative <2000JA8333>.



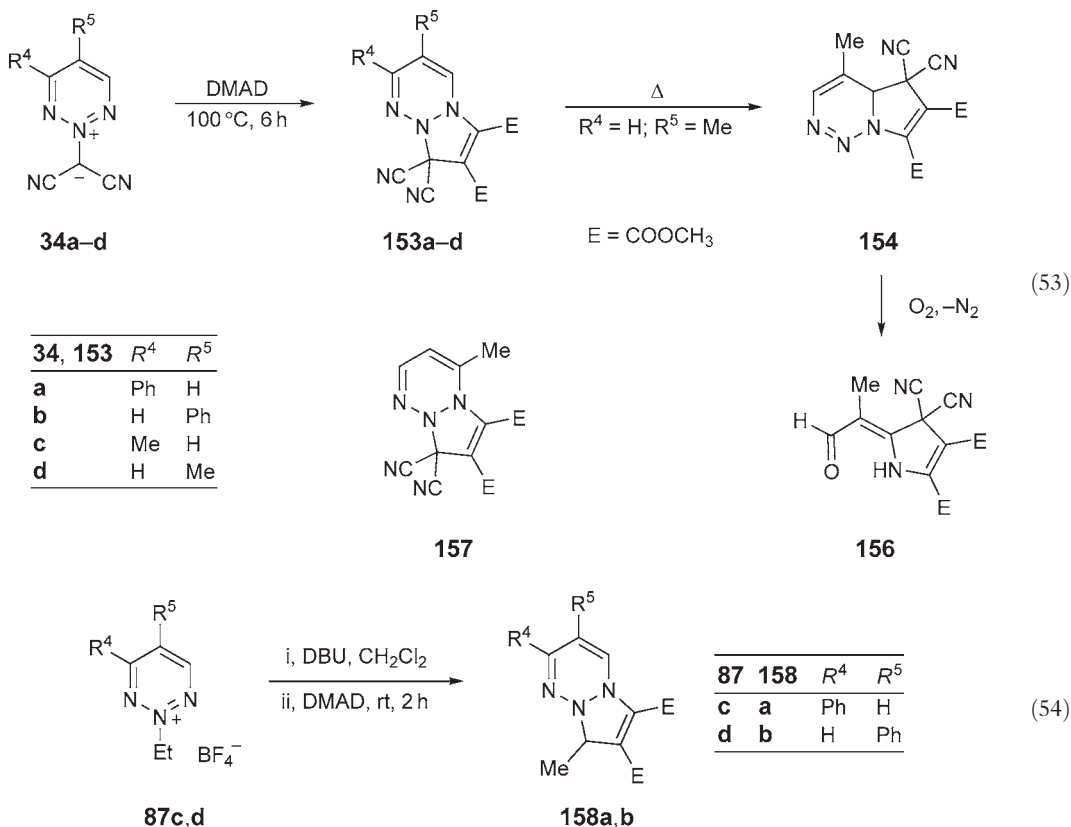
Scheme 10 Thermal reaction of 4,6-dimethyl-1,2,3-triazine with C_{60} .

The formation of **146** and **147a** and **147b** was interpreted in terms of two parallel, independent reaction paths. The reaction leading to **146** was comprised of release of 2,4-dimethylazete **149** and its [4+2] addition to C_{60} followed by electrocyclic ring opening (exothermic by $26.3\text{ kcal mol}^{-1}$) of the azetine **150**.

Compound **147a** is believed to be formed from the addition of the biradical **151** (product of H-migration within **148**) to C_{60} generating **152**, which, after a sequence of steps, eventually forms **147a** via **147b** <2001JOC8187>. Thus, these reactions do not represent direct Diels–Alder additions of C_{60} to **17m** but are reactions of fragmentation products of **17m** with the latter. The temperature applied is probably sufficient to allow formation of an energy-rich intermediate (here **149**).

1,2,3-Triazininium dicyanomethylides **34a–d** react with DMAD at 100 °C in a 1,3-dipolar cycloaddition to yield the bicyclic adducts **153**, which were isolated and completely characterized spectroscopically. They are stable under inert gas at 0 °C, but in $CDCl_3$ solution a slow rearrangement to **154** is observed which is sensitive to oxygen and eventually forms **156** upon workup (Equation 53) <2004EJO4234>.

While in the case of **153c** (42%), a second product (19%) was observed and identified as the pyrazolo[1,2-*a*]-[1,2,3]triazine **157**, adduct **153a** was formed completely site-selectively. Further, the 2-ethyl-1,2,3-triazinium salts **87c** and **87d** react in the presence of base and DMAD to yield the adducts **158**, albeit in poor yield (Equation 54) <2004EJO4234>.



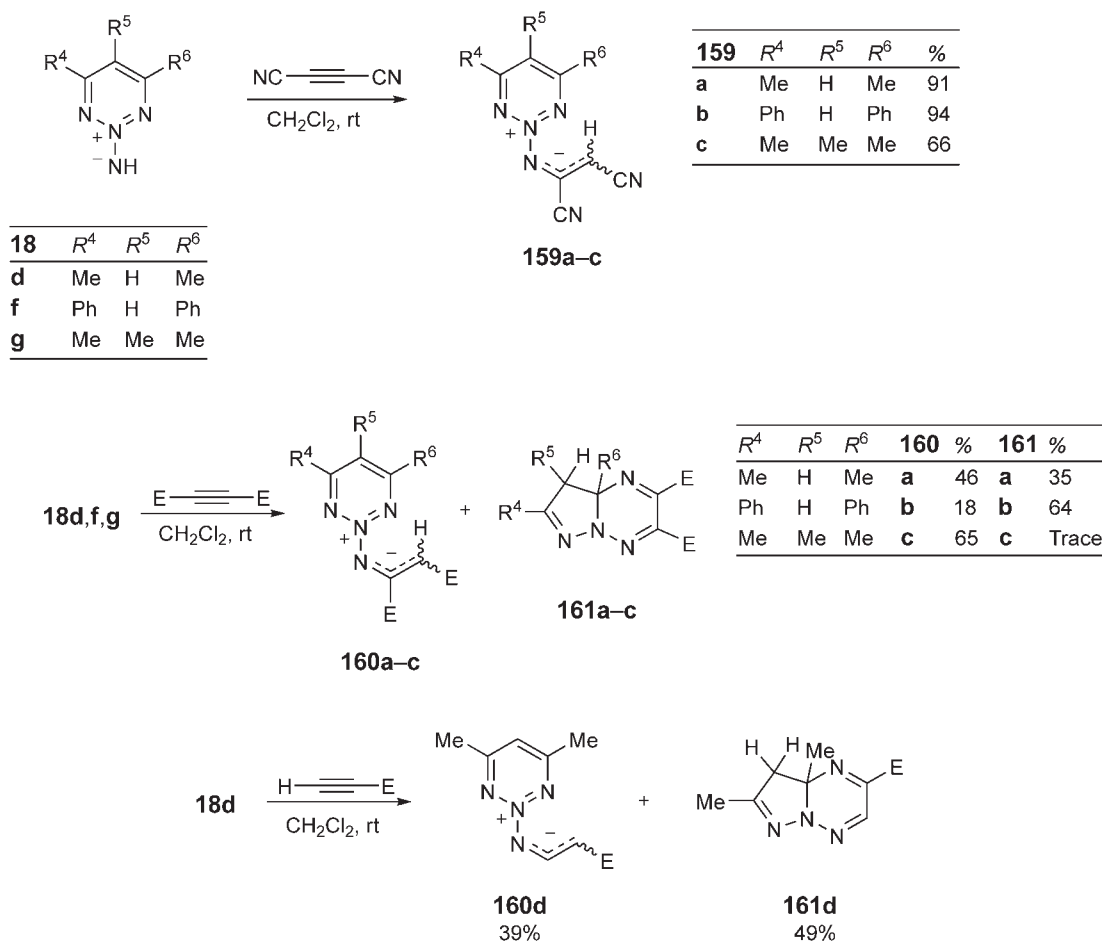
1,2,3-Triazine 2-imines **18d,f,g** undergo Michael-type additions and 1,3-dipolar cycloadditions with electron-deficient alkynes. While the products **159a–c** (from conjugate addition) are the sole products formed with ethynedicarbonitrile, the corresponding adducts **160a–c** from DMAD ($E-C\equiv C-E$ with $E = \text{COOCH}_3$) are always accompanied by bicyclic products **161a–c** originating from 1,3-dipolar cycloaddition followed by rearrangement. Methyl propiolate forms **160d** and **161d** from **18d** (Scheme 11) <1988YZ1056>. See also <1996CHEC-II(6)483> for a brief mention of the results with DMAD.

Several pyrrolidinoalkenes and -cycloalkenes have been added addition-direction-selectively to the N-1,C-4 positions of 1,2,3-benzotriazine **2** (freshly prepared from **162** and used without purification). Release of N_2 and pyrrolidine from intermediate **163** afforded quinolines with various side chains and annelations in low to satisfactory yields from **162** <1998CPB332>. Equation (55) gives one example.

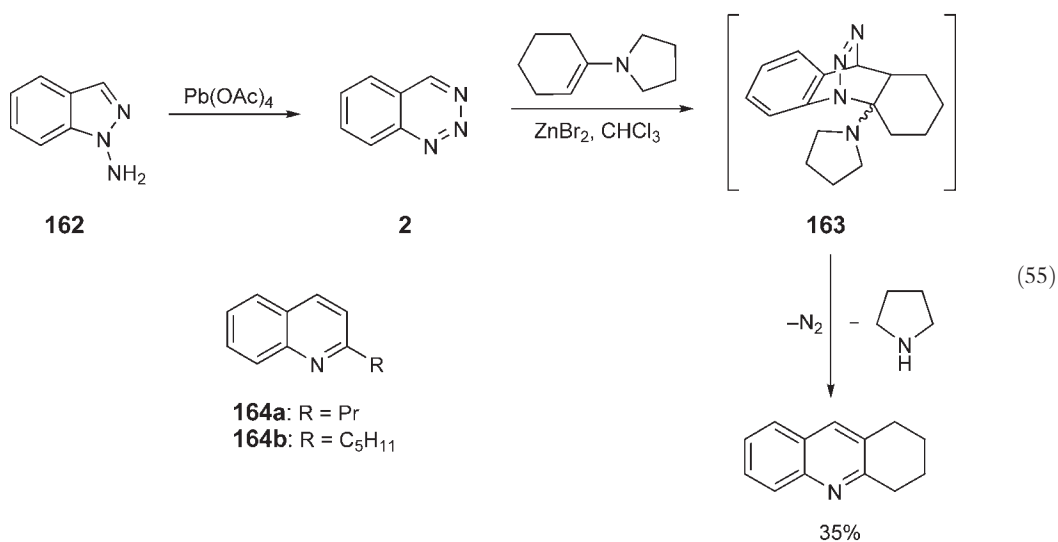
Alkaloids **164a** and **164b** have been prepared accordingly from **2** and the pyrrolidine enamines of 2-pentanone and 2-heptanone <1998CPB332>, and a series of 2-arylquinoline and 2-arylquinol-4-one alkaloids have been prepared from **2** and its 6-methoxy derivative with suitably designed enamines <1999CPB1038>.

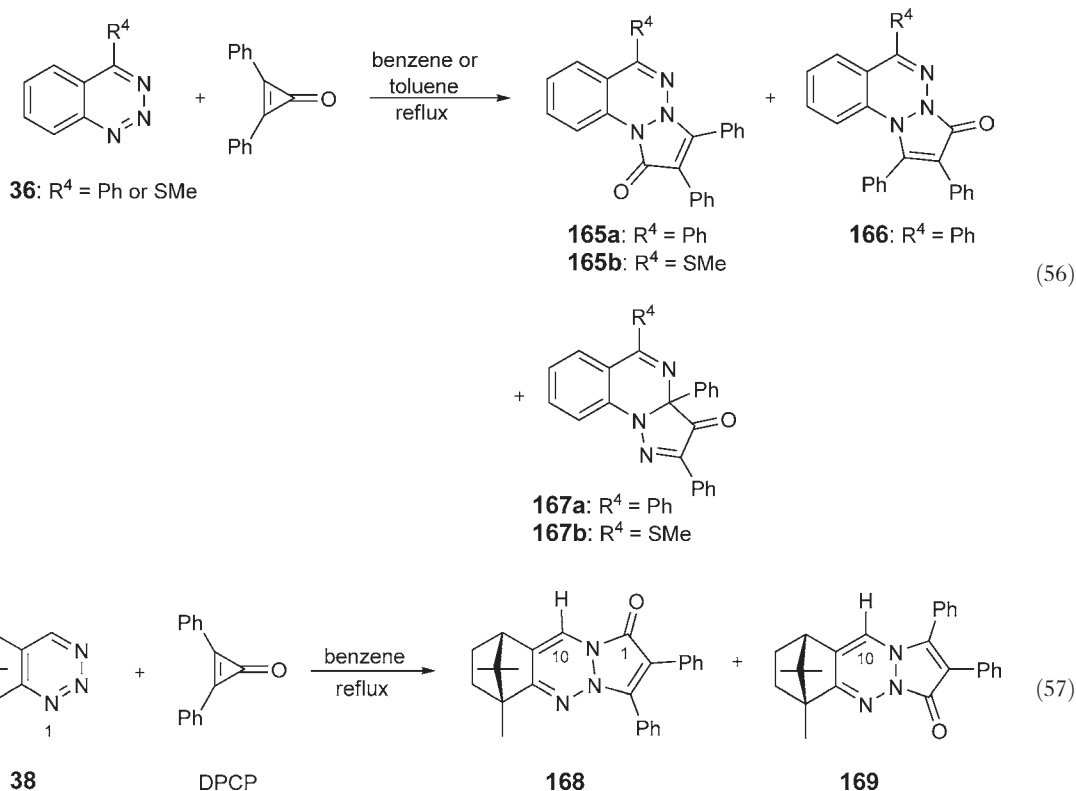
Diphenylcyclopropenone (DPCP) has been reported to give three types of products with 4-phenyl-1,2,3-benzotriazine (**36**; $R = \text{Ph}$) (Equation 56). While products **165a** (38%) and **166** (8%) are formed in boiling benzene, **167a** requires higher temperatures (boiling xylene) for its formation in appreciable amounts (39%), and control experiments revealed that it did not form from rearrangement of either **165a** or **166**. In refluxing toluene, the thioether **36** ($R^4 = \text{SMe}$) reacts with DPCP to give adducts **165b** and **167b**. Structures **165a** and **167b** had been confirmed by single crystal X-ray structure determinations, and a multistep explanation for the formation of **167** has been offered <1980CC808>.

More recently, the cycloaddition of DPCP to camphortriazine **38** has been reported to give two 1:1 adducts **168** and **169** in 26% and 65% yields, respectively, via addition across the C(1)–C(2) bond of DPCP (Equation 57) <2000JHC1663>. The linear annelation in the products might be favored by the steric influence of the 8-Me group of **38** (in contrast to the angular additions of DPCP to **36** as mentioned above), and a 0.53 ppm downfield shift found for the 10-H (7.68 ppm as result of a *peri*-effect with the $C=O$ group) in **168** compared to 7.15 ppm for 10-H in **169** is compatible with this connectivity.



Scheme 11 Reactions of electron-poor alkynes with 1,2,3-triazine 2-imines.



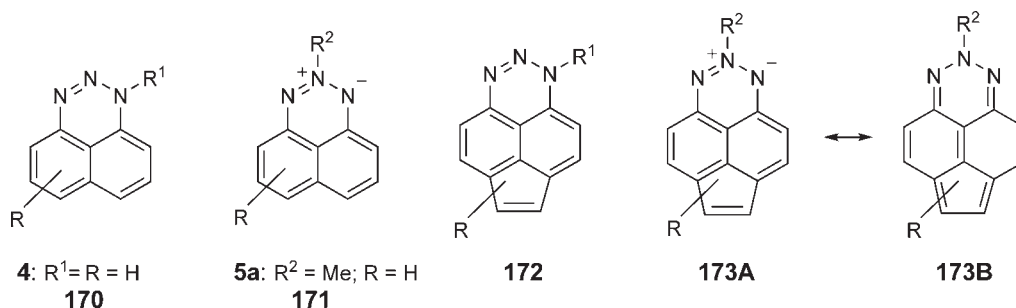


9.01.6 Reactivity of Nonconjugated Rings

9.01.6.1 Naphtho[1,8-*de*]-1,2,3-triazines and Related Compounds

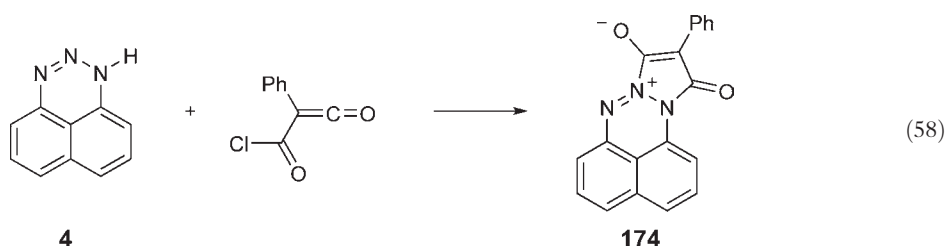
This class has not received attention in CHEC-II(1996), except for one example of a cycloaddition, while the literature prior to 1975 has been reviewed thoroughly by Neunhoeffer [<1978HC\(33\)3>](#) with regard to

- preparation of 1*H*-naphtho[1,8-*de*]-1,2,3-triazines **170**, naphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ides **171**, as well as of acenaphtho[5,6-*de*]triazines **172** and **173**;
- N-alkylation, N-arylation, and N-amination of **170** ($R^1 = \text{H}$), N-alkylation of 6,7-dihydroderivatives of **172** ($R^1 = \text{H}$), and oxidation of the products;
- bromination, nitration, and sulfonation of **171** and **173** ($R^2 = \text{Me}$, $R = \text{H}$);
- aryl/ethyl exchange by treatment of **171** ($R^2 = \text{Ar}$, $R = \text{H}$) with triethylphosphite, reaction of **171** ($R^2 = \text{alkyl}$, $R = \text{H}$) with benzoyloxy (substitution products only) and 2-cyano-2-propyl radicals (substitution and addition products) and with DPPH (6,6'-dehydrodimerization);
- hydrogenation of **171** ($R^2 = \text{Me}$, $R = \text{H}$) to 1,8-diaminonaphthalene and of **172** to 5,6-diaminoacenaphthenes;
- triazine ring opening of **170** ($R^1 = \text{NH}_2$) with lead tetraacetate (LTA), generating naphthalene 1,8-diyl (1,8-dehydronaphthalene), and trapping reactions thereof;
- photolysis of **170** ($R^1 = \text{Me}$) in the presence of benzene, cyclohexene, and vinyl bromide (ethyne equivalent) and of **172** ($R^1 = \text{Me}$, $R = \text{H}$) in the presence of vinyl bromide and 1,2-dichloroethene;
- $[12\pi+2\pi]$ dipolar cycloaddition of DMAD to **171** ($R^2 = \text{Me}$, $R = \text{H}$) giving **173** ($R^2 = \text{Me}$, $R = 6,7\text{-(COOMe)}_2$); and
- physical properties, especially as regards light absorption, since all naphtho[1,8-*de*]triazines are deeply colored. Compound types **170** and **172** as a rule are red (or orange, brown, or violet) while **171** and **172** tend to be blue (or blue-green or even black). The enhanced basicity of **170** compared to **171** allows separation of the former by crystallization of salts.

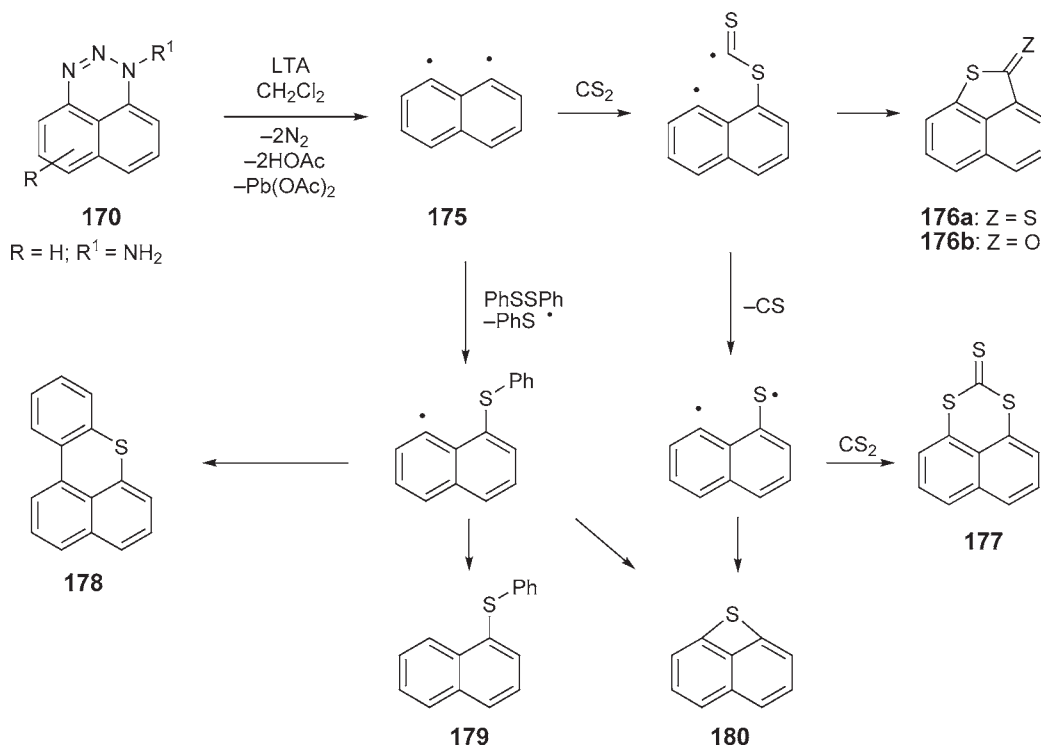


In addition, tables of individual compounds of type **170–173** known prior to the mid-1970s have been given <1978HC(33)3>. UV/Vis spectral data of various naphtho[1,8-*de*]triazines have been listed in **Table 11** (Section 9.01.3.4). Relevant chemical information on the title compounds that appeared after 1975 is given below.

(Chlorocarbonyl)phenylketene as a reactive bielectrophile is reacted with N-1,N-2 of **4** to give the deep-violet tetracyclic compound **174** (Equation 58) <1980JA3971>.



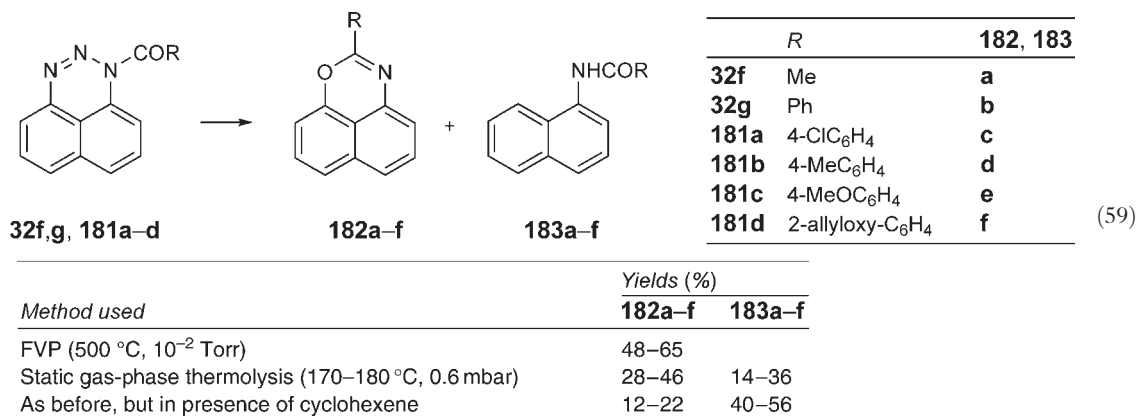
The study of 1,8-dehydronaphthalene **175**, prepared by LTA oxidation of **170** ($R^1 = NH_2$, $R = H$) <1969JC760, 1969JC765>, has been extended to trapping with carbon disulfide, generating **176a** and **176b**, **177**, and **180** <1981J(P1)413>, and with diphenyl disulfide, generating **178**, **179**, and **180** <1983TL821> (Scheme 12).



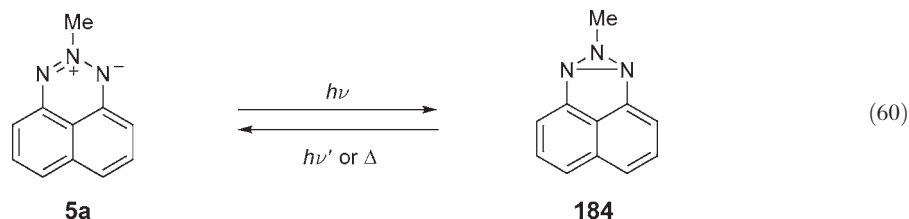
Scheme 12 Trapping of 1,8-dehydronaphthalene **175** with carbon disulfide and diphenyl disulfide.

When prepared in benzene, 1,8-dehydronaphthalene does not react with fullerene C_{60} but with the solvent to generate 6b,10a-dihydrofluoranthene, which in turn undergoes a [4+2] cycloaddition to C_{60} , generating 1,2-(7,10-etheno-6b,7,8,9,10,10a-hexahydrofluorantheno)[60]fullerene <1994TL6661>.

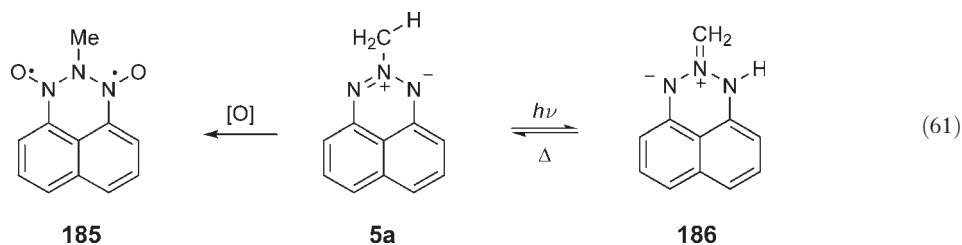
Acetylation of **4** may be achieved using NaH in Et_2O under reflux for 2 h <1970JC298>, and both acetyl and benzoyl derivatives **32f** and **32g** and aroyl derivatives **181a–d** could be obtained in moderate yields by treatment with the corresponding acyl chlorides in the presence of triethylamine in chloroform at 0 °C. Thermolysis of compounds **32f** and **32g**, and **181a–d** effected release of N_2 with rearrangement to **182a–f** and **183a–f** (Equation 59) as follows <2005T10507>:



In addition to the light-induced reactions already reviewed elsewhere <1978HC(33)3>, the reductive degradation of **4** to 1-aminonaphthalene by irradiation in triethyl- or diethylamine as solvent should be mentioned <2002TH1>. 2-Methylnaphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide **5a** is photostable toward broad-band UV or 254 nm irradiation in ether (298 K) or in the crystal (303 and 213 K), but upon excimer laser excitation (351 nm) at 10 or 85 K the blue color of **5a** is bleached with formation of the triaziridine **184** (Equation 60). The latter is stable in liquid methyltetrahydrofuran (MTHF) at 110 K but is degraded upon 254 nm irradiation to several colorless products <1986AGE828>; see also Section 9.01.3.4 and Table 11.



Compound **5a** is also of interest as an inhibitor of photooxidation of polybutadiene. It has been suggested that **5a** forms a bis-nitroxide **185** in the polybutadiene film during the initial phase of the irradiation (in air) acting later as an inhibitor of photooxidation <1981MI261>; see also <1980CIL418>. Alternatively, reversible formation of a photo- tautomer **186** as a light-utilizing pathway has been tentatively suggested (Equation 61) <1981MI261>.

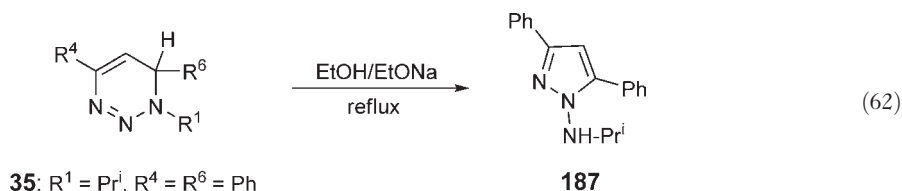


9.01.6.2 Dihydro-1,2,3-triazines

In a review on dihydrotriazine chemistry, the possible isomeric dihydro-1,2,3-triazines have been categorized but no mention of their relative importance or the factual existence of some of them has been made, and only the preparation of some 2,5-dihydro-1,2,3-triazines has been mentioned briefly <1985AHC1>.

9.01.6.2.1 1,6-Dihydro-1,2,3-triazines

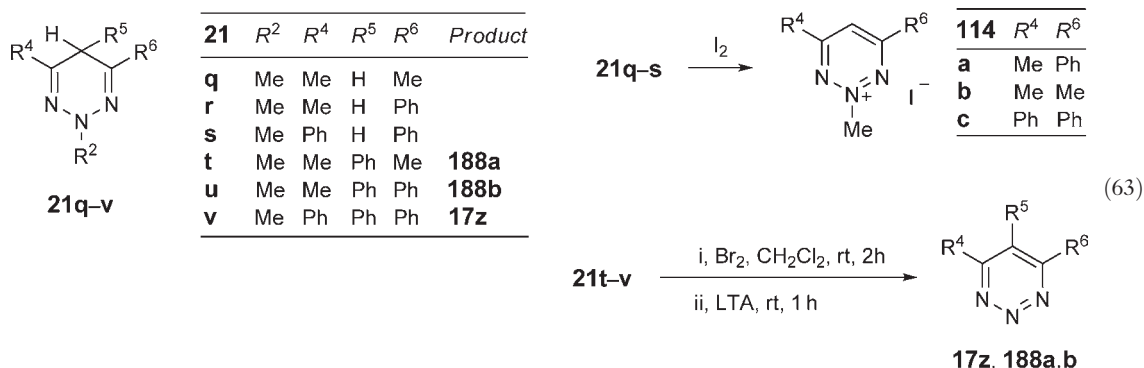
There is only one case known about the reactivity of 1,6-dihydro-1,2,3-triazines. Compound **35** reacts with an excess of sodium ethoxide in ethanol at reflux to effect ring contraction to 1-(isopropylamino)-3,5-diphenylpyrazole **187** (Equation 62) <1996H(43)1759>.



9.01.6.2.2 2,5-Dihydro-1,2,3-triazines

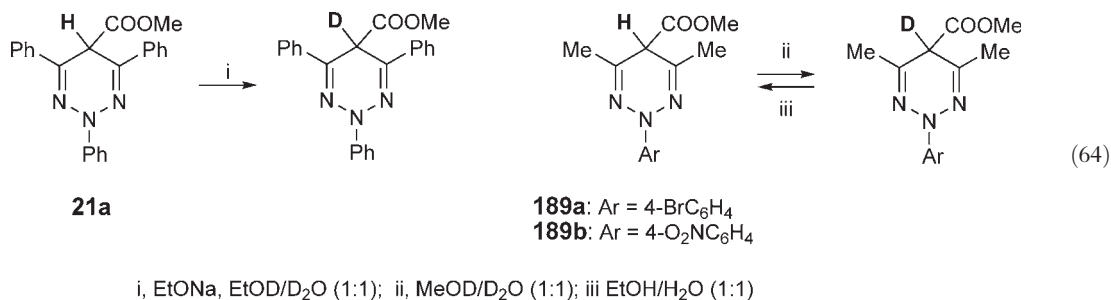
Air oxidation of 2-unsubstituted-2,5-dihydro-1,2,3-triazines afforded the fully unsaturated 1,2,3-triazines, whereas with MCPBA (2 equiv in CH_2Cl_2 at 0°C) the corresponding 2-oxides were obtained. 2-Methyl-2,5-dihydro-1,2,3-triazines, on the other hand, under the same conditions gave 2-methyl-1,2,3-triazoles together with 2-methyl-2,5-dihydro-1,2,3-triazin-5-ones. The latter type of ketone is formed as the main product, together with di(2-methyl-2,5-dihydro-1,2,3-triazin-5-yl), by the action of potassium superoxide under oxygen. The latter product appears to be the main product in an argon atmosphere <1990TL7193, 1992CPB2283>. This detail has not been mentioned explicitly in CHEC-II(1996) <1996CHEC-II(6)483>.

In addition to these cases, the oxidation of 4,6-disubstituted-2-methyl-2,5-dihydro-1,2,3-triazines **21q-s** by I_2 gives 2-methyl-1,2,3-triazinium iodides **114a-c** <1990TL7193>, whereas the treatment of **21t-v** with bromine followed by LTA generated the N-2-demethylated 1,2,3-triazines **17z** and **188a** and **188b** (Equation 63) <1992CPB2283>.



Oxidation of 2,5-dihydro-1,2,3-triazine **21g** with ceric ammonium nitrate (CAN) gave almost complete decomposition of starting material; products **119b** and **17m** were isolated in low yield <1996J(P1)2511>. For oxidations of 2-(1-chloroethoxycarbonyl)-2,5-dihydro-1,2,3-triazines **118** with the same reagent, see Section 9.01.5.4.

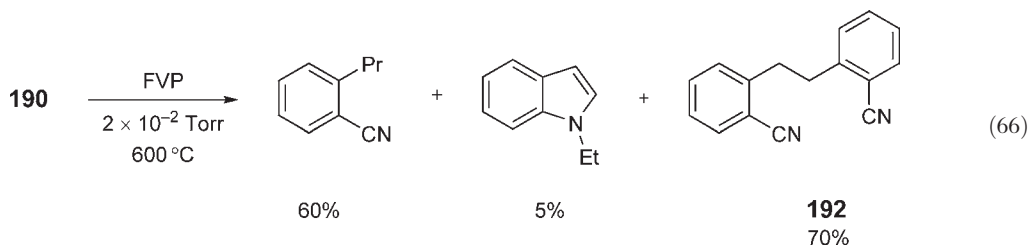
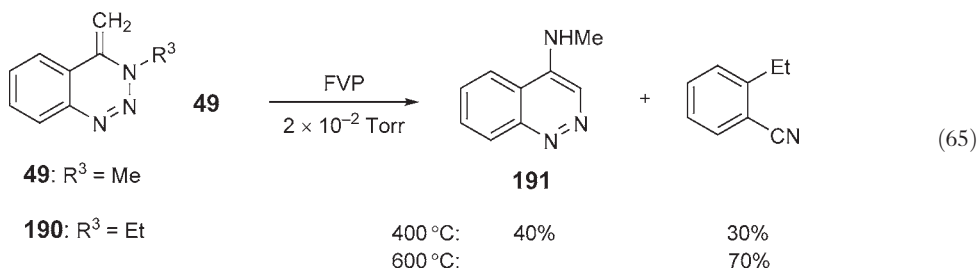
Since in a compound like **21a** C-4 and C-6 are carbonyl-C-atom-like, and thus render **21a** analogous to a triacylmethane, easy H/D-exchange at C-5 is a logical consequence. This exchange requires the presence of alkali in the case of **21a** <2006JOC5679> but works with MeOD/ D_2O alone in the case of **189a** and **189b** (Equation 64) <1990J(P1)3321>.



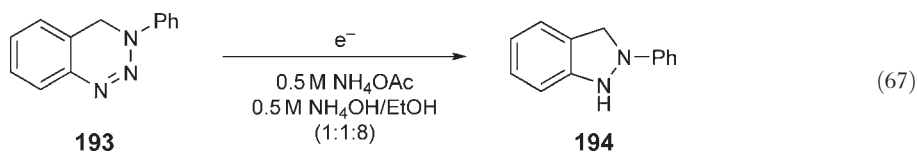
9.01.6.2.3 3,4-Dihydro-1,2,3-benzotriazines

Long-known reactions of these compounds have been listed in the 1978 review and are best explained by ring opening between N-2 and N-3 to generate diazonium amide zwitterions. From the latter, all reaction products formed through azo coupling, displacement of diazonium by OH or Cl, and reduction of diazonium to the amine function can be explained, although one reference given there [<1897JPR356>](#) should be supplemented by [<1895JPR257>](#). In addition, the photolysis of 3-phenyl-3,4-dihydro-1,2,3-benzotriazine to give 1-phenylbenzazetine, benzaniline, and 5,6-dihydrophenanthridine has been treated in the same review [<1978HC\(33\)3>](#) as well as in [<1984CHEC\(3\)369>](#).

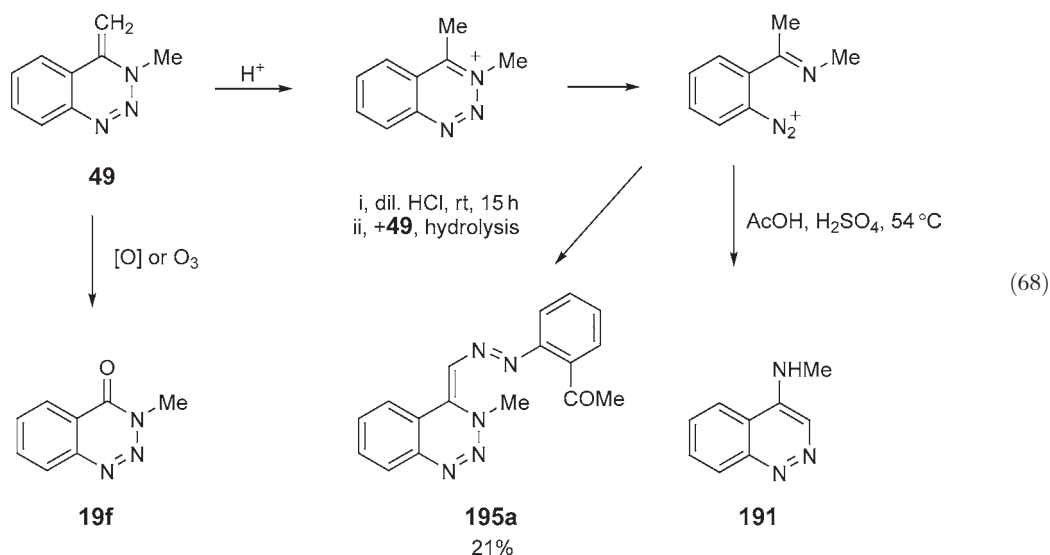
FVP of compound **49** is reported to give 4-methylaminocinnoline **191** and 2-ethylbenzonitrile at 400 °C ([Equation 65](#)), while the corresponding 3-ethyl derivative **190** is degraded at 600 °C to 2-propylbenzonitrile, *N*-ethylindole, and the dinitrile **192** ([Equation 66](#)) [<1985TL941>](#).



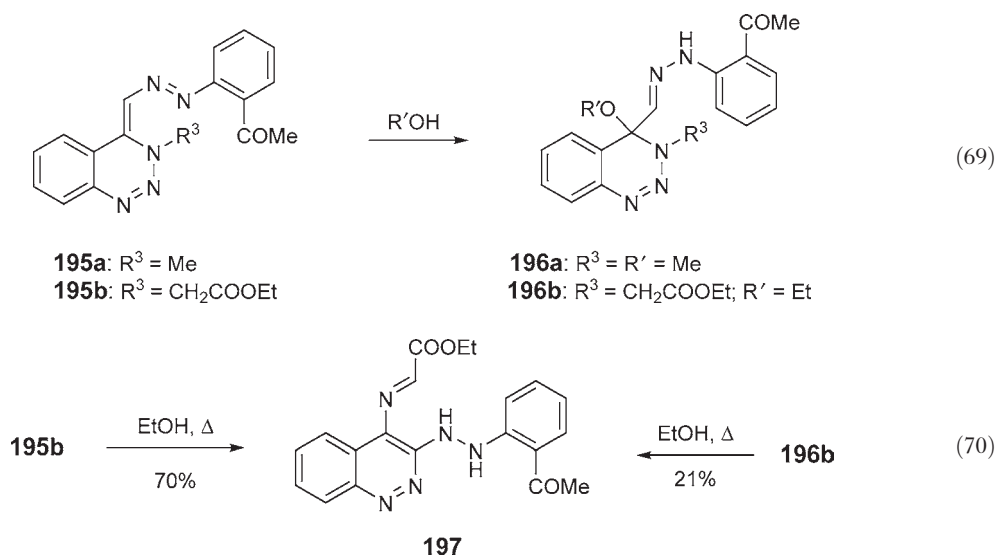
3-Phenyl-3,4-dihydro-1,2,3-benzotriazine **193** undergoes ring contraction to 2-phenylindazoline **194** upon cathodic reduction ([Equation 67](#)) [<1976BSF433>](#). For a related study, see [<1979ACB233>](#); whereas for an analogous electroreduction of 3-phenyl-3,4-dihydro-1,2,3-benzotriazin-4-one **19n** and electroreductive degradation of **193** by HCl/EtOH to *N*-benzylaniline, see [Section 9.01.5.6](#).



Compound **49** is transformed into 3-methyl-3,4-dihydro-1,2,3-benzotriazin-4-one **19f** by oxygen or ozone and degraded by acid to **191** and **195a** ([Equation 68](#)) [<1985CJC2455>](#). The formation of **191** is made plausible by a so-called Dimroth rearrangement (see [Scheme 8](#), [Section 9.01.4.5](#) for a related but thermal process).



3-Alkyl-4-(arylazomethylene)-3,4-dihydro-1,2,3-benzotriazines **195a** and **195b** tend to add alcohols at C-4 with formation of hydrazones **196a** and **196b** (Equation 69). Heating of **195b** and **196b** in EtOH causes rearrangement to the cinnoline **197** (Equation 70) <1991JHC1709>.

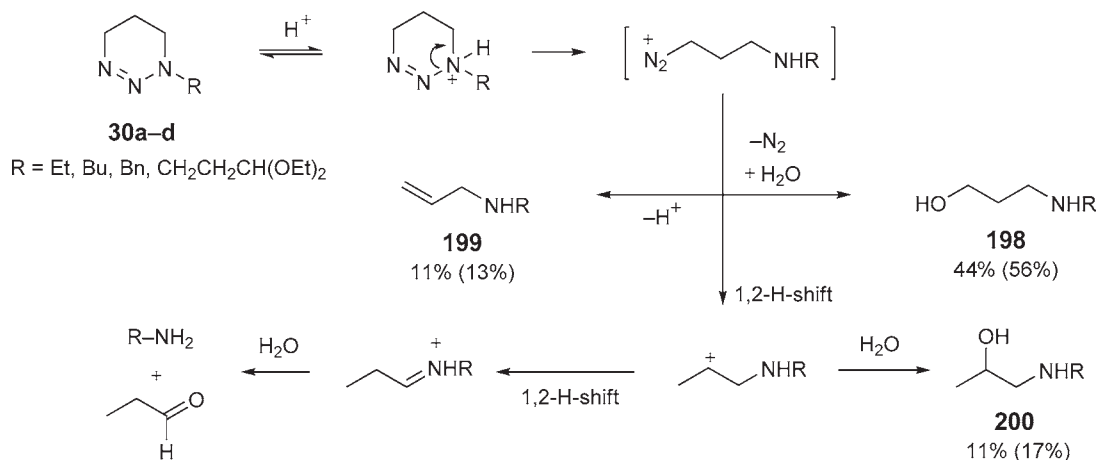


The ring-chain tautomerism typical for 4-hydroxy-3,4-dihydro-1,2,3-benzotriazines, and permanent ring transformations based on this tautomerism, have been treated previously in Section 9.01.4.5.

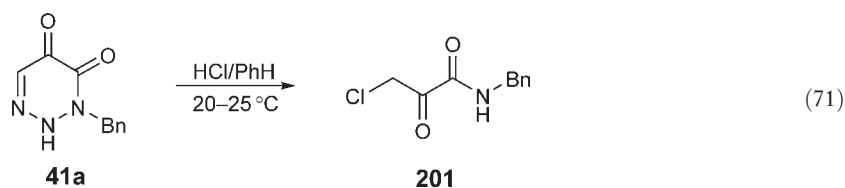
9.01.6.3 Tetrahydro-1,2,3-triazines ('Triazinines')

This class, representing cyclic triazenes, has a general tendency to undergo hydrolytic degradation initiated by ring opening and release of N_2 . The hydrolysis (MeCN/aqueous buffer, 5 h) of 1-alkyl-1,4,5,6-tetrahydro-1,2,3-triazines **30a-d** results in five degradation products, namely 3-alkylamino-1-propanol **198**, *N*-alkyl-2-propenylamine **199**, 1-alkylamino-2-propanol **200**, propanal, and amine $R-NH_2$ (Scheme 13) <1997JOC8660>. The yields given refer to $R = Et$ (Bn) after 5 h at 25 °C as determined by ^1H NMR analysis.

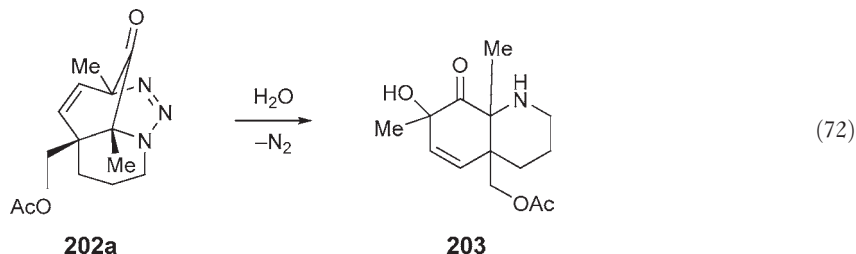
Bubbling hydrogen chloride gas through a benzene solution of the dione **41a** caused ring opening with release of N_2 and formation of *N*-benzyl-3-chloro-2-oxopropanamide **201** (Equation 71) <1995RJO1005>.



Scheme 13 Acid degradation of 1-alkyl-1,4,5,6-tetrahydro-1,2,3-triazines.



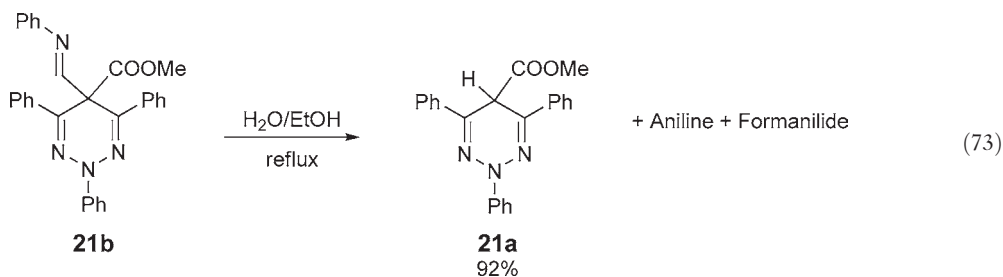
The bridged tetrahydro-1,2,3-triazinone **202a** gave a 75% yield of the octahydroquinolinone **203** upon exposure to atmospheric moisture for 20 days and chromatography on silica gel (Equation 72) <1988JOC391>.



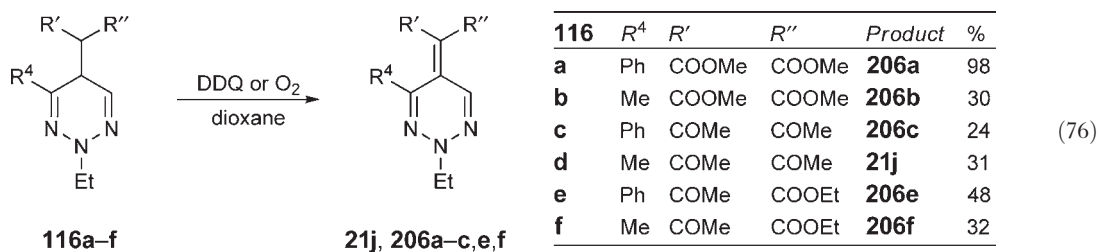
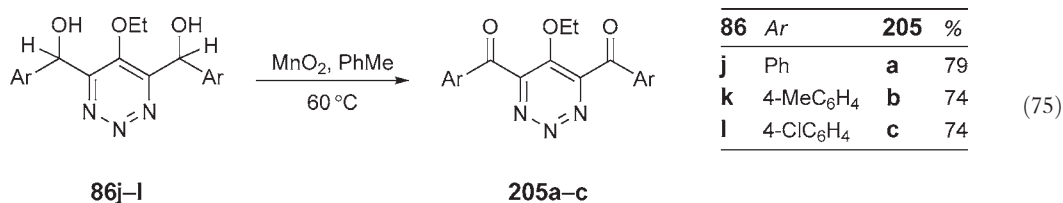
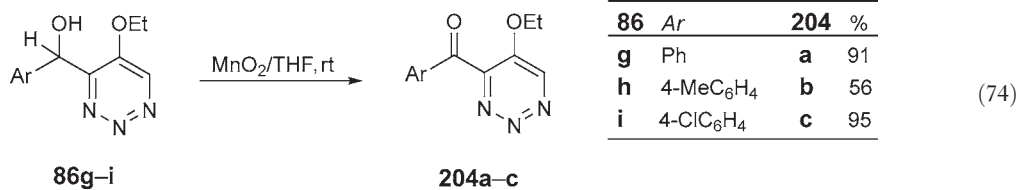
9.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

9.01.7.1 Reactions Involving Carbon Substituents

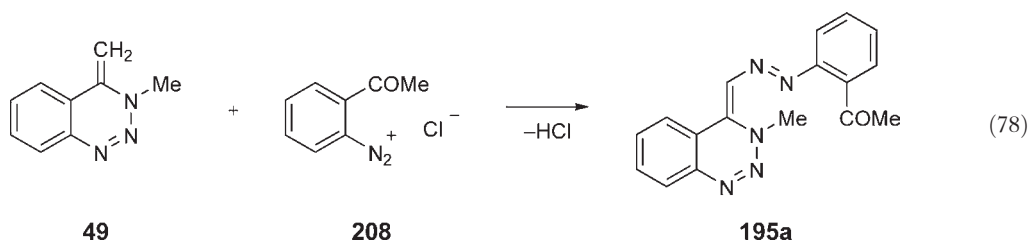
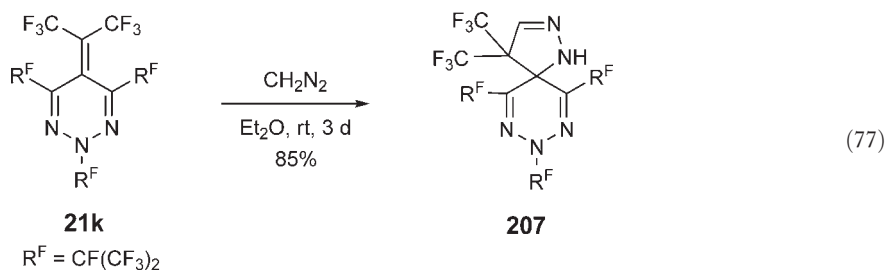
5-Acyl groups in 5,5-diacyl-2,5-dihydrotriazines such as **21b** may be released in refluxing aqueous ethanol in the sense of a retro-Claisen condensation (Equation 73). The intermediacy of a C-5 carbanion (or carbanion equivalent) in this degradation to **21a** is supported by deuterium uptake at that position when the reaction is carried out in EtOD/D₂O <2006JOC5679>. For a related release of a 5-alkoxyethanedioyl group from eight 4,6-disubstituted 5-alkoxy-carbonyl-5-(alkoxyethanedioyl)-2-aryl-2,5-dihydro-1,2,3-triazines, see <1990J(P1)3321>.



Arylhydroxymethyl groups at C-4 and C-6 of 5-ethoxy-1,2,3-triazines **86g–l** are oxidized by MnO_2 to aryl groups (Equations 74 and 75) <1998MI119>. 5-Diacylmethyl-2,5-dihydro-1,2,3-triazines **116a–f** may be dehydrogenated by either air oxygen or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane to yield **21j** and **206a–c,e,f** (Equation 76) <2003S413>.

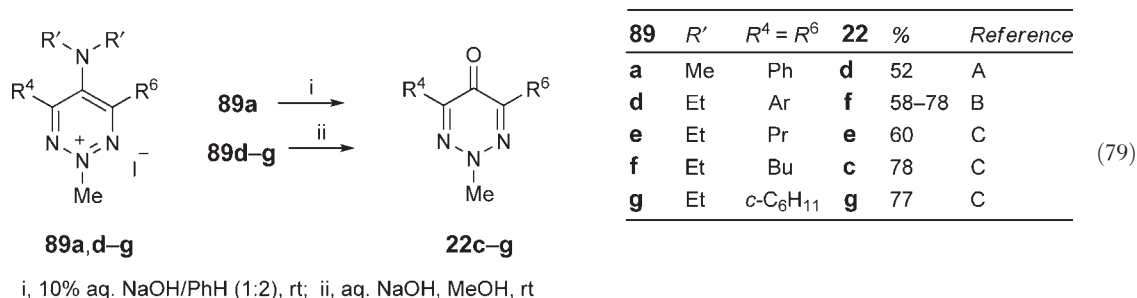


A 1,3-dipolar cycloaddition of diazomethane across the exocyclic double-bond transforms **21k** into the spiro compound **207** (Equation 77) <1987CC1697, 1988T2583>, and the enamine-like terminus of the methylene group in **49** is attacked by 2-acetylbenzenediazonium chloride **208** to form the azo compound **195a** under neutral or basic conditions (Equation 78) <1984ACB185>.

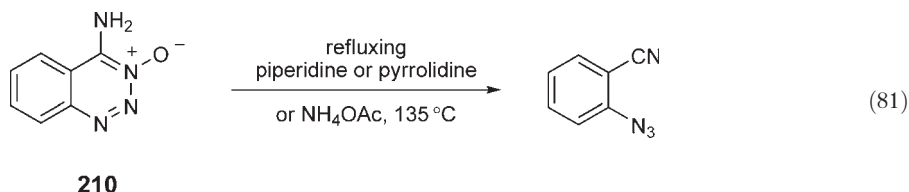
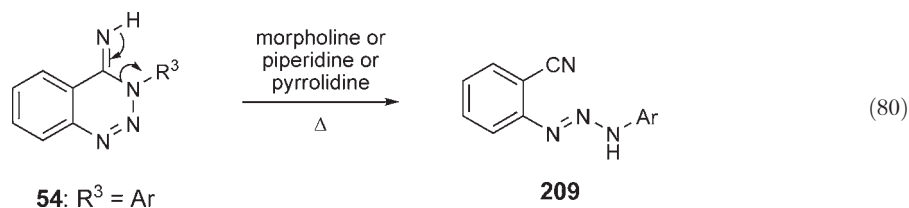


9.01.7.2 Reactions of Amino and Imino Groups

In addition to the cases of displacement of 5-amino functions in 2-EWG-substituted 1,2,3-triazin-2-ium salts yielding 2-EWG-substituted 2,5-dihydro-1,2,3-triazin-5-ones (EWG = COOMe, 2,3-(dialkylamino)cyclopropenylum, picryl) <1979CB1535, 1984CHEC(3)369>, examples of hydrolysis of 4,6-disubstituted-5-dialkylamino-2-methyl-1,2,3-triazinium salts **89a** and **89d–g** generating 2-methyl-2,5-dihydro-1,2,3-triazin-5-ones **22c–g** have been reported (Equation 79) (<1985BCJ1073> (A), <2002HCO325> (B), <2003H(59)477> (C)).



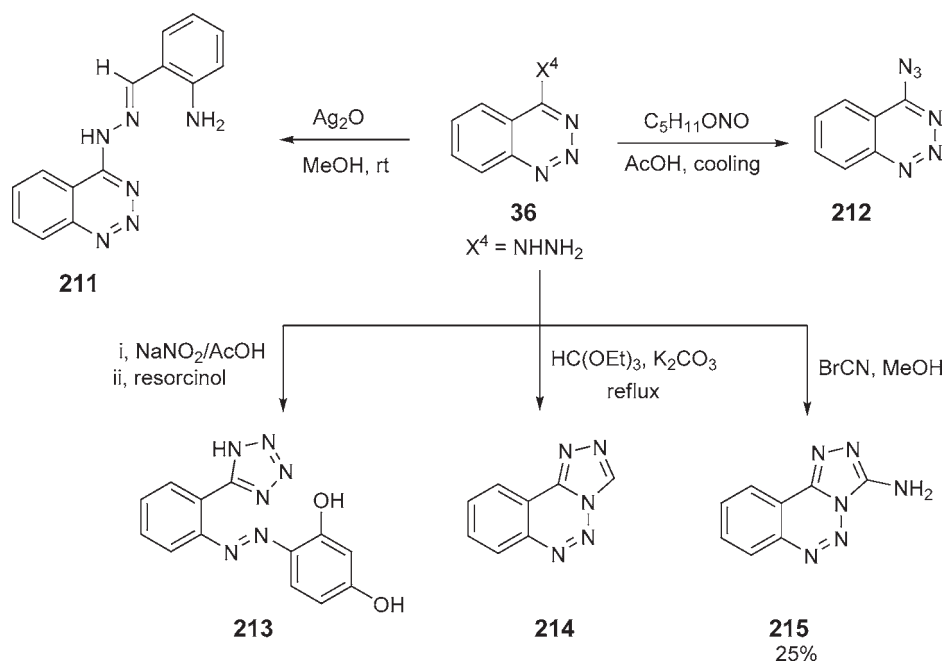
The NH proton of 3-aryl-3,4-dihydro-1,2,3-benzotriazin-4-imines is sufficiently acidic to be abstracted by base leading to opening of the triazine ring <1984CHEC(3)369>. A further example for this reactivity is the transformation of **54** ($R^3 = \text{Ar}$) to the triazenes **209** in good yield (Equation 80) <1974J(P1)611>, but compare with Equations (28) and (29) in Section 9.01.5.4! A related process is the ring opening of 4-amino-1,2,3-benzotriazine 3-oxide **210** in boiling piperidine or pyrrolidine <1974J(P1)611> or fused ammonium acetate as shown in Equation (81) <1961JCS4930>.



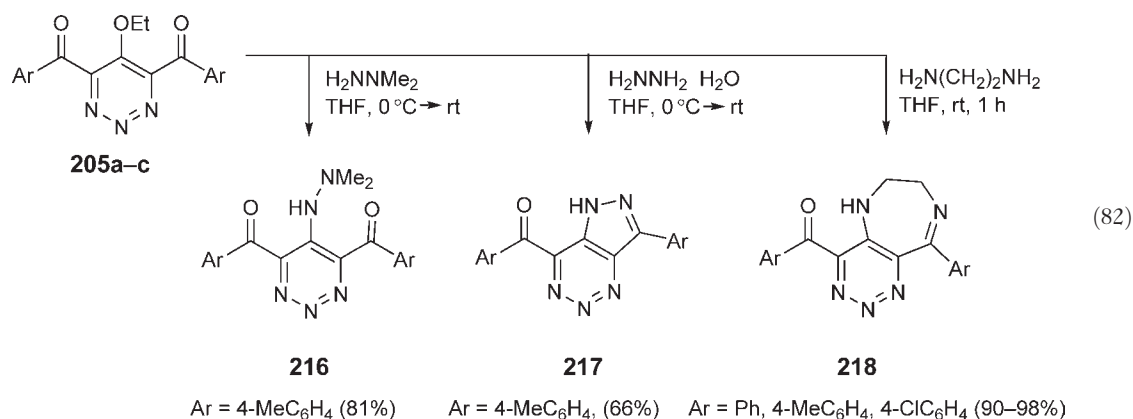
Attempted preparation of the parent 1,2,3-benzotriazine **2** from 4-hydrazino-1,2,3-benzotriazine (**36**: $X^4 = \text{NHNH}_2$) by dehydrogenation and N_2 release instead gave the hydrazone **211** together with a small amount of benzonitrile <1975J(P1)31>. Treatment of 4-hydrazino-1,2,3-benzotriazine with pentyl nitrite afforded 4-azido-1,2,3-benzotriazine **212**, while (deviating from the statement made in <1984CHEC(3)369>) reaction with sodium nitrite in AcOH followed by trapping with resorcinol gave the 2-(tetrazol-5-yl)azobenzene **213** <1971JHC785>. 1,2,4-Triazole annulations of **36** ($X^4 = \text{NHNH}_2$) have been achieved with C_1 reagents such as triethyl orthoformate, leading to **214** <1970JOC3448>, and cyanogen bromide, affording **215** <1971JHC785> (see Scheme 14).

9.01.7.3 Reactions of Hydroxy (Alkoxy) Substituents and Oxo Groups

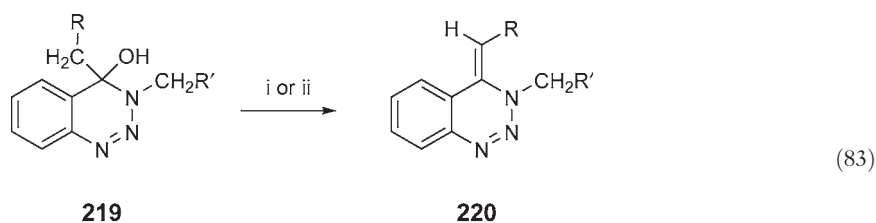
In 4,6-diaroyl-1,2,3-triazines **205a–c**, the 5-ethoxy group can be displaced by good nucleophiles (Equation 82) <1998MI119>, leading to products **216–218**. Cyclizations with one carbonyl group ensue when a second nucleophilic site is present in the N-nucleophile. The reaction starts with an attack at C-5 (not at one of the acyl groups) as a bimolecular nucleophilic substitution at an electron-poor arene bearing an activated leaving group.



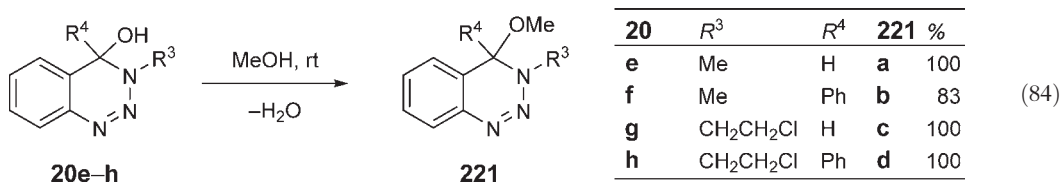
Scheme 14 Transformations of 4-hydrazino-1,2,3-benzotriazine.



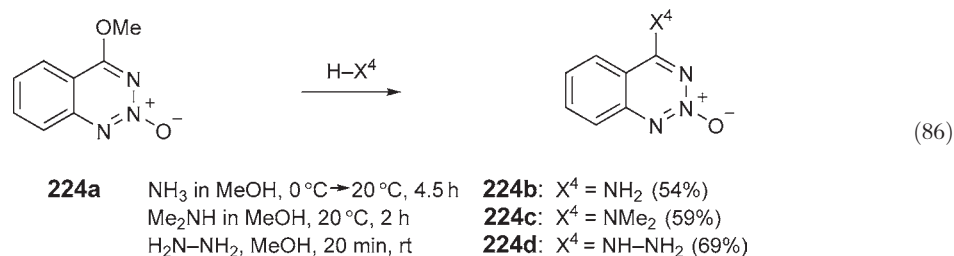
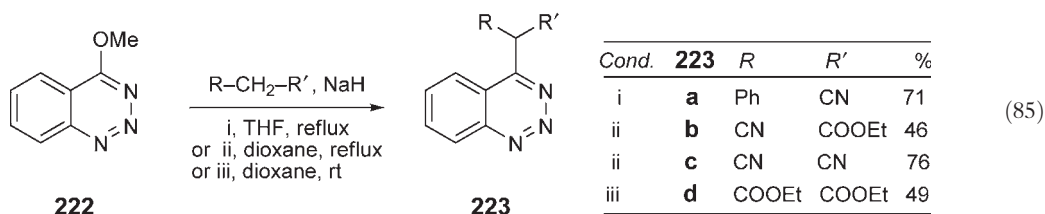
4-Alkyl-4-hydroxy-3,4-dihydro-1,2,3-benzotriazines **219** are dehydrated readily under a variety of conditions to yield the 4-alkylidene compounds **220** (Equation 83) (<1985CJC2455> (A), <1987CJC292> (B)). Also, the 4-OH group in **20e–h** may be displaced readily by a methoxy group to afford the methyl ethers **221** in very good yield in the absence of α -hydrogen atoms in the C-4 side chain (Equation 84). If R^4 is Me or Et, however, the yield of methoxylated product may drop to 22–25% <1987CJC292>.



R = H; R' = H, CN: i, CHCl₃, Al₂O₃, rt (A)
R = Me; R' = H: ii, PhH, *p*-TsOH, reflux (B)

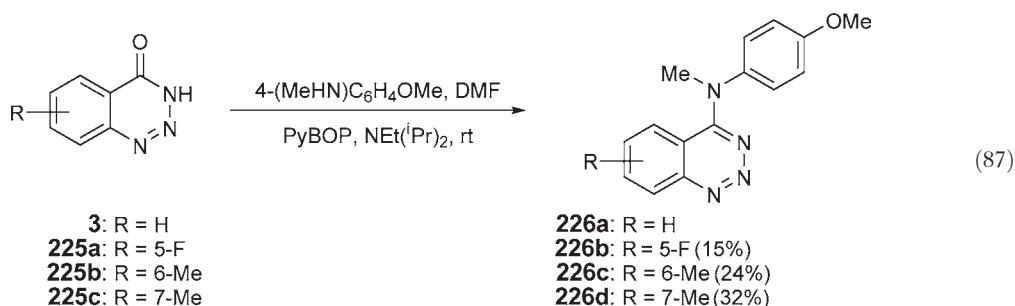


The activated MeO group in 4-methoxybenzotriazine **222** (like in an imidoester) may be exchanged by anions of methylene-active compounds in an aprotic medium (Equation 85) <1990H(31)895>, or by a hydrazine moiety in the transformation to 4-hydrazino-1,2,3-benzotriazine with hydrazine hydrate in methanol <1975J(P1)31>. On the other hand, the methoxy group may be demethylated by boron tribromide to generate the benzotriazinone **3** in 67% yield <1986J(P1)1249>. The similarly activated MeO group in the benzotriazine 2-oxide **224a** may be exchanged with amino or hydrazino groups to generate the 2-oxides **224b–d** (Equation 86) <1988J(P1)1509>. With KOH in MeOH/H₂O at 20 °C, **224a** is transformed into 3,4-dihydro-4-oxo-1,2,3-benzotriazine 2-oxide **91** <1988J(P1)1509>.



Moderate yields of thiones are obtained by treatment of 3,4-dihydro-1,2,3-benzotriazin-4-ones with P₄S₁₀ in refluxing pyridine or toluene. The same conditions have been applied to 2-alkyl-1,2,3-benzotriazin-4-ones, generating the corresponding 4-thiolates <1984CHEC(3)369>.

Early attempts to convert 1,2,3-benzotriazinone **3** into 4-chloro-1,2,3-benzotriazine using PCl₅/POCl₃ under reflux generated only 2-chlorobenzonitrile <1956JCS3242> and it has been claimed that 4-chloro-1,2,3-benzotriazine is unknown <1983CC1344>. In a recent patent <2006WO2006/074223>, it is claimed that this compound had been prepared by reaction of **3** with POCl₃ in the presence of ethyldiisopropylamine in toluene at room temperature followed by aqueous (!) workup. The crude brown product gave a 4% yield of *N*-methyl-(4-methoxyanilino)-1,2,3-benzotriazine **226a** after treatment with *N*-methyl-*p*-anisidine. Improved yields of analogous benzotriazines **226b–d** have been obtained from **225a–c** by reaction with the above-mentioned aniline in DMF in the presence of ethyldiisopropylamine and (benzotriazol-1-yloxy)tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP) at room temperature (Equation 87) <2006WO2006/074223>. Heteroannelated 1,2,3-triazin-4-ones are converted using phosphorus oxychlorides via the pyridinium or 4-dimethylaminopyridinium salts <1995JHC1417, 2000NN39> or via 4-(1,2,4-triazol-1-yl) derivatives <2001JOC4776, 2000NN39>.

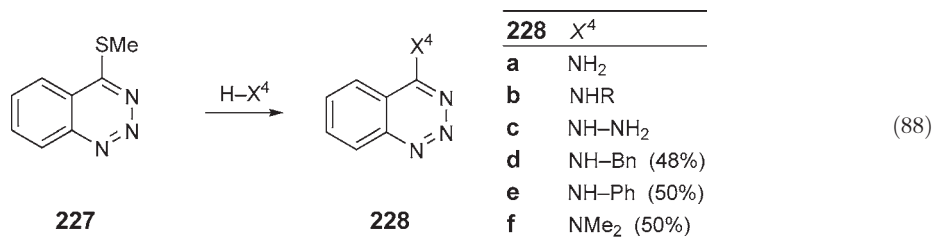


9.01.7.4 Sulfur Functional Groups

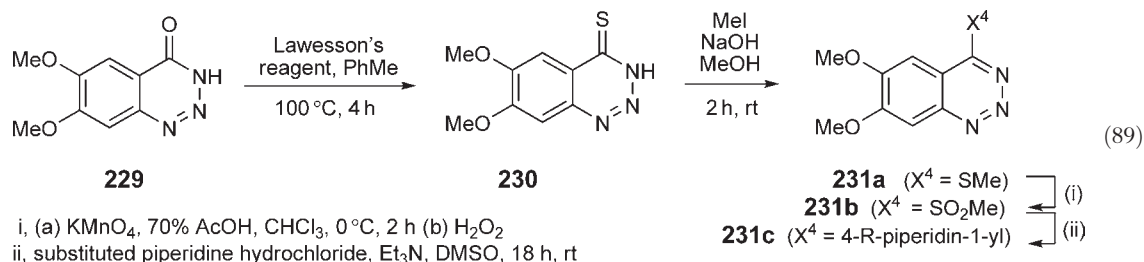
3,4-Dihydro-1,2,3-benzotriazin-4-thiones react with ammonia, amines, hydrazine, and hydroxylamine to yield 4-amino-, 4-hydrazino-, and 4-hydroxylamino-1,2,3-benzotriazines <1984CHEC(3)369>.

Methyl iodide, in the presence of NaOMe in abs. MeOH at room temperature, transforms 3,4-dihydro-1,2,3-benzotriazin-4-thione into 4-methoxy-1,2,3-benzotriazine **222** (64%) <1986J(P1)1249>. The same reagent at reflux temperature is reported to methylate thiones at sulfur, for example, to generate 4-methylthio-1,2,3-benzotriazine **227** (79%) <1971JHC785>. 4-Benzylthio-, 4-phenacylthio-, and 4-ethoxycarbonylmethylthio-1,2,3-benzotriazines have been prepared similarly <1971JHC785>.

Compound **227** reacts with ammonia, primary amines, and hydrazine in refluxing ethanol to the corresponding 4-amino- and 4-hydrazino-1,2,3-benzotriazines **228a–c** <1984CHEC(3)369> and **228d** and **228e** <1970JC765>, while **228f** is formed from **227** with dimethylamine in MeOH at room temperature (Equation 88) <1989J(P1)543>.



Lawesson's reagent was found quite suitable to convert 6,7-dimethoxy-3,4-dihydro-1,2,3-benzotriazin-4-one **229** to the corresponding thione **230**, which was methylated to **231a**. Oxidation of the latter furnished the methylsulfone **231b**, which in turn underwent displacement by several 4-substituted piperidines (Equation 89) <1990CPB2179>.

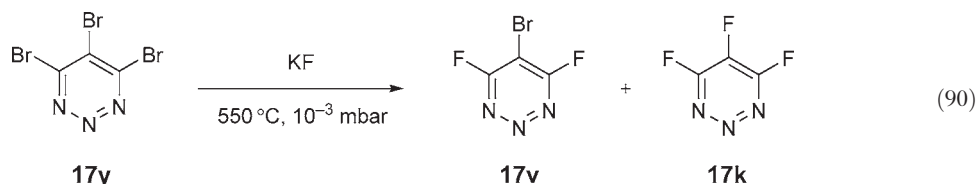


9.01.7.5 Halogen displacements

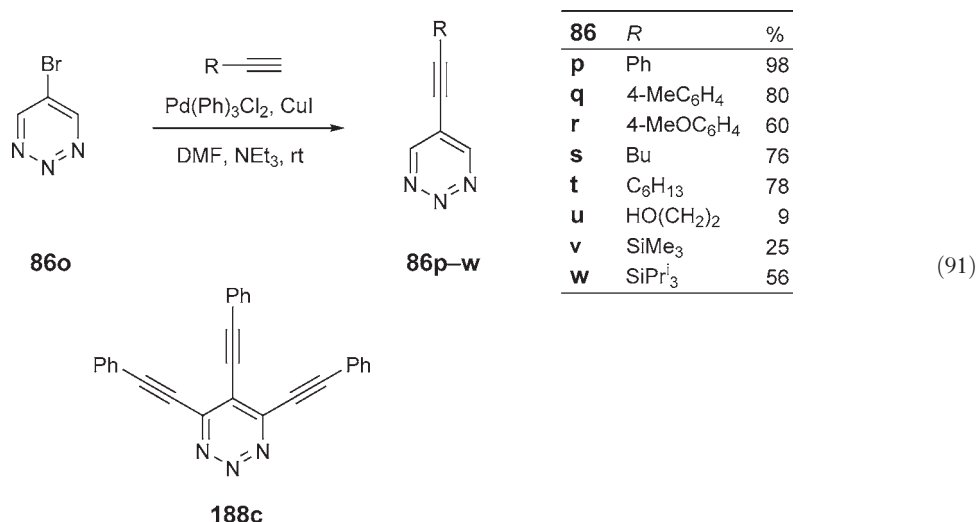
The following reactions have been reviewed in CHEC(1984) and CHEC-II(1996):

- 5-chloro-4,6-bis(dimethylamino)-2-methyl-1,2,3-triazinium iodide upon treatment with malononitrile affords 5-dicyanomethylenc-4,6-bis(dimethylamino)-2-methyl-2,5-dihydro-1,2,3-triazine <1984CHEC(3)369>;
- the transformation of 4,6-disubstituted 5-halo-1,2,3-triazines into 2,5-dihydro-1,2,3-triazin-5-ones and the displacements of two or three chlorine atoms in 4,5,6-trichloro-1,2,3-triazine **17x** <1996CHEC-II(6)483> with
 - amines, generating 4,6-diamino-5-chloro-1,2,3-triazines,
 - methoxide, phenoxide, or ethanethiolate to afford 4,6-dimethoxy-5-chloro- and 4,5,6-trimethoxy-1,2,3-triazine, 4,6-di(phenoxy)-5-chloro-, and 4,5,6-tri(ethylthio)-1,2,3-triazine, respectively,
 - KF or KF/1,1,1,3,3,3-hexafluoropropene to generate trifluoro- and chlorofluoro-1,2,3-triazines or perfluoroisopropyl-1,2,3-triazines, respectively.

The electroreduction of several 5-halo-1,2,3-triazines under argon has been reviewed in Section 9.01.4.3. Displacement of bromine from 4,5,6-tribromo-1,2,3-triazine **17y** with KF at elevated temperature and low pressure has been explored recently; the 4- and 6-bromine atoms are replaced selectively first, giving a 1:1 mixture of **17v** and **17k** (Equation 90) <1999SAA695>.



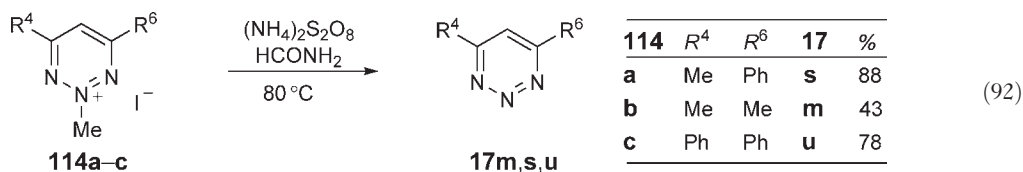
While the displacement of the 4- and 6-Br atoms in **17y** by dimethylamine has been known for some time <1979CB1529>, the formation of 4-anilino-5,6-dibromo-1,2,3-triazine in 70% yield from **17y** has been reported recently <2003TH1>. All three Br-atoms of **17y** have been displaced by methoxy groups in 91% yield, but attempted substitution of 5-bromo-1,2,3-triazine **86o** by an alkoxy moiety led to gas evolution and decomposition. Nucleophilic substitution at C-5 in 1,2,3-triazines seems to be disfavored, and *ab initio* calculations demonstrate C-5 to be more negative than C-4 and C-6 <2003TH1>. 5-Bromo-1,2,3-triazine **86o** is, however, susceptible to Sonogashira couplings with alkynes to form 5-alkynyl-1,2,3-triazines **86p-w** (Equation 91), and **17y** reacts by trisubstitution with phenylethyne, generating **188c** under the same conditions <2003TH1>.



9.01.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms

9.01.8.1 Reactions of Carbon Substituents

4,6-Disubstituted-2-methyl-1,2,3-triazinium iodides **114a-c** are demethylated to the triazines **17m,s,u** by reaction with formamide and diammonium persulfate (Equation 92) <1991H(32)2015>. This special case has already been mentioned in Section 9.01.5.6 together with the removal of 2-dicyanomethylene groups from the 1,2,3-triazinium dicyanomethylides **34** (R⁵ = H; R⁴, R⁶ = Me, Et, Ph) under the same conditions; see also <1996CHEC-II(6)483>. Cycloadditions of 2-ethyl-1,2,3-triazinium tetrafluoroborates and 1,2,3-triazinium 2-dicyanomethylides have been treated in Section 9.01.5.7.



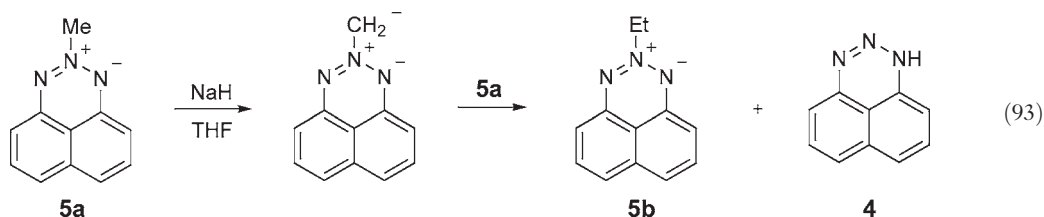
Hydrolysis of 2-(1-chloroethoxycarbonyl)-2,5-dihydro-1,2,3-triazine **118b** in MeCN/H₂O (1:1) at 60 °C readily affords the corresponding 2-deacylated-2,5-dihydrotriazine **21g** (90%) <1996J(P1)2511>.

For the rearrangement of 3-substituted-3,4-dihydro-1,2,3-benzotriazin-4-imines **54** (R³ = Bn, Ar) to the isomeric 4-benzyl- (or aryl-) amino-1,2,3-benzotriazines **36**, see Section 9.01.4.4. A substituent shift from N-2 to N-3 in 2-methyl- (2-aryl-) 1,2,3-benzotriazin-2-ium-4-olates to give the 3-methyl- (3-aryl-) 3,4-dihydro-1,2,3-benzotriazin-4-ones by irradiation in acetonitrile has been reviewed previously <1984CHEC(3)369>.

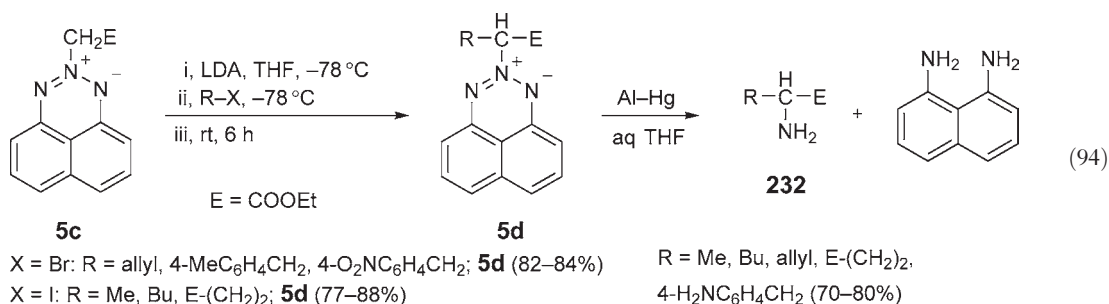
Reduction by lithium aluminium hydride (LAH) or addition of phenylmagnesium bromide transforms the aroyl groups in 3-aroyle-3,4-dihydro-1,2,3-benzotriazin-4-ones **93b** and **93c** into more hydrolyzable 3-(1-hydroxy-1-arylalkyl) groups. Accordingly, the parent benzotriazinone **3** is reached in both cases prior to or during aqueous workup <1960JOC1501>. 3-Substituents such as CH₂OMe or CH(Me)OEt, which had served as N-3 protecting groups in benzotriazinone 1-oxides, are removed readily with conc. HCl in MeOH at room temperature in good yields <1989J(P1)543, 1996CHEC-II(6)483>.

The OH group in 3-hydroxymethyl-3,4-dihydro-1,2,3-benzotriazin-4-one is replaced by chlorine under treatment with thionyl chloride in chloroform <1956USP2758115> and by bromine under treatment with phosphorus tribromide in acetonitrile <1955DEP927270>. 3-Chloromethyl-3,4-dihydro-1,2,3-benzotriazin-4-one is used for the manufacture of Azinphos methyl by exchange of the chlorine with *O,O'*-diethyl-dithiophosphate in the presence of sodium bicarbonate in acetone <1955DEP927270>.

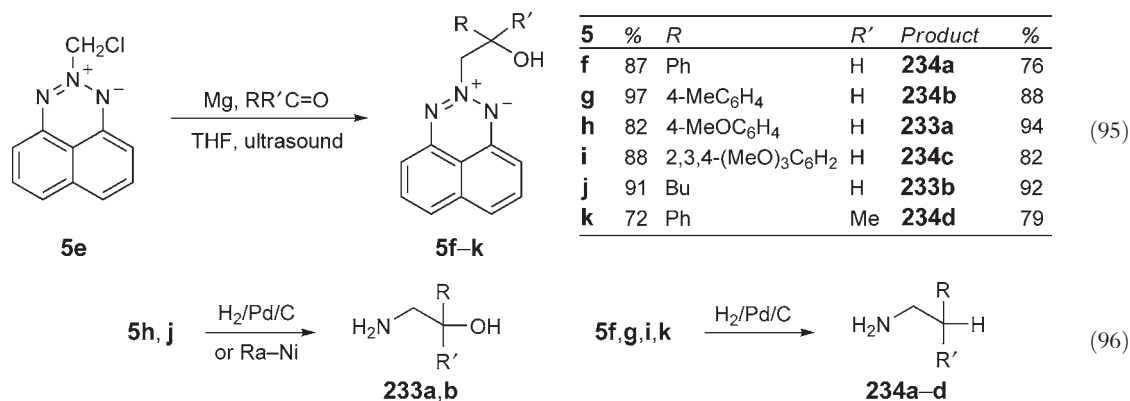
When 2-methylnaphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide **5a** is treated with NaH in THF, a mixture of 2-ethylnaphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide **5b** and naphtho[1,8-*de*]-1,2,3-triazine **4** is obtained, very likely by nucleophilic attack of the methylene anion upon the methyl group of unreacted **5a** (Equation 93) <2000TL4685>.



α -CH Acidity in compounds such as **5a** seems to be general; one α -H-atom in **5c** thus may be substituted by lithiation followed by reaction with alkyl halides yielding **5d**. Reductive cleavage of the triazine ring in **5d** releases an α -amino acid ester **232** in good overall yield and 1,8-diaminonaphthalene (Equation 94) <2000TL6665>.



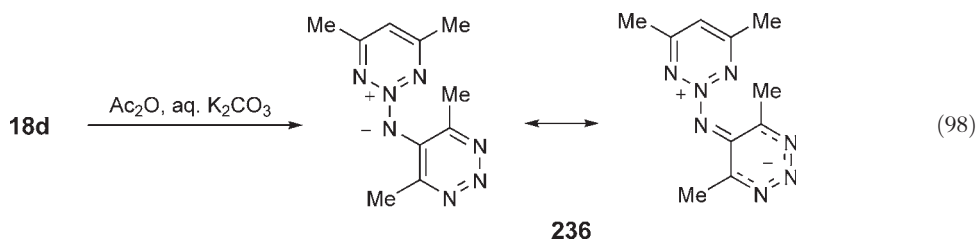
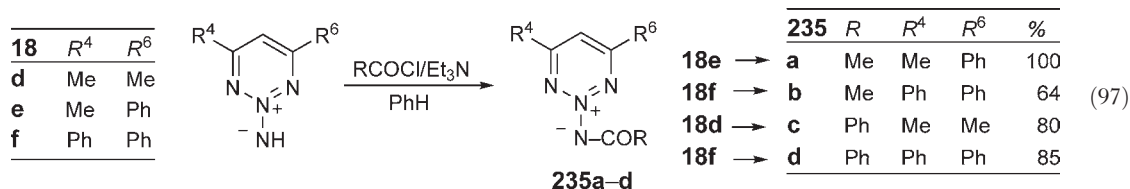
2-Chloromethylnaphtho[1,8-*de*]-1,2,3-triazin-2-ium-1-ide **5e**, on the other hand, was found to be unreactive toward butyllithium under a variety of conditions and was also reluctant to form the corresponding Grignard reagent. However, when a mixture of **5e**, magnesium, and an aromatic aldehyde (or valeraldehyde or acetophenone) in THF was sonicated, the β -branched products **5f-k** were obtained in good yields. Catalytic hydrogenation of the latter released 1,8-diaminonaphthalene in all cases and either the β -amino alcohols **233** or the primary amines **234** resulted (Equations 95 and 96) <2000TL4685>.



9.01.8.2 Transformation of Nitrogen Substituents

The deprotonation of 2-amino-1,2,3-triazinium salts **97a,c,d** to 1,2,3-triazinium 2-imines **18d,f,g** has been treated in Section 9.01.5.2 (see Equation 19), and for the conversion of **18d,f,g** with electron-deficient alkynes into Michael adducts and cycloadducts, see Scheme 11 (Section 9.01.5.7). 4,6-Diphenyl-1,2,3-triazine 2-imine **18f** has been methylated with MeI at the imino N-atom to give 2-dimethylamino-4,6-diphenyl-1,2,3-triazinium iodide, and 4,6-dimethyl-1,2,3-triazine 2-imine **18d** was protonated using conc. HBr in Et₂O to afford 2-amino-4,6-dimethyl-1,2,3-triazinium bromide in 83% yield, or further transformed with nitrous acid into 4,6-dimethyl-1,2,3-triazine, respectively <1988YZ1056>.

The imine function in the 2-imines **18d–f** is acylated readily with acetyl or benzoyl chloride to generate the *N*-acyl species **235a–d** (Equation 97); however, treatment of **18d** with acetic anhydride in the presence of potassium carbonate affords the 2-(1,2,3-triazin-5-yl)imine **236** (Equation 98) <1988YZ1056>.

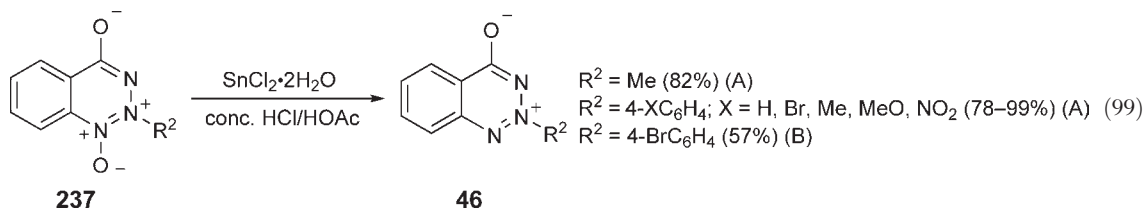


For reactions of 3-amino-3,4-dihydro-1,2,3-benzotriazin-4-one such as ring opening effected by acid or hydroxyl ion, oxidation with LTA to give benzocyclopropanone, and reductive deamination with zinc and acetic acid, see <1984CHEC(3)369>. Deamination of 1-aminonaphtho[1,8-*de*]-1,2,3-triazine to generate the parent **4** may be effected with nitrous acid or diphenylnitrosamine in high yield <1969JC756>, while treatment with LTA gives 1,8-dehydronaphthalene (see Section 9.01.6.1).

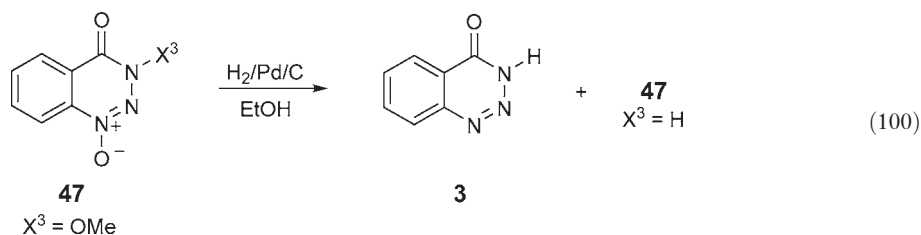
9.01.8.3 Transformation of Oxygen Substituents

The deoxygenation of 1,2,3-triazine 1- and 2-oxides by catalytic hydrogenation to give 2,5-dihydro-1,2,3-triazines has been reviewed in Section 9.01.5.6 (Equation 46). 4,5,6-Triaryl-1,2,3-triazine 2-oxides are transformed into the corresponding 1,2,3-triazines by treatment with triethyl phosphite <1985LA1732>. In contrast to other heteroaromatic *N*-oxides, 4,6-dimethyl-1,2,3-triazine 2-oxide does not transfer its oxygen to alkenes under catalysis by [dioxo(tetramesitylporphyrinato)ruthenium(vI)] <1991TL7435>.

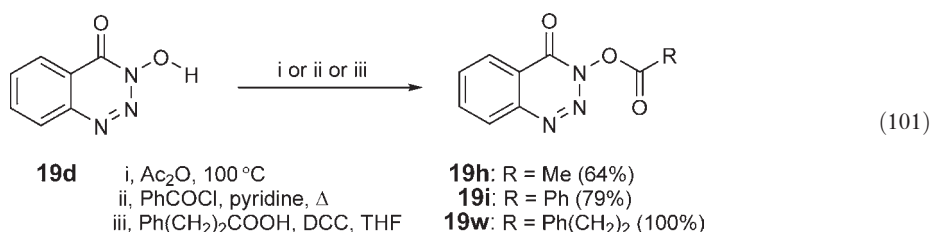
For reductive ring contraction of 1,2,3-benzotriazine 3-oxides to 3-aminoindazoles, see Section 9.01.5.6. Reduction of 2-methyl- or 2-aryl-1,2,3-benzotriazin-4-olate 1-oxides **237** with stannous chloride in concentrated hydrochloric acid/acetic acid at 0–5 °C gave benzotriazin-4-olates **46** (Equation 99) (<1974JOC2710> (A), <1972JOC1587> (B)).



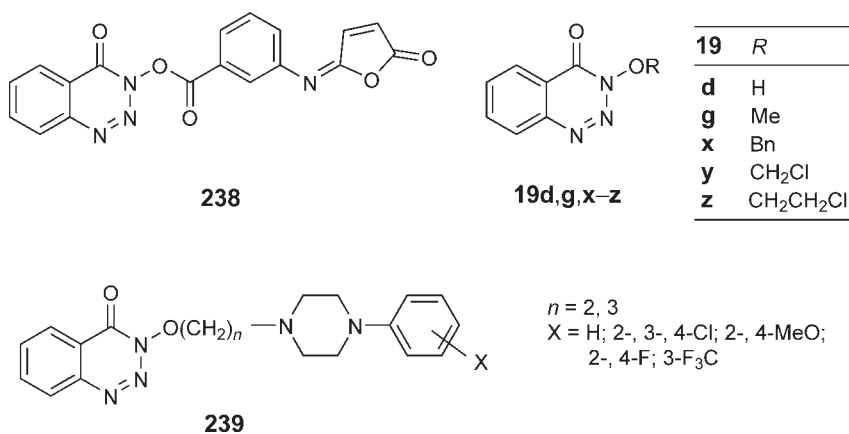
Hydrogenation of 3-methoxy-3,4-dihydro-1,2,3-benzotriazin-4-one 1-oxide **47** ($X^3 = \text{OMe}$) afforded benzotriazinone **3** and the 1-oxide **47** ($X^3 = \text{H}$) as a minor product when the rapid uptake of H_2 was stopped after 1 equiv of hydrogen had been absorbed (Equation 100) <1989J(P1)543>.



Acylation of the 3-OH group in **19d** works well with acetic anhydride and benzoyl chloride <1977CJC630> (Equation 101), and a free acid like dihydrocinnamic acid as acylating agent may be used together with dicyclohexylcarbodiimide (DCC). Reduction of **19w** with tributylstannane in the presence of azobisisobutyronitrile (AIBN) in boiling benzene gives ethylbenzene <1989TL2341>.

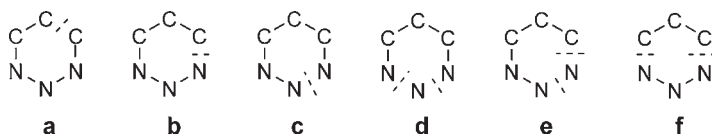


From **19d** a variety of active esters (e.g., of fluoren-9-yloxycarbonyl- α -amino acids <1996CHEC-II(6)483> or of 3-maleidobenzoic acid-derived **238** <1991S819>) as well as peptide coupling reagents may be prepared, as sulfonates **19** ($X^3 = \text{OSO}_2\text{Me}$ or OSO_2Ph) <1974TL3089> or 3-(diethylphosphoryloxy)-3,4-dihydro-1,2,3-benzotriazin-4-one (DEPBT, **19e**) <1996SC1455, 1999OL91>. Alkylation of **19d** is carried out readily with dimethyl sulfate in aqueous NaOH at room temperature in 55% yield <1977CJC630> or with diazomethane in Et_2O to give **19g** (87%) <1989J(P1)543>, with benzyl bromide in aqueous NaOH/EtOH at room temperature, affording **19x** (62%) <1978CJC1616>, and also with dichloromethane or 1,2-dichloroethane in the presence of diethylamine, generating **19y** and **19z** (19%). These latter two reactions are side reactions in peptide coupling when the dichloroalkanes mentioned are used as solvents <1998TL6515>. A series of 3-piperazinylalkoxy-3,4-dihydro-1,2,3-benzotriazin-4-ones **239** have been prepared as serotonin 5-HT receptors <2000BMC533>.



9.01.9 Ring Syntheses from Acyclic Compounds

The 1,2,3-triazine ring system may be built from the following types of precursors or precursor combinations:



C-C-N-N-N-C (**a**). This is a new mode which has not been used previously.

Reactions starting from types b–f from the early literature have been reviewed in both CHEC(1984) <1984CHEC(3)369> and CHEC-II(1996) <1996CHEC-II(6)483>. Additional references to early work not quoted so far either in CHEC(1984), CHEC-II(1996), or <1978HC(33)3> are given in square brackets.

C-C-C-N-N-N (**b**). The synthesis of 3,4-dihydro-1,2,3-benzotriazin-4-ones and -4-imines has been treated in CHEC(1984) and CHEC-II(1996) as a [5+1] mode with N-3 as the one-atom fragment via triazenes. Type **b** comprises cyclizations of 1-(2-acylphenyl)triazenes, preferentially in the presence of base.

[3-Alkyl (or 3-aryl-) 1-(2-alkoxycarbonylphenyl)triazene cyclizations: <1955JA6562, 1956CR2094, 1972CJC2544, 1972JOC1587, 1979HCA971, 1981JOC856>; 3-alkyl- (or 3-aryl-) 1-(2-cyanophenyl)-triazene cyclizations: <1964JCS3663, 1970JJC765, 1974J(P1)609>; dehydration of 1-(2-acetylphenyl)-3-aryltriazenes on alumina: <1975CJC3714, 1985CJC2455>].

N-C-C-C-N-N (**c**). The cyclization of 1-(2-azidophenyl)diaoethane, giving 4-methyl-1,2,3-benzotriazine, and of 2-aminophenylketone hydrazones using LTA, affording 4-substituted 1,2,3-benzotriazines; the synthesis of 2-methyl- or 2-aryl-1,2,3-benzotriazin-2-ium-4-olate 1-oxides from 2-nitrobenzaldehyde methyl- or arylhydrazones by oxidation with LTA (or more advantageously, with phenyliodine(III) diacetate <1989J(P1)543>); and the electrochemical oxidation of 2-(hydroxylamino)benzhydrazide to give 3,4-dihydro-1,2,3-benzotriazin-4-one **3** or of 1-(2-hydroxylaminobenzyl)-1-phenylhydrazine, yielding 3-phenyl-3,4-dihydro-1,2,3-benzotriazine **193** have been reviewed in CHEC(1984).

N-C-C-C-N+N (**d**). This very widely used mode was amply treated in CHEC(1984) and CHEC-II(1996) and comprises diazotizations with nitrous acid of

- 2-amino-4'-methoxybenzophenonimine giving 4-(4-methoxyphenyl)-1,2,3-benzotriazine;
- 2-aminoaryl aldioximes or ketoximes affording 1,2,3-benzotriazine 3-oxides [<1982JOC4323, 1984JOC296>];
- 2-aminobenzenecarboxamides giving 3,4-dihydro-1,2,3-benzotriazin-4-ones [<1979J(P1)2203, 1980J(P1)633, 1985HCA892, 1986ZC166, 1986ZC250, 1991T8917, 1992JHC1309>];
- 2-aminobenzhydroxamic acids or derivatives thereof [<1977CJC630, 1978CJC1616>];
- 2-aminobenzhydrazides using 1, 1–2, or 2–5 equivalents of HNO₂ [<1980JCM246, 1988JOC208, 1989FA465>];
- 2-aminobenzothioamides giving 3,4-dihydro-1,2,3-benzotriazin-4-thiones [<1969JHC779>];
- 2-aminobenzamidines reacting to 4-amino-1,2,3-benzotriazine or 3-substituted-3,4-dihydro-1,2,3-benzotriazin-4-imines [<1970JOC2289, 1971JOU2516>];
- 2-aminobenzamidoximes giving 4-amino-1,2,3-benzotriazine 3-oxides; and
- 2-aminobenzylamines and 2-aminobenzylhydrazines.

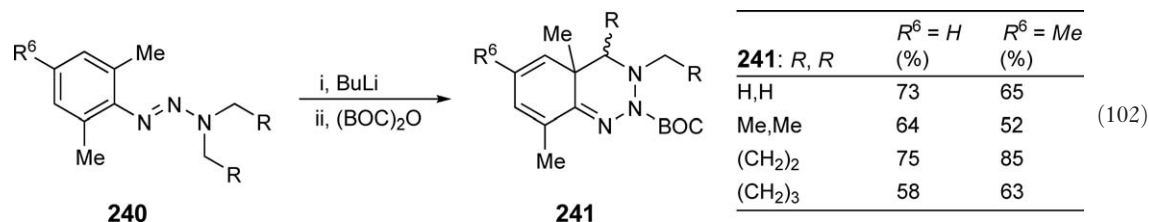
2-Aminobenzonitriles may be transformed into 3,4-dihydro-4-oxo-1,2,3-benzotriazine 2-oxides under nitrating conditions (CHEC-II(1996)). For diazotizations of naphthalene-1,8-diamines yielding 1*H*-naphtho[1,8-*de*]-1,2,3-triazines under various conditions, see the following sources of information: using HNO₂: <1940LA52, 1967LA150, 1969JJC769>, using pentyl nitrite: <1969JJC756>, using diphenylnitrosamine: <1967CB1646>.

C-C-C-N-N+N (**e**). In principle, this mode is a variant of type **b** since a triazene is first formed from a 2-acyldiazonium ion by reaction with a primary alkylamine, and the triazene is in turn cyclized (see CHEC(1984) and CHEC-II(1996)). [Additional sources of information given as follows: (1) with diazotized anthranilates as starting materials: <1977CJC1701, 1979AP842>; (2) by diazotizing 2-aminobenzaldehyde, 2-aminophenylketones, or 2-aminobenzophenones followed by immediate coupling of the diazonium ion with a primary amine in the presence of Na₂CO₃ or K₂CO₃, giving 3-substituted-4-hydroxy-3,4-dihydro-1,2,3-benzotriazines <1983CJC179, 1984ACB185, 1985CJC2455, 1987CJC292>].

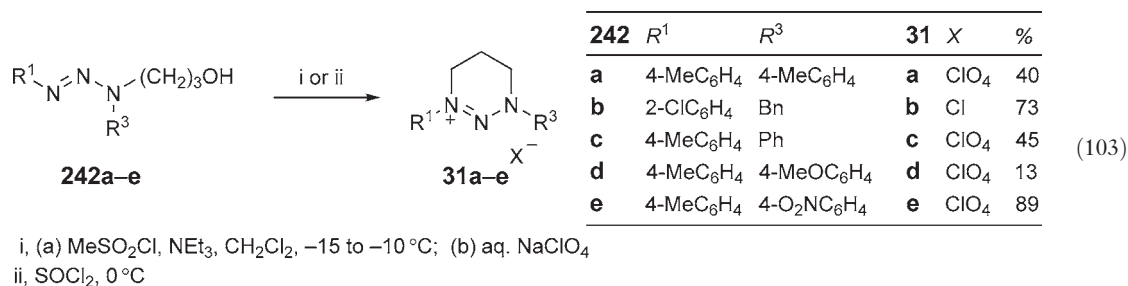
C-C-C+N-N-N (**f**). The only case reviewed (in CHEC(1984)) is the reaction of triazenes with chloroformylketenes <1978CB2173>.

Recent syntheses not reviewed previously or published from 1995 onward are reviewed below.

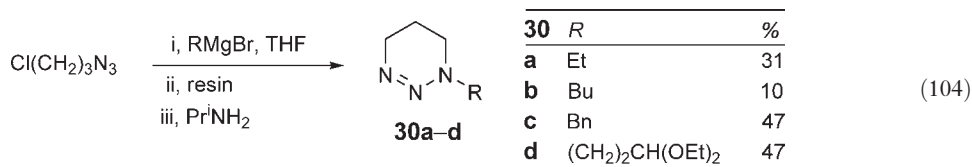
C-C-N-N-N-C (**a**). Treating 1-(2,6-dimethylphenyl)-3,3-dialkyltriazenes **240** with BuLi in THF, followed by addition of di-*tert*-butyldicarbonate as a quenching electrophile, affords 3-alkyl-2-(*tert*-butoxycarbonyl)-4a,8-dimethyl-2,3,4,4a-tetrahydro-1,2,3-benzotriazines **241** (Equation 102) <2002AGE484>.



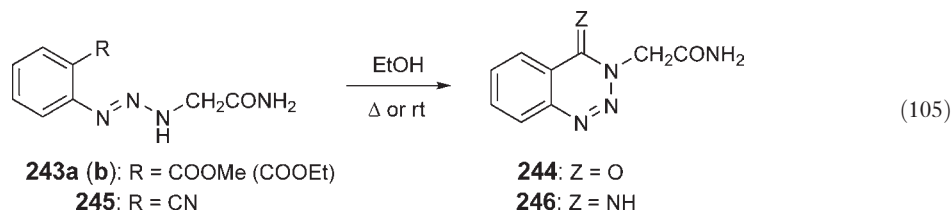
C-C-C-N-N-N (**b**). 1,3-Diaryl-3-(3-hydroxypropyl)triazenes **242a** and **242c-e** had earlier been cyclized to 3,4,5,6-tetrahydro-1,2,3-triazinium perchlorates **31a** and **31c-e** by treatment of the former with methanesulfonyl chloride and triethylamine in dichloromethane followed by workup with aqueous sodium perchlorate solution <1979CB445, 1984CHEC(3)369> (in the latter reference, the reaction was depicted as starting from the 3-chloropropyltriazenes). This procedure has been modified for 1-(2-chlorophenyl)-3-benzyl-3-hydroxypropyltriazene **242b**, using thionyl chloride both as solvent and reactant, to generate the analogous 3-chloropropyltriazene which cyclized spontaneously to **31b** (Equation 103) <2002BMC3001>.



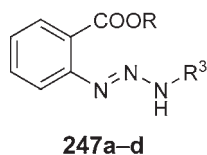
The reaction of 1-azido-3-chloropropane with Grignard reagents, followed by breakup of the Mg-triazene complex on Dowex resin, affords 1-alkyl-3-(3-chloropropyl)triazenes which on concentration undergo cyclization to 1-alkyl-1,4,5,6-tetrahydro-1,2,3-triazines **30a-d**; isopropylamine is added to neutralize any HCl (Equation 104) <1997JOC8660>.



3-(Carbamoylmethyl)-3,4-dihydro-1,2,3-benzotriazin-4-one **244** was obtained from 3-(carbamoylmethyl)-1-(2-alkoxycarbonyl)phenyltriazene **243a** and **243b** by heating in a minimum volume of ethanol. Similarly, 3-carbamoylmethyl-3,4-dihydro-1,2,3-benzotriazine-4-imine **246** was obtained simply by dissolving **245** in a minimum amount of ethanol (Equation 105) <1996JOC210>. The same procedure has also been applied to 1-(2-cyanophenyl)-3-(3-bromophenyl)triazene, giving 3-(3-bromophenyl)-3,4-dihydro-1,2,3-benzotriazin-4-imine <1995JME3482>.

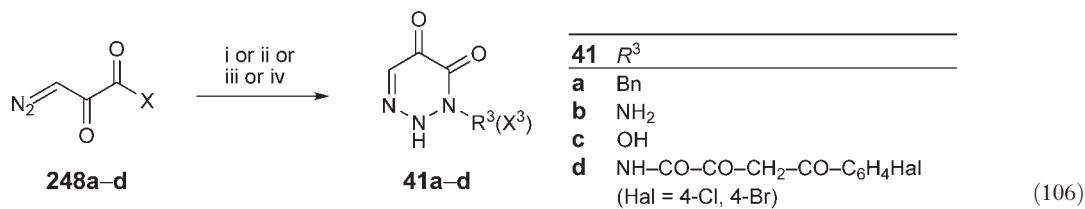


Finally, the base-catalyzed cyclization of several triazenes **247a-d** to the corresponding benzotriazinones has been investigated with emphasis on kinetics, mechanism, and steric and electronic effects <1990CCC2468, 1990CCC2692, 1996CCC751, 1998CCC2075>.



247	<i>R</i>	<i>R</i> ³
a	Et	Ar
b	Ar	Ph
c	Alkyl	Ph
d	Me	2-subst. phenyl

N-C-C-N-N (c). 3-Diazo-2-oxopropionic acid derivatives **248a-d** have been cyclized under a variety of conditions to 2,3,4,5-tetrahydro-1,2,3-triazine-4,5-diones **41a-d** (Equation 106).



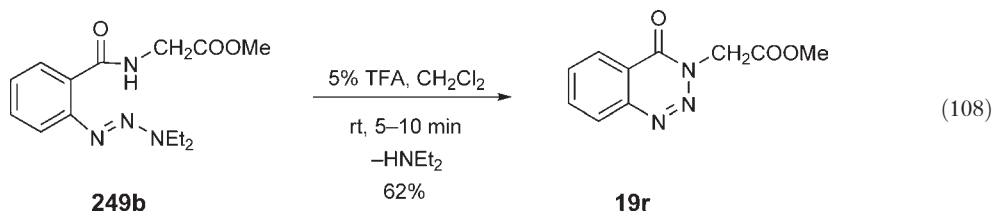
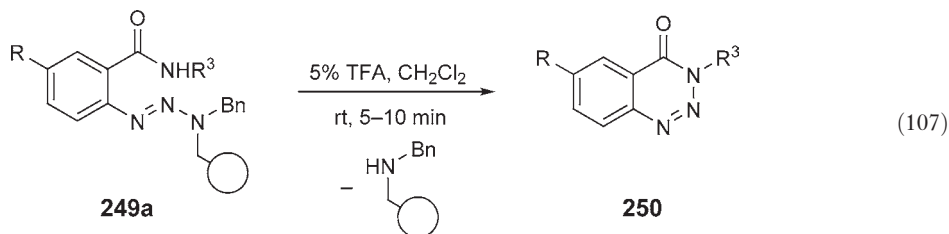
248a (X = NHBn) i, NaOEt, EtOH, rt, giving **41a** (52%) <1995RJO1005>

248b (X = OR, NHR, CHN₂) ii, H₂NNH₂·H₂O, dioxane, rt, giving **41b** <1995RJO1005>

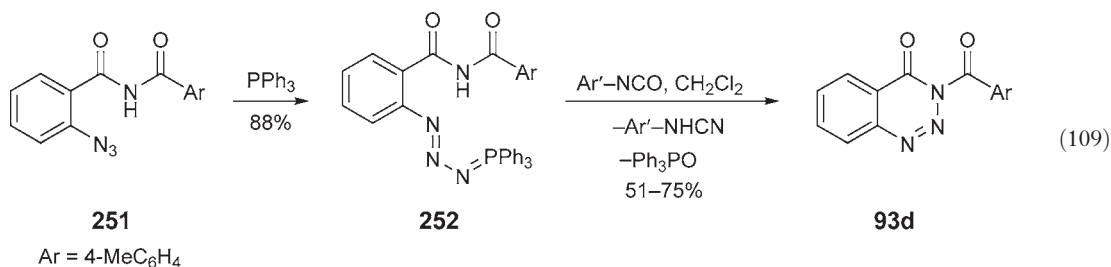
248c (X = OR (R = Et, Pr, Bn), iii, H₂NOH, EtOH, rt, giving **41c** (42–50%) <1993RJO1928>

248d (X = NHNH₂), iv, 5-(4-Hal-phenyl)-2,3-dihydrofuran-2,3-dione (Hal = Cl, Br), giving **41d** (42–46%) <1995RJO1109>

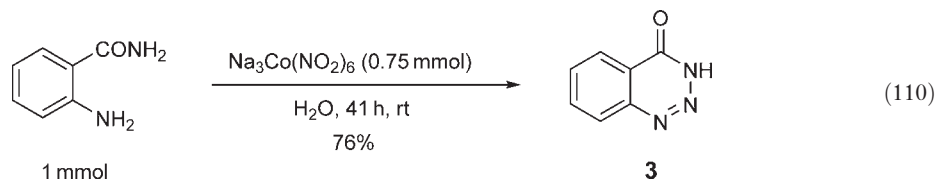
A series of more than 40 polymer-bound triazenes **249a** have been released from the polymer by mild acid treatment effecting the heterolysis of the triazene N(2)–N(3) bond to give (by cyclization of the resulting diazonium ions) the corresponding 3,4-dihydro-1,2,3-benzotriazin-4-ones **250** (Equation 107). 3-Methoxycarbonylmethyl-3,4-dihydro-1,2,3-benzotriazin-4-one **19r** has been obtained from **249b** under the same conditions (Equation 108) <2004JCO38>.



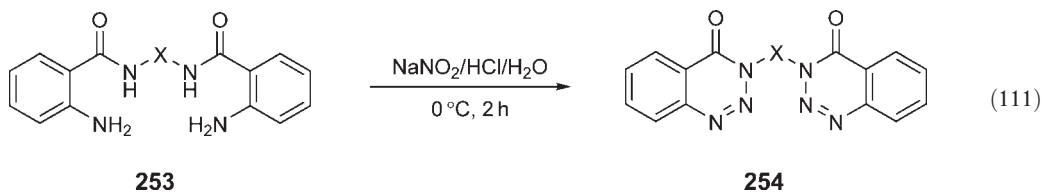
The Staudinger reaction of 2-azido-*N*-(4-toluoyl)benzamide **251** with triphenylphosphine allows the isolation of the triphenylphosphineimine **252**, which reacts in an aza-Wittig reaction with aryl isocyanates to give (unexpectedly) 3-(4-toluoyl)-3,4-dihydro-1,2,3-benzotriazin-4-one **93d** (Equation 109) <2000T4079>.



N-C-C-C-N+N (*d*). For PM3 studies on the ring-closure reaction of 2-carbamoylbenzenediazonium ion, see Section 9.01.2.11. The diazotization of 2-aminobenzenecarboxamides for the preparation of 3,4-dihydro-1,2,3-benzotriazin-4-ones has also been applied recently <1995JME1493, 1997JHC1391, 1998FA350>. As a new nitrosation agent, trisodium hexakis(nitrito-*N*)cobaltate(III) in water has been applied to 2-aminobenzenecarboxamide (Equation 110) <1997JOC7165>.

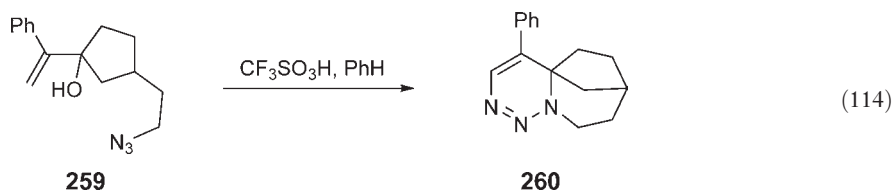
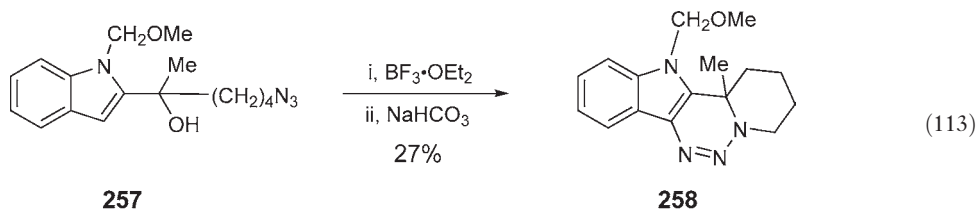
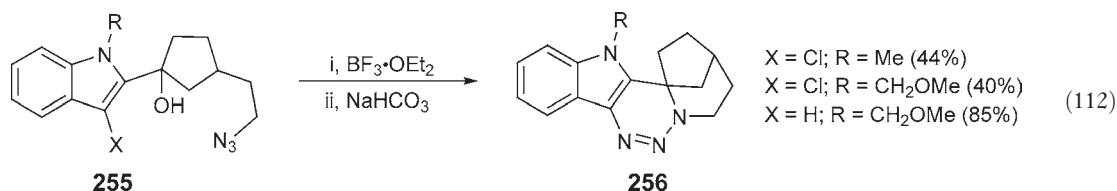


1,ω-Bis-[(2-aminobenzoyl)amino]alkanes **253** have been reacted with nitrous acid to form 3,3'-(1,ω-alkylen)di(3,4-dihydro-1,2,3-benzotriazin-4-ones) **254** (X = (CH₂)_{*n*} with *n* = 2–7; also, branched alkyls are used) (Equation 111) <2006JHC731>.

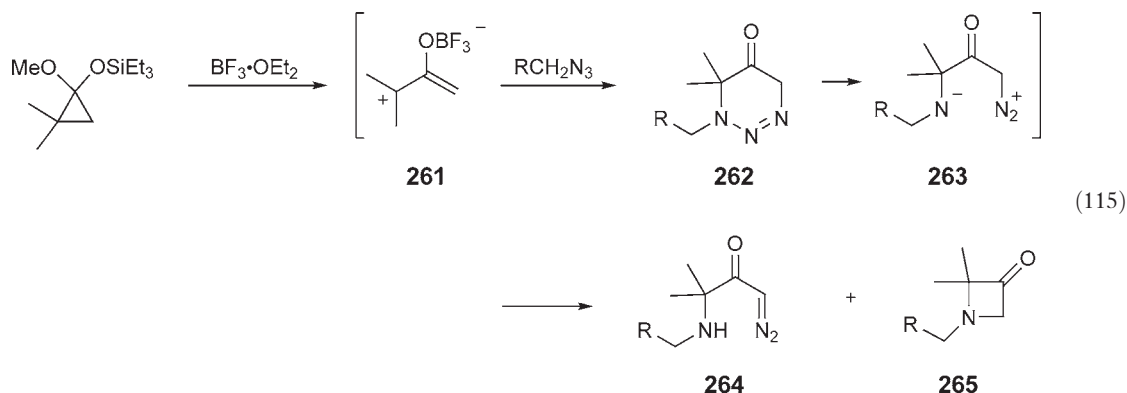


The diazotization of 1,8-diaminonaphthalenes to prepare 1*H*-naphtho[1,8-*de*]-1,2,3-triazines has also been applied recently <1994RJO487, 2005T10507>.

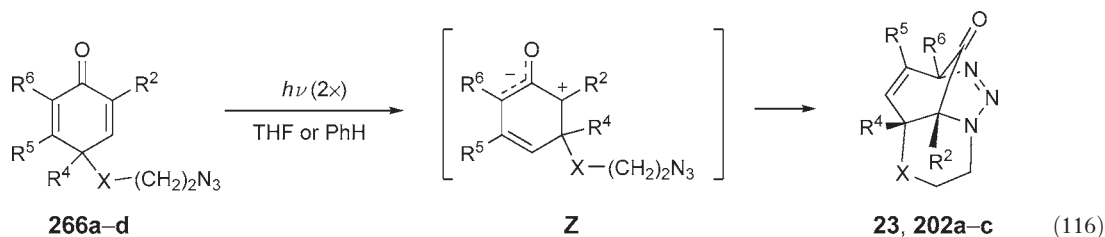
C-C-C + *N*-N-N (*f*). Several cases of intramolecular cycloadditions of azido groups to allyl ions and photochemically generated zwitterions have been reported. Treatment of the indoles **255** and **257** with boron trifluoride etherate results in the formation of triazines **256** and **258** (Equations 112 and 113), and, after heterolysis, the cyclopentanol **259** furnishes the spiroannellated dihydro-1,2,3-triazine **260** (Equation 114) <1994JOC2682>.



The addition of (mostly benzylic) azides, R-CH₂-N₃, to the oxyallyl cation **261** gives rise to a short-lived tetrahydrotriazine **262**, which, in turn, undergoes ring opening to form (via **263**) products **264** and **265** (Equation 115) <2000OL1657>.



Upon irradiation, 2,5-cyclohexadienones **266a–d** form the secondary photo-zwitterion [<1966JA4895> Z](#), which undergoes intramolecular cycloaddition of the tethered azido group to afford the tricyclic tetrahydro-1,2,3-triazinones **23** and **202a–c** (Equation 116) ([<1984TL1011>](#) (A), [<1988JOC391>](#) (B)). Structure **23** has been confirmed by a single crystal X-ray structural analysis (see [Section 9.01.3.1](#)).



Solvent	266	R^2	R^4	R^5	R^6	X	Product	%	Reference
THF	a	Me	Me	H	Me	CH ₂	202b	64	A
PhH	b	Me	Me	H	Me	O	202c	75	A
PhH	c	MeO	COOMe	MeO	H	CH ₂	23	10	B
PhH	d	Me	CH ₂ OAc	H	Me	CH ₂	202a	17	B

9.01.10 Ring Syntheses by Transformation of Another Ring

1,2,3-Triazines may be prepared from three- and five-membered rings using suitable methods of ring enlargement. In CHEC(1984) [<1984CHEC\(3\)369>](#) and CHEC-II(1996) [<1996CHEC-II\(6\)483>](#), the relevant literature up to 1993 has been reviewed as follows.

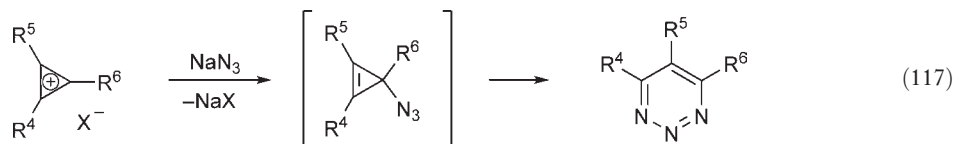
Three-membered rings are used as starting materials in the

- reaction of tetrahalocyclopropenes C₃X₄ (X = Cl, Br) with trimethylsilylazide, giving trichloro- and tribromo-1,2,3-triazine (**17x,y**) (CHEC(1984));
- thermolysis of cyclopropenylazides (CHEC(1984) and CHEC-II(1996)) [further examples hitherto not included: [<1985BCJ1073, 1991SI1099>](#)];
- formation of 4,5-diphenyl-1,2,3-triazine from 2-chloro-2,3-diphenyl-2H-azirine with diazomethane (CHEC(1984) and CHEC-II(1996)).

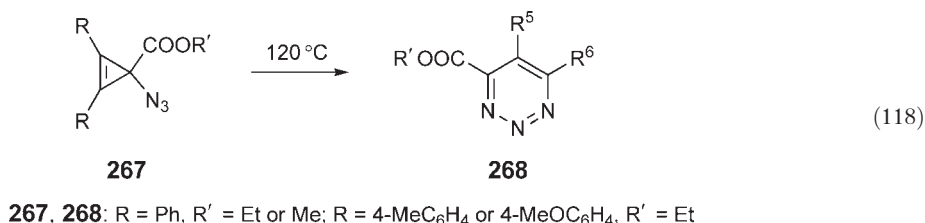
1,2,3-Triazines have been prepared from five-membered rings as follows. The oxidation of 1-aminopyrazoles seems to be the most effective and widely applied method. Sodium periodate is the most efficient reagent for oxidation. In CHEC-II(1996) (p. 504), sodium perchlorate has been mentioned erroneously as the reagent instead of sodium periodate [<1989H\(29\)1809>](#) [additional reference: [<1992CEX321>](#)]. LTA has been used to oxidize 1- or 2-aminoindazoles to 1,2,3-benzotriazines (CHEC(1984) and CHEC-II(1996)) [additional sources of

information: <1981JCM324, 1986EJM87, 1988J(P1)1509>]. Another approach lies in the 1,3-dipolar cycloaddition of ethynedicarboxylic esters to 1,2,3-triazole 1-oxides, where the primary cycloadduct undergoes three rearrangement steps, eventually affording a 2,5-dihydro-1,2,3-triazine (CHEC-II(1996)).

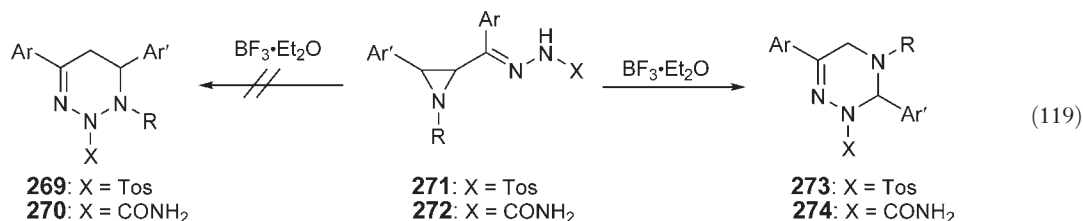
Several applications of ring enlargements of three-membered rings have appeared in the recent literature. 1,2,3-Triazines continue to be made available from cyclopropenylazides, which are prepared generally from cyclopropenylum salts but are not isolated in most cases (Equation 117).



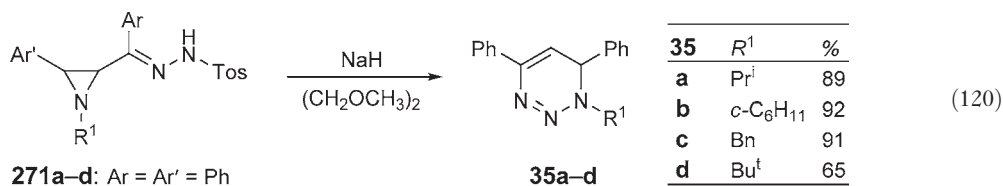
Recent efforts using this approach have been directed at preparing 5-diethylamino-4,6-di(4-halophenyl)- or di(4-methylphenyl)-1,2,3-triazines (four examples; Hal = F, Cl, Br) <2002HCO325>, 4,6-dialkyl-5-diethylamino-1,2,3-triazines (five examples; 39–51%) <2003H(59)477>, and 5-diethylamino-4,6-diphenyl-1,2,3-triazine <2005AXE93>. On the other hand, four 3-azidocyclopropene-3-carboxylates **267** have been isolated, characterized spectroscopically, and thermolyzed to afford the corresponding 1,2,3-triazines **268** (Equation 118) <1993LA367>.



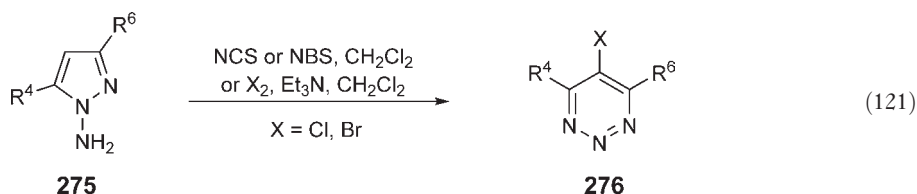
The products reported as obtained from (1-alkyl-3-arylaziridin-2-yl)-arylmethanone tosylhydrazones **271** <1996H(43)305> and semicarbazones **272** <1994NKK893>, respectively, by treatment with boron trifluoride etherate are not tetrahydro-1,2,3-triazines **269** and **270** but 2,3,4,5-tetrahydro-1,2,4-triazines **273** and **274** (Equation 119), as proven by a single crystal X-ray structural analysis for **273** (R = *c*-C₆H₁₁, Ar = Ar' = Ph) <1998H(48)769>.



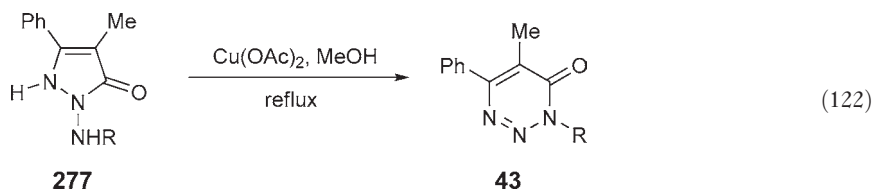
However, treatment of the above-mentioned tosylhydrazones **271** with NaH in dimethoxyethane did give 1,6-dihydro-1,2,3-triazines **35a–d** (and seven further examples with different Ar groups and R¹ = *c*-C₆H₁₁) in good yields (Equation 120) <1996H(43)1759>.



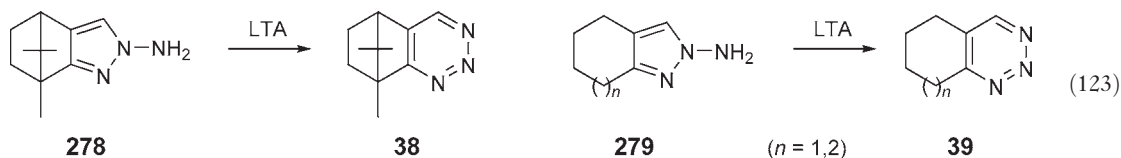
Five-membered rings have been used as follows. The electrooxidation of *N*-aminopyrazoles has been investigated with an emphasis on mechanism and solvent effects <1990CPB1524>. Oxidation of 3,5-disubstituted-1-aminopyrazoles **275** with halogenating agents affords 4,6-disubstituted 5-halo-1,2,3-triazines **276** (eight examples; Equation 121) <1988CPB3838>, but halogenation at C-4 of the pyrazole may compete with the oxidation of the amino function. If R⁴ = H, halogenation may also occur at C-4 of the triazine.



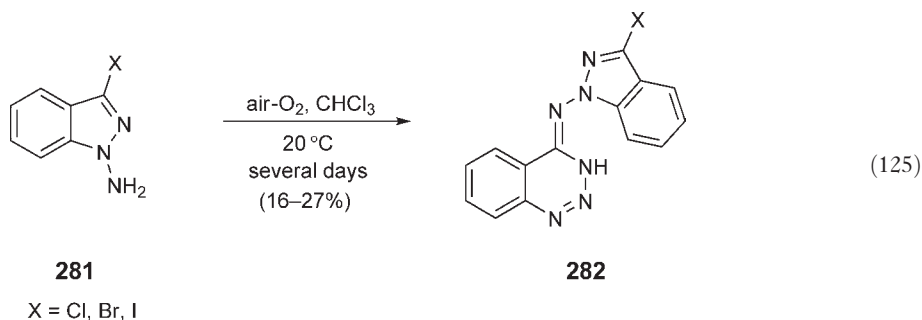
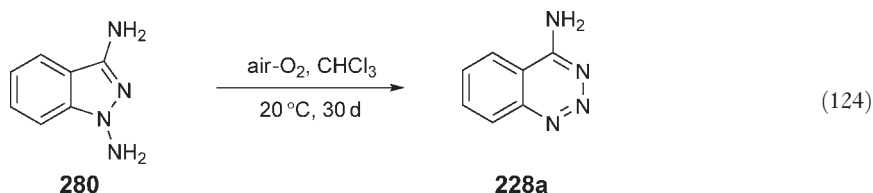
Copper(II) acetate in refluxing methanol has been used to prepare 3-alkyl-5-methyl-6-phenyl-3,4-dihydro-1,2,3-triazin-4-ones **43** from 2-(alkylamino)-4-methyl-5-phenyl-1,2-dihydropyrazol-3-ones **277**. Alternatively, this conversion may be reached, albeit in a slow reaction, using air oxygen in presence of sodium hydrogencarbonate (Equation 122) <2006EJO3021>.



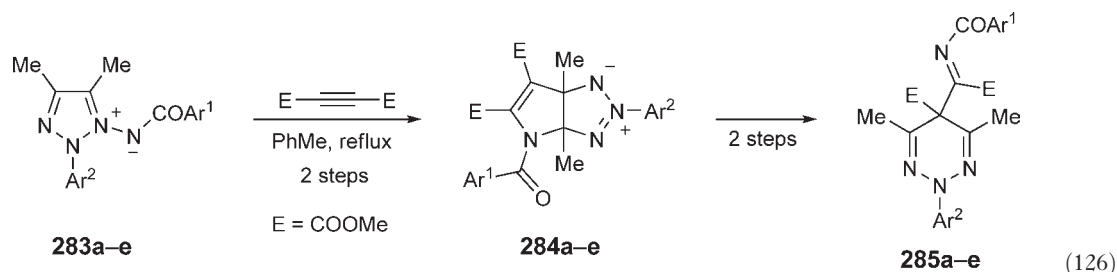
The annelated 1-aminopyrazoles **278** and **279** may be oxidized to annelated triazines **38** <1977H(8)319> and **39** ($n = 1, 2$) <1986H(24)907> using LTA (Equation 123).



Slow autoxidation in chloroform solution transforms 1,3-diaminoindazole **280** into 4-amino-1,2,3-benzotriazine **228a** (Equation 124) <2001CHE567>, and, under similar conditions, 1-amino-3-haloindazoles **281** are oxidized to 4-(3-haloindazol-1-yl)imino-3,4-dihydro-1,2,3-benzotriazines **282** (Equation 125) <1994CHE1174>.

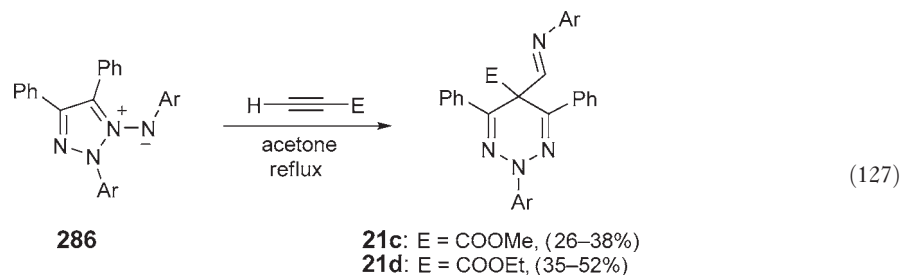


1,3-Dipolar cycloaddition of DMAD to 2-aryl-4,5-dimethyl-1,2,3-triazol-1-ium-1-acylimides **283a-e** results in formation of **284a-e** and finally of 2,5-dihydro-1,2,3-triazines **285a-e**, together with by-products derived from Michael addition of the imido N-atom to DMAD (Equation 126) <2000TL10337>.



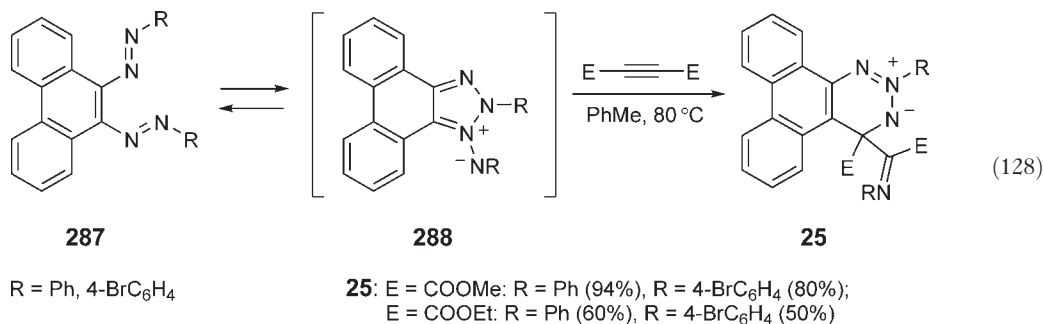
283–285	Ar ¹	Ar ²
a	Ph	Ph
b	Ph	4-MeC ₆ H ₄
c	Ph	4-ClC ₆ H ₄
d	Ph	4-O ₂ NC ₆ H ₄
e	4-O ₂ NC ₆ H ₄	Ph

Pyrrolo[2,3-*d*][1,2,3]triazol-2-ium-1-ides analogous to **284** had been prepared earlier independently by dehydrogenation of their 5,6-dihydro precursors with manganese dioxide and thermolysis to give 2,5-dihydro-1,2,3-triazines (CHEC-II(1996)) <1993JCM78>. When 2-aryl-4,5-diphenyl-1,2,3-triazol-1-ium-1-(*N*-arylimides) **286** were reacted with methyl or ethyl propiolate, 2,5-dihydrotriazines **21c** and **21d** were obtained in low to medium yields (Equation 127) <2006TL1721, 2006JOC5679>.



286, **21**: Ar = Ph, 4-BrC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 4-O₂NC₆H₄

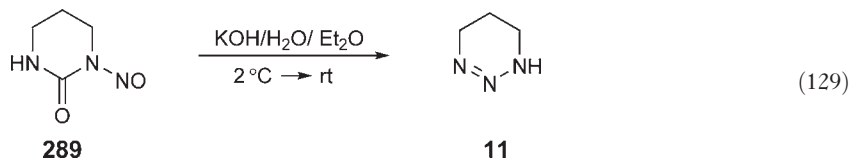
9,10-Bisarylazophenanthrenes **287** are in equilibrium with phenanthro[9,10-*d*][1,2,3]triazol-1-ium 1-arylimides **288** and as such are accessible to cycloadditions. With dimethyl and diethyl acetylenedicarboxylate, respectively, adducts **25** are formed in medium to good yields (Equation 128) <1991CIL549, 1996J(P1)1623>.



The synthetic scope of 1,2,3-triazol-1-ium-1-imides has been reviewed <1994H(37)571>. The reactions of several 2,4,5-triaryl-1,2,3-triazol-1-ium-1-arylimides with dipolarophiles may be followed by monitoring the decay in the UV absorption ($\lambda \geq 400$ nm) of the imides and were found to be dipole LUMO-controlled concerted cycloadditions with second-order rate constants and significantly negative activation entropies. Variation of the dipolarophiles reveals that

triazolium imides are type I dipoles. Substituent effects have also been investigated in detail, and the addition direction selectivity agrees with *ab initio*-calculated orbital coefficients and HOMO and LUMO energies <1992J(P2)1103>.

Transformations of a six-membered ring into a 1,2,3-triazine connectivity are rare. Two isomeric *N*-amino-4-methyl- (phenyl-) quinazolin-2-ones have been transformed with LTA into 4-methyl- (phenyl-) 1,2,3-benzotriazine in 23–24% yield <1975J(P1)31>; see also CHEC(1984). A recent example is the rearrangement of the cyclic nitrosourea **289** under the influence of strong alkali into the unstable tetrahydro-1,2,3-triazine **11** (Equation 129) <1997SC1569>; see also <2006BML427>.



9.01.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Methods

In this section, brief comments are made on the suitability of synthetic methods presented in Sections 9.01.9 and 9.01.10 or in the corresponding chapters of previous editions, explicitly with reference to the examples (by equation numbers) from the more recent literature. However, in order to assess fully the merits of a given method of synthesis of a particular substance or class of substances, all relevant publications in this field, also including the very early ones, need to be evaluated. This, however, would dramatically exceed the scope and time span of the chapter, since it is devoted mainly to the literature from 1995 until the present. In addition, the early literature on synthetic methods of 1,2,3-triazines has been amply reviewed <1998HOU(E9c)530, 2004SOS(17)223>. Thus, reference to specific original publications is kept to a minimum here. If specific procedures, even with experimental details, are needed, the reader planning a synthesis is kindly referred to the above-mentioned sources.

9.01.11.1 Monocyclic 1,2,3-Triazines

While there are various methods available to prepare 1,2,3-triazines bearing alkyl, aryl, halogen, and electron-donating substituents, methods for preparation of 1,2,3-triazines bearing EWGs are rare. There is one reliable method to prepare 1,2,3-triazine-4-carboxylic esters starting from cyclopropenylazides, but there is no such method to prepare a nitrotriazine. Sometimes there are ways out of this dilemma: 4-acyl and 4,6-diacyl-1,2,3-triazines may be prepared by lithiation, (1-hydroxy)alkylation of alkoxy-1,2,3-triazines, and subsequent dehydrogenation of the hydroxyalkyl groups (see Equations (43) and (44) (Section 9.01.5.5) and Equations (74) and (75) Section 9.01.7.1).

Fully unsaturated 1,2,3-triazines are best prepared by transformations of three- and five-membered rings (see Section 9.01.10). Cycloprop-2-enylazides, generated by addition of azide ion to a cyclopropenylum ion, are either prepared and thermolyzed *in situ* or isolated first and then thermolyzed. The latter variant was used to prepare 1,2,3-triazine-4-carboxylates (Equation 118). If all three substituents on the starting cyclopropenylum ion are equal, only one cyclopropenylazide, and thus only one 1,2,3-triazine, is possible. Otherwise, if there are two or three different substituents attached to the cyclopropenylum ion, the azide ion may enter at a position additionally activated by inductive effects. In this case, the results are still predictable (see Equation 118).

More flexibility is associated with the oxidative ring enlargement of *N*-aminopyrazoles. These starting materials are prepared readily by treatment of the pyrazoles with either HOS in aqueous alkali <1985LA1732, 1993LA367, 1998MI119> or with sodium hydride followed by addition of MSH <1985JOC5520, 1993LA367, 1998MI119>. Unsymmetrical 3,5-disubstituted pyrazoles give mixtures of 1-aminopyrazoles, the separation of which is possible but not needed, since ¹⁵N labeling of the added amino group reveals that this group provides N-2 of the 1,2,3-triazine <1986J(P1)1249>. Oxidants used in the past have now been replaced completely by sodium or potassium periodate (first introduced by Okatani *et al.* <1989H(29)1809>), including for the preparation of the sensitive parent compound **1** (in 46%, and with an improved procedure <2003TH1>, in 54% yield).

9.01.11.2 Di- and Tetrahydro-1,2,3-triazines

The C–C–C–N–N–N mode **b** of cyclization is represented by the cyclization of 1-aryl-3-alkyl- (or aryl-) (3-hydroxypropyl)-triazenes giving 3,4,5,6-tetrahydro-1,2,3-triazinium salts **31** (Equation (103), Section 9.01.9) and by the preparation of 1-alkyl-1,4,5,6-tetrahydro-1,2,3-triazines **30** (Equation 104). There is flexibility in the choice of substituents (alkyl, aryl). Highly functionalized 2,3,4,5-tetrahydro-1,2,3-triazin-4,5-diones (CA: 2,3-dihydro-1,2,3-triazine-4,5-diones) **41** are available from the cyclization of 3-diazo-2-oxopropionic acid derivatives, but variation seems to be limited to the choice of the N-3 substituent (Equation 106).

The preparation of annelated 1,6-dihydrotriazines (Equations (112)–(114) Section 9.01.9) in the C–C–C + N–N–N (f) mode by intramolecular cycloaddition of a tethered azide group to allyl cation sites is a special case as are the [3+3] cycloadditions of azido groups to allyl or oxyallyl cations (Equations 115 and 116). 1-Alkyl-4,6-diaryl-1,6-dihydro-1,2,3-triazines may also be prepared from (1-alkyl-3-arylaziridin-2-yl)arylmethanone tosylhydrazones or -semicarbazones (Equation (120) Section 9.01.10) by the action of sodium hydride (but note the erroneous structural assignment of the product from the action of boron trifluoride on the same starting materials; see Equation 119).

2-Aryl-2,5-dihydro-1,2,3-triazines, also with electron-withdrawing substituents, are available via 1,3-dipolar cycloaddition of electron-poor dipolarophiles (DMAD, maleonitrile, etc.) to 1,2,3-triazole 1-oxides <1987CC706, 1990J(P1)3321> or 1,2,3-triazol-1-ium imides (Equations (126) and (127) Section 9.01.10). The electronic properties of the aryl groups introduced with the triazolium precursor may vary widely. If alkenes are used as dipolarophiles, thermolysis of the adducts has to be combined with oxidation by manganese dioxide <1993JCM78>.

9.01.11.3 1,2,3-Benzotriazines and 3,4-Dihydro-1,2,3-benzotriazin-4-ones

This class of compounds is made available predominantly by the four cyclization modes, C–C–C–N–N–N (**b**), N–C–C–C–N–N (**c**), N–C–C–C–N + N (**d**), and C–C–C–N–N + N (**e**) (see Section 9.01.9), and recent applications have been shown in Equations (105) and (107)–(111). From these modes, the N–C–C–C–N + N route is the most widely applied one, with Equation (110) representing an improvement insofar as a new diazotization agent is introduced. All reactions are easily performed and widely applicable, since the terminal N-atom becoming N-3 may be introduced as a carbamoyl, carbohydroxyamide, or carbohydrazide group, determining at the same time the N-3 substituent.

The oxidative ring enlargement of 1-aminoindazoles (Equations 124 and 125) is another important method. The 1-amino group is introduced by application of HOS, and again, as unraveled from a ¹⁵N labeling experiment, the amino group of 1-amino-3-methoxyindazole provides N-2 of the benzotriazine <1986J(P1)1249>. Thus, the same product is obtained both from the 1- and 2-aminoindazole. The C-3 substituent may be alkyl, electron-rich aryl, or methoxy, and the oxidant frequently is LTA, though, alternatively, air oxygen can be applied (Equations 124 and 125). The highly reactive parent **2**, however, has to be prepared by slow addition of LTA in dry solvents in the presence of calcium oxide to minimize the danger of attack by nucleophiles (including any formed during the oxidation, e.g., acetate) on the sensitive, electrophilic triazine ring.

A new method was found to prepare 2,3,4,4a-tetrahydro-1,2,3-benzotriazines following the rare C–C–N–N–N–C mode (**a**). The azo link in 1-(2,6-dimethylphenyl)-3,3-di(primary alkyl)triazenes activates the α -methylene groups at N-3 sufficiently to undergo lithiation and, at the same time, most likely complexes the Li-atom brought in by metalation with BuLi. The carbanionic carbon in turn attacks a phenyl carbon atom *ortho* to N-1, which is novel, since otherwise functionalized carbon atoms such as CN or a carbonyl group at C-2 are attacked (Equation (102) Section 9.01.9). No predictions regarding a wider applicability, though, are possible at present.

9.01.11.4 Naphtho[1,8-de]triazines

Introduction of N-2 in the N–C–C–C–N + N (**d**) mode by diazotization of a free NH₂ group in 1,8-diaminonaphthalenes (one of the two amino groups may be alkylated or arylated) using a variety of diazotizing agents such as aqueous sodium nitrite in the presence of mineral or acetic acid, or NO⁺-transfer reagents such as nitrosodiphenylamine, is a reliable and often applied method.

9.01.12 Important Compounds and Applications

Among the compounds of interest here, 3,4-dihydro-1,2,3-benzotriazin-4-ones clearly dominate with respect to biological activity or utility as reagents in synthesis.

9.01.12.1 Insecticides

Azinphos methyl **19b** and Azinphos ethyl **19c** are persistent insecticides (plant protection agents) of low volatility and low solubility. For access to the literature prior to 1983, see CHEC(1984) <1984CHEC(3)369>. A vast number of early publications on Azinphos insecticides is made available through a 1978 review <1978HC(33)3>. More recent reports have appeared on handling, storage, and toxicity of Azinphos ethyl **19c** <1993MI277>, on photochemical degradation of Azinphos methyl **19b** in water, giving degradation quantum yields, rate constant, and half life of degradation <2001FEB554>, on the detection of **19b** and **19c** by immunological assay <1999JFA1276, 1999JFA1285> and the analysis of **19c** by MS <2001ANC5441>, also under the aspect of developing a standardized analytical technique of high sensitivity <1986OMS785>; see also Section 9.01.3.7.

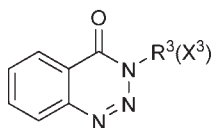
9.01.12.2 Compounds Showing Various Biological Activities

Pharmacological effects have been reported for specific compounds as follows:

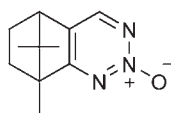
- strong central nervous system (CNS) stimulation by ‘camphortriazine’-2-oxide **95** <2000JHC1663>;
- local anaesthetic activity of 3-(2-diethylaminoethylaminocarbonylmethyl)-3,4-dihydro-1,2,3-benzotriazin-4-one **291a** is comparable to that of lidocaine <1999EJM1043>;
- antidepressant activity (exceeding that of trazodone) of 3-{3[4-(3-chlorophenyl)piperazin-1-yl]propyl}-3,4-dihydro-1,2,3-benzotriazin-4-ones **291b** and **291c** <1987EJM337>;
- anticonvulsant activity of 3-benzyl-3,4-dihydro-1,2,3-benzotriazin-4-ones <1997JHC1391>.

Following are the other significant biological effects that have been reported:

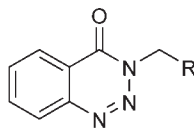
- specific matrix metalloprotein inhibition by 2-arylthio-5-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-ylmethyl)cyclopentanecarboxylic acid **291e** <2003JME3840> and *N*-hydroxy-2-[2-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethyl]-3-(4'-chlorobiphenyl-4-thio)propionamide **291d** <2002BMC531>;
- photoinduced DNA cleavage by the ligand radical species released from tris(3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one)iron(III) **80** <2000CCC69>; see also Section 9.01.5.1;
- 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one **19d** as mediator in the Mn-peroxidase-catalyzed oxidation of benzylic alcohols <2004JMO1>.



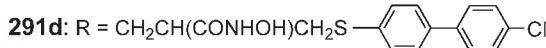
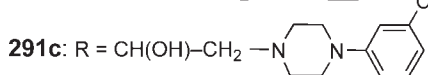
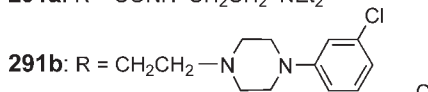
19b: $R^3 = \text{CH}_2\text{S}-\text{P}(\text{S})(\text{OMe})_2$
19c: $R^3 = \text{CH}_2\text{S}-\text{P}(\text{S})(\text{OEt})_2$
19d: $X^3 = \text{OH}$
19e: $X^3 = \text{OP}(\text{O})(\text{OEt})_2$
290: $X^3 = \text{OP}(\text{O})(2\text{-MeC}_6\text{H}_4)_2$



95



291a: $R = \text{CONH}-\text{CH}_2\text{CH}_2-\text{NEt}_2$



9.01.12.3 Coupling Reagents in the Synthesis of Amides and Peptides, Formation of Active Esters

The use of 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (Dhbt-OH, **19d**) as an additive in peptide synthesis by either the carbodiimide or active ester method, and the preparation of such esters from 9-Fluorenylmethyloxycarbonyl (Fmoc)-protected amino acids and a method to prepare analogues of Dhbt-OH have been reviewed up to 1992 in CHEC-II(1996). Always crucial is the conservation of optical purity of the amino acid building blocks in amide or peptide synthesis, and addition of **19d** is effective in conserving this optical purity. Both the formation of active esters from **19d** and the suppression of racemization by **19d** are regarded as due to the nucleophilic character of its anion <1970CB2024>; see also Section 9.01.4.2.

Recently publications have appeared on

- the preparation of *N*-BOC-protected amino acid amides using methyl- or ethylammonium salts of **19d** and DCC in good yields and good optical purity <1992S285>; and
- a method of amide formation using DCC and **19d** in derivatization of solid supports for oligonucleotide synthesis <1997TL1651, 1998TL5975>;
- the use of 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) in connection with **19d** in peptide synthesis without danger of epimerization <2002MI319>, and practical details of this method <1999MI162>;
- peptide syntheses with benzyloxycarbonyl-protected arginine by using the **19d**/DCC-activated ester method <2003JA4436>;
- the coupling of a Cys-containing peptide with a peptide thioester in the presence of silver chloride and **19d** <1998TL7901>;
- the preparation of 4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl esters of Fmoc-amino acids and their use in solid-phase peptide synthesis <1988J(P1)2887>, and applications of this method <1990MI257>;
- 3-(diethoxyphosphoryloxy)-3,4-dihydro-1,2,3-benzotriazin-4-one (DEBT, **19e**) as coupling reagent in peptide synthesis with no detectable racemization <1996SC1455, 1999OL91, 2000SC4233, 2000TL9373, 2001JA1862, 2002MI95, 2005MI55>;
- the new peptide-coupling reagent 3-[di(2-methylphenyl)phosphinyloxy]-3,4-dihydro-1,2,3-benzotriazin-4-one (DtpODhbt, **290**) <2004JOC62>.

9.01.12.4 Other Applications

The potential of 2-methylnaphtho[1,8-*de*]triazin-2-ium-1-ide **5a** as a stabilizer against photooxidation has been mentioned (see Section 9.01.6.1). 3-Acyloxy-3,4-dihydro-1,2,3-benzotriazin-4-ones are reduced smoothly by tributylstannane upon initiation by AIBN to give the corresponding norhydrocarbons, which constitutes a mild method of decarboxylation (see Section 9.01.8.3).

9.01.13 Further Developments

9.01.13.1 Theoretical methods

Another computational study of aromaticity was based on *n*-center delocalization indexes (*n*-DIs) and led to the conclusion that the order of stability within a series of position isomers (here 1,2,3-, 1,2,4-, and 1,3,5-triazine) is not controlled by aromaticity. The least stable isomer was found to be the most aromatic one (relative energies in kcal mol⁻¹, *6*-DIs in parentheses) within that series: 1,2,3-triazine **1** (44.0, 2.75), 1,2,4-triazine (27.3, 2.47), and 1,3,5-triazine (0.0, 2.32); for comparison: benzene 2.67 <2006T12204>; compare Section 9.01.2.8.

Computations at the B3LYP/cc-pVDZ level have also been used to optimize N–N and C–N bond lengths and to calculate Wiberg bond indexes, lone pair acceptor orbital stabilization interactions, and total energies of twelve azines including **1** <2006ACT2057>; see Section 9.01.2.8.

Metal ion binding (π and σ modes) of azines has been investigated at the MP2(FULL)/6-311+G(2d, 2p) level based on MP2/6-31G* optimized geometries. For the parent **1**, a σ^6 type of complex (monodentate linkage) could be located but was transient with respect to the more stable σ^8 type (bidentate linkage of the metal ion). For Li⁺, Na⁺, K⁺, Mg⁺⁺ and Ca⁺⁺ complexation energies between –130 and –25 kcal mol⁻¹ have been estimated <2006PCA10148>.

The CASSCF method using 6-31G** and 6-31++G** bases has been applied to obtain optimized geometries for the ground and $^1(\pi, \pi^*)$ lowest excited state of the 1:1 complex of **1** and water, showing a single bent (N-1)···H-O bond in both states <2007MI87>; see also Section 9.01.2.12.

pK_a -values (in DMSO, precision ± 1.1) for C(4)-H of 33.0 and of 30.4 for C(5)-H of **1** have been predicted <2007T1568>; see also Section 9.01.2.13.

Both the energetics and transition state geometries for the uncatalyzed 1,4-dihydrogenation of **1** in comparison with benzene, the other monocyclic triazines, and various other azines have been calculated using the MPWB1K/6-311+G(3df, 2p) method with B3LYP/6-31+G(d) geometries (MPWB1K is a new functional <2004PCA6908> based on a modified Perdew-Wang exchange functional and Becke's meta correlation functional). For the two modes (1,4 and 2,5) of dihydrogenation of **1** the following activation barriers and reaction enthalpies (in kJ mol⁻¹ for 0 K) have been derived: 1,4-H₂ 199, -55; 2,5-H₂ 187, -79. These values show that 2,5-dihydrogenation of **1** is both kinetically and thermodynamically favored <2007JA924>; see also Sections 9.01.2.15 and 9.01.5.6.

9.01.13.2 Structure, Reactivity and Applications

The molecular structure of bis[tri-(4-methylphenyl)phosphine]-3,4-dihydro-1,2,3-benzo-triazin-4-onato-silver(I) has been determined. While the Ag-N bond length of 2.277(3) Å is normal, the Ag-O distance of 2.928(2) Å is regarded as elongated. The 108.8° Ag-N-C angle is consistent with a weak bond between Ag and the carbonyl oxygen. Silver complexes of heterocyclic amide structures are regarded as important for thermographic imaging systems <2006JCX587>.

1-Amino-8-fluoronaphthalene may be prepared by action of hydrogen fluoride (70%)/pyridine (30%) on 1H-naphtho[1,8-*de*]-1,2,3-triazine **4** under nitrogen at room temperature <2007WO2007/049124>. This reductive degradation supplements Section 9.01.6.1.

A DFT-B3LYP/6-31G(d) study on the energetics of the rearrangement of cycloadducts of acetylenic esters to the cyclic tautomer **286** (Ar = Ph) of bis(phenylazo)stilbene confirms **286** as the active dipole <2007JOC367>, see Equation (127) in Section 9.01.10.

In a recent patent syntheses of active esters from 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one **19d** with 9-fluorenylmethoxycarbonyl (Fmoc) amino acids and the esterification of carboxylic acids using bis(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxalate have been described <2005WO2005/007634>; see Section 9.01.12.3.

3,4-Dihydro-1,2,3-benzotriazin-4-one **3** may be used as an additive to a silver deposit solution increasing the solderability of copper surfaces <2007USA2007/0056464>.

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Biographical Sketch



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9.02

1,2,4-Triazines and their Benzo Derivatives

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9.02.1 Introduction

Remarkable progress in the chemistry of 1,2,4-triazines has been achieved during the last three decades, which is well documented in the literature, including thousands of original papers, review articles, patents, and monographs. There is, however, a simple indicator of growing interest in this class of heterocyclic compounds, which is based on an estimation of how the subject is reflected in textbooks. The difference is obvious from comparison of the first edition of the well-known textbook, *Heterocyclic Chemistry*, written by J. A. Joule and G. F. Smith (Chapman & Hall Publishing Company, 1972), in which no attention was paid to this class of heterocyclic compounds, with the fourth edition of the same textbook, issued in 2000 (J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell Science, Oxford, 2000). Indeed, for many years, 1,2,4-triazines have been a focus of attention for chemists and biologists. This interest is explained partly by the development of new drugs (e.g., the effective anticonvulsant, lamotrigine, and anticancer drug, tirapazamine), luminescent materials, dyes, specific ligands for complexation with metals, and other compounds based on 1,2,4-triazines. The main reason, however, appears to be the great synthetic potential of 1,2,4-triazines, exhibiting an unusual pattern of reactivity toward nucleophiles and electrophiles, reductive and oxidative agents, the ability to participate in the Diels–Alder and 1,3-dipolar cycloadditions, and other ring-transformation reactions.

The chemical behavior of 1,2,4-triazines appears to be related to the mutual positions of nitrogen atoms in the ring. Indeed, 1,2,4-triazines belong to a unique family of azaheterocycles, which can be regarded as 4-aza analogs of pyridazines with their specific repulsion of n-electron pairs, 4-azapyrimidines with their characteristic ring-opening and ring-transformation reactions, or 2-aza analogs of pyrazines with their ability to undergo nucleophilic diaddition reactions. These features open wide possibilities for development of the chemistry of 1,2,4-triazines and their condensed systems as a promising branch of heterocyclic chemistry.

Over 25 years have passed since the chemistry of 1,2,4-triazines and their benzo derivatives was first reviewed thoroughly by professor Hans Neunhoeffer in his excellent monograph <1978MI191>, and then in CHEC(1984) <1984CHEC(2)385>. A series of monographs and review papers on the chemistry of 1,2,4-triazines and their numerous derivatives, reflecting a growing interest in this heterocyclic system, have been published later <B-1988MI95, 1989AHC(46)73, 1992H(33)931, 1996CHEC-II(6)507, 1997MI333, 1998RCR633, 1998RJO297, 1999MI125, 1998HOU(E9c)582, 1999PHA791, 2000PS315, 2001PHA195, 2001PHA275, 2002AHC(82)261, 2004SOS(17)357, 2004PAC1621>. In 1996, a new chapter dealing with various aspects (chemical, physical, biochemical, agrochemical, medicinal, etc.) of 1,2,4-triazines and their condensed systems was presented in CHEC-II(1996) <1996CHEC-II(6)507>.

Since 1996, a great number of reviews and original papers have been published, covering various aspects of the chemistry of 1,2,4-triazines: methods for the synthesis and modification of 1,2,4-triazines and their benzo derivatives, including ring-transformation reactions <1998RJO297, 2004SOS(17)357>, synthesis and reactivity of 1,2,4-triazine N-oxides <1998RCR633, 2002AHC(82)261>, fluorine-containing 1,2,4-triazines <1999PHA791>, significance of

1,2,4-triazines as plant-protection agents <2001PHA195> and biologically active compounds <1999MI125, 2000PS315, 2001PHA275>, as well as analytical studies on complexes of 1,2,4-triazines with metals <1997MI333>.

One of the features of the current state of heterocyclic chemistry is a growing interest in the so-called S_N^H methodology (nucleophilic aromatic substitution of hydrogen) and related processes initiated by a nucleophilic attack at unsubstituted carbon in π -deficient azaaromatics: addition of nucleophiles (A_N), oxidative elimination of hydrogen from σ^H -adducts, or 'auto'-aromatization of σ^H -adducts, the tandem addition (A_N - A_N) or substitution (S_N^H - S_N^H) reactions, and other transformations <B-1994MI1>. All aspects of this relatively new branch of the chemistry of 1,2,4-triazines are discussed in detail in this chapter.

Another feature of the last decade is wide application of X-ray crystallography. Indeed, nearly 20% of recently published papers contain the X-ray crystallography data for 1,2,4-triazines or their metal complexes, and this trait of 1,2,4-triazine chemistry has also been reflected in this chapter.

9.02.2 Theoretical Methods

1,2,4-Triazine is a very electron-deficient system. The data from quantum-chemistry calculations, as well as experimental data on electron density distribution obtained by ^{13}C nuclear magnetic resonance (NMR) (see Section 9.02.3.3.2), indicate that 1,2,4-triazines are more electron-deficient compounds than pyridines, pyrimidines, pyrazines, or pyridazines (Table 1, Figure 1) <1989AHC(46)73, 1996CHEC-II(6)507, 2001JHC901, 2003CHE616>.

Table 1 ($\sigma+\pi$) Charge distribution in molecules of some 1,2,4-triazines (CNDO/2)

1,2,4-Triazines	N-1	N-2	C-3	N-4	C-5	C-6	Reference
Unsubstituted	-0.043	-0.101	0.155	-0.134	0.099	0.040	1988KGS525
1,2,4-Triazine ^a	-0.235	-0.292	0.308	-0.496	0.127	0.038	2003CHE616
2H-1,2,4-Triazinium ^a	-0.145	-0.361	0.460	-0.474	0.202	0.070	2003CHE616
3-Methoxy-	-0.024	-0.140	0.309	-0.184	0.114	0.017	1988KGS525
3-Methylthio-	-0.034	-0.119	0.201	-0.159	0.105	-0.026	1988KGS525
3-Phenyl-	-0.048	-0.116	0.183	-0.163	0.111	0.026	1988KGS525
5-Methoxy-3-phenyl- ^b			0.190		0.239	-0.002	2001JHC901
1-Methyl-5-methoxy-3-phenyl-1,2,4-triazinium tetrafluoroborate ^b			0.233		0.280	0.104	2001JHC901

^a*Ab initio* quantum-chemistry calculations with HF/6-31G** basis set <2003CHE616>.

^b*Ab initio* quantum-chemistry calculations with STO-3G basis set <2001JHC901>.

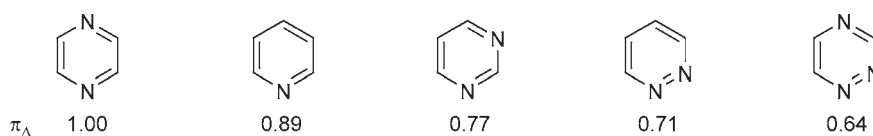


Figure 1 π -Deficiency values ($\pi\Delta$) for selected azines (a lower value refers to a more π -deficient system).

Calculations of ($\sigma+\pi$) charge distribution in some 1,2,4-triazine molecules by both semi-empirical (e.g., complete neglect of differential overlap (CNDO/2)) and *ab initio* methods show that C-3 and C-5 carbons are the most electrophilic positions in the ring (Table 1), and are likely to be attacked by nucleophiles <1988KGS525, 1989AHC(46)73, 1996CHEC-II(6)507, 2001JHC901, 2003CHE616>. These calculations correlate satisfactorily with ^{13}C NMR data (see Section 9.02.3.3.2 and reviews <B-1988MI95, 1992H(33)931>).

The basic character of the nitrogen atoms in simple 1,2,4-triazines is changed as follows: $\text{N-4} > \text{N-2} > \text{N-1}$, as can be seen from both calculated ($\sigma+\pi$) charge distribution indexes (Table 1) and experimental ^{14}N and ^{15}N NMR data (see Table 6, Section 9.02.3.3.3) <1988KGS525, B-1988MI95, 1989AHC(46)73, 1992H(33)931, 2003CHE616>.

A theoretical study has been performed in order to estimate the ability of 1,2,4-triazines to undergo N-protonation reactions. The *ab initio* calculations, obtained using HF/6-31G**, have shown that the $\text{N}_2\text{-H}$ triazinium cation is the most stable thermodynamically; similar characteristics have been obtained for $\text{N}_1\text{-}$ and $\text{N}_2\text{-H}$ 1,2,4-triazinium salts derived from protonation of 6-phenyl-1,2,4-triazine <2003CHE616>.

Attempts have also been made to use calculations in order to explain the observed site selectivity in N-alkylation of 1,2,4-triazines (see Section 9.02.5.5.2), as well as reactivity of *N*-alkyl-1,2,4-triazinium salts <1989T6499, 1992H(33)931, 2001JHC901>. In particular, *ab initio* quantum-chemistry calculations with the STO-3G basis set, performed for 5-methoxy-3-phenyl-1,2,4-triazine and the corresponding N₍₁₎-methyl-1,2,4-triazinium cation, have shown that the reactivity of C-6 toward nucleophiles has to be enhanced dramatically after quaternization of the N-1 nitrogen atom (Table 1) <2001JHC901>.

Nonempirical calculations were applied to estimate tautomerism of 3,4-dihydro-6-methyl-3-thioxo-1,2,4-triazin-5(2*H*)-one and its anion. The 2*H*,4*H*-thione tautomer was shown to be the only stable one in the gas phase <2000GOB605>.

Theoretical studies of ruthenium complexes with asymmetric intercalative ligands, bearing the fragments of 3-(pyridin-2-yl)-5,6-diphenyl-1,2,4-triazine, 3-(pyridin-2-yl)-1,2,4-triazino[5,6-*f*]acenaphthylene, and 3-(pyridin-2-yl)-1,2,4-triazino[5,6-*f*]phenanthrene, were carried out <2005ICA3430>. It was shown that the trend in the DNA-binding affinities of this series of complexes could be explained reasonably by the calculated planarity of intercalative ligands, some frontier molecular orbital (FMO) energies of the complexes, and the planarity area of the intercalative ligands <2005ICA3430>.

Also, theoretical considerations of the FMO interactions have been performed in order to explain the regioselectivity observed in the Diels–Alder reaction of 5-acetyl-3-methylthio-1,2,4-triazine with enamines <2005T8148>.

9.02.3 Experimental Structural Methods

9.02.3.1 X-Ray Crystallography

The X-ray crystallographic data obtained for a number of derivatives during the last decade indicate clearly that the 1,2,4-triazine ring is not an ideal aromatic system, and the structure with double bonds between the N-2 and C-3, N-4 and C-5, and N-1 and C-6 atoms contributes greatly to the ground state of these molecules. Indeed, in a number of very simple 1,2,4-triazines studied, such as 3-amino- <2002AXC431>, 3-methylthio- <1998AXC550>, and 3,6-diphenyl-1,2,4-triazine <2005UP>, the N(2)–C(3) bond distances proved to be shorter than those between the C(3) and N(4) atoms. Also, it is worth noting that the N(4)–C(5) bond distances (1.310–1.314 Å) are much shorter in comparison with that of the corresponding C=N bond (1.333 Å) in pyrazine (Table 2). In addition, the angles between atoms in the triazine ring are not equal to the ideal 120°, varying considerably in the range from 114° to 127° (Table 3).

Table 2 Bond distances (Å) in some 1,2,4-triazines

Bonds	3-Amino-	3-Methylthio-	3,6-Diphenyl-	Bond distances for a reference compound
N(1)–N(2)	1.334	1.350	1.341	1.346 (pyridazine)
N(2)–C(3)	1.351	1.330	1.333	
C(3)–N(4)	1.358	1.350	1.350	
N(4)–C(5)	1.311	1.314	1.310	1.333 (pyrazine)
C(5)–C(6)	1.394	1.396	1.398	1.388 (pyrazine)
C(6)–N(1)	1.319	1.315	1.331	1.333 (pyrazine)

Table 3 Angles (deg) in some 1,2,4-triazines

Angles	3-Amino-	3-Methylthio-	3,6-Diphenyl-	Angles in the reference compound
N(1)N(2)C(3)	118.04	117.31	118.97	118.90 (pyridazine)
N(2)C(3)N(4)	125.09	126.80	124.86	126.75 for pyrimidine N(1)C(2)N(3)
C(3)N(4)C(5)	114.71	114.52	115.25	116.29 for pyrimidine C(2)N(3)C(4)
N(4)C(5)C(6)	122.02	121.01	122.18	121.90 (pyrazine)
C(5)C(6)N(1)	120.59	121.51	119.74	121.90 (pyrazine)
C(6)N(1)N(2)	119.48	118.81	118.95	119.28 (pyridazine)

The list of relatively simple 1,2,4-triazines for which the X-ray data have been obtained involves 3-amino-1,2,4-triazin-5(2*H*)-one <2002MI723> and a great number of phenyl derivatives: 3,6-diphenyl-5-cyano-1,2,4-triazine <2002RJOC744>, 5,6-diphenyl-3-(pyrazin-2-yl)-1,2,4-triazine <2002AXE1321>, 3,6-diphenyl-5-(1-methylindolyl-3)-1,2,4-triazine 4-oxide <1998RJO420>, 5-benzyl-6-oxo-3-phenyl-1,6-dihydro-1,2,4-triazine <1995CPA51>, 3,6-diphenyl-5-(2-phenyl-1,2-dicarba-*closo*-dodecaboranyl-1)-1,2,4-triazine <2004RCB1175, 2004RCB1223>, 3,3',6,6'-tetraphenyl-5,5'-bi-1,2,4-triazine <1996ZK667>, 5,5'-dimethoxy-3,3'-diphenyl-6,6'-bi-1,2,4-triazine <1996ZK65>, and various di- and trisubstituted 1,2,4-triazines <1996JOM355, 1996T14905, 1997MI23, 1997ZK83, 2000JCX423, 2000RJO1050, 2002J(P1)2549, 2004TL3249>.

X-Ray data have also been reported for a series of partly hydrogenated 1,2,4-triazines bearing the oxo group including 2,3-dihydro-1,2,4-triazin-3-ones <2002JCS(P1)2549>, 2,5-dihydro-1,2,4-triazin-5-ones <1998RCB682, 2002MI723>, 1,6-dihydro-1,2,4-triazin-6-ones <1995CPA51, 1996AXC2865, 1999JHC627, 2004ZFA841, 2005TL1997>, as well as substituted 1,2,4-triazin-3,5-diones <1996MI97, 1996RJC572, 1998RCB682, 2000T5909, 2004MC63>, 1-phenyl-4*H*-1,2,4-triazin-5,6-diones <2003H(60)2123>, and 3-thioxo-2*H*-1,2,4-triazin-5-ones <1996SC2075, 2004ICA2245>.

Also, the X-ray crystallographic data for a number of tetrahydro-1,2,4-triazines <1998H(48)769>, including 1,4,5,6-tetrahydro-1,2,4-triazin-5-ones <1998SUL163, 1999TL8675, 2001JST167, 2001TL2393>, 5-hydroxy-5-methoxy-carbonyl-6-methyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine <2000JOC2820>, 6-methyl-3-thioxo-1,2,4-triazin-5-(2*H*,4*H*)-one, 2-thio-6-azathymine <1995JCD3035>, 4-amino-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-thione-5-one <1998ZFA1969>, 5,6-diphenyl-5-methoxy-1,2,4-triazacyclohex-1-(6)-ene-3-thione <1998T11271, 2003JST93>, 4-methyl-5,6-diphenyl-5-ethoxy-1,2,4-triazacyclohex-1-(6)-ene-3-thione <2003JST93>, and 4-methyl-5,6-diphenyl-5-hydroxy-1,2,4-triazacyclohex-1-(6)-ene-3-thione <1999JST73>, are available in the literature.

The following hexahydro derivatives of 1,2,4-triazines have been analyzed by X-ray crystallography: 1-*t*-butyl-1,2,4-triazine-3,5-dione <2000T5909>, 1-methyl-(*S*)-5-benzyl-1,2,4-triazine-3,6-dione <1999JOC163>, 3-benzyl-1-cyclohexyl-1,2,4-triazine-3,6-dione <1998JOC9128>, and a number of more complicated bicyclic compounds <2002RCB1381>.

5,7-Dimethyl-3-phenyl-1,2,4-benzotriazine <1998AXC405>, 3-dimethylamino-7-methyl-1,2,4-benzotriazine <1998CJC426>, 3-amino-5-methyl-1,2,4-benzotriazine 1-oxide <2001JCX397>, 3-amino-1,2,4-benzotriazine 2-oxide and 3-acetamido-1,2,4-benzotriazine 4-oxide <2001JOC107>, and the ion-radical salt of 1,3-diphenyl-1,2,4-benzotriazinium with tetracyanoquinodimethane <1996JA13081> are derivatives of the 1,2,4-benzotriazine family for which the X-ray data have been obtained during the last decade. Further, benzo[*e*]- <1998JOC10027, 2005H(65)279> and benzo[*c*]-annelated 1,2,4-triazines <1999CHE486> have been characterized by X-ray analysis data.

A variety of condensed heterocyclic systems, such as pyrrolo[1,2-*a*]- <1997J(P1)1829>, pyrrolo[1,2-*b*]- <1995ZK69>, and pyrrolo[1,2-*d*]-1,2,4-triazines <1996JCD1617>, pyrazolo[4,3-*e*]- <1996H(43)1513, 2000H(53)2175>, imidazo[2,1-*c*]- <1996TL901>, and imidazo[4,5-*e*]-1,2,4-triazines <1996JHC949, 2003MC190>, thiazolo[3,2-*b*]- <2001H2189, 2005TL31>, thiazolo[4,3-*c*]- <1999J(P1)1067>, and thiazolo[4,5-*e*]-1,2,4-triazines <2004RCB1279>, 1,2,4-triazolo[1,2-*a*]- <2003H(61)493>, 1,2,4-triazolo[3,4-*f*]- <2002MI853>, 1,2,4-triazolo[4,3-*d*]- <1997J(P1)1047, 2002MI165>, and 1,2,4-triazolo[5,1-*d*]-1,2,4-triazines <2004RJO94, 2004RJO85>, dipyrrolo[1,2-*b*:3,2-*e*]-annelated <2001JHC205> and other types of fused 1,2,4-triazines <1996AXC3213, 1996ZK663, 1996RCB2971, 1996T11349, 1997CC757, 1997MC109, 1998CC983, 1998JA2989, 1998RJO408, 1999T13457, 2000AXC472, 2000H(53)323, 2000KFZ39, 2000PCJ494, 2001JHC877, 2001ZFA1173, 2002JHC703, 2003JCD325>, have been elucidated by X-ray crystallography.

A considerable body of X-ray crystallographic data concerns heterocyclic ligands or metal complexes which bear the 1,2,4-triazine ring as a substructural unit <1995CC1633, 1996JCD2061, 1996ZK65, 1998ZFA1969, 1999AXC1092, 1999ZFA1411, 1999ZFA1908, 2000EJI1877, 2000H(53)1155, 2000H(53)1737, 2000NJC931, 2000ZNB1074, 2001CC1512, 2001IC7091, 2001JCD1326, 2001TML704, 2001ICC12, 2001ICC462, 2001ZFA815, 2002JCD3265, 2002ICC596, 2002ZFA2887, 2002ZNB547, 2003AXE713, 2003EJI2711, 2003IC2950, 2003ICA197, 2003ICA389, 2003JCD325, 2003JCD1675, 2003MC165, 2003OL4595, 2003ZFA2438, 2004AXE937, 2004ICA2245, 2004JIB423, 2004MI49-1, 2004RCB1175, 2004RCB1223, 2004RJC1015, 2004ZFA403, 2004ZFA625, 2004ZFA627, 2005ICA476, 2005ICA2057, 2005ICA3430, 2005JCC1631, 2006TL869>. An example of a 1,2,4-complex is given in Figure 2 <2006TL869>.

A number of biologically active compounds of the 1,2,4-triazine family have been obtained and studied by X-ray crystallography. The list includes 3,5-diamino-6-aryl-1,2,4-triazines <1995AXC440, 1995AXC685, 1996AXC2627, 1999JCX163, 2000AXC362>, as analogs of the well-known anticonvulsant drug lamotrigine (Figure 3) <1999JCX701, 2001JST53>, and antibacterial sulfonamides <2005EJM377>. Also, aza-analogs of pyrimidine bases and their nucleosides, such as 2-thio-6-azathymine <1995JCD3035>, 6-aza-5-*t*-butyl-2'-deoxyuridine,

6-aza-5-cyclopropyl-2'-deoxyuridine, and 6-aza-5-(2'-thienyl)-2'-deoxyuridine <1998NN187>, 6-aza-2'-deoxy-2'-arabino fluorouridine <2004AXC884>, 1-[(2-hydroxyethoxy)methyl]-6-azaisocytosine <1995H(41)293>, and 2-methyl-6-aza-2'-deoxyisocytidine <2003AXCo194> are well represented in X-ray studies.

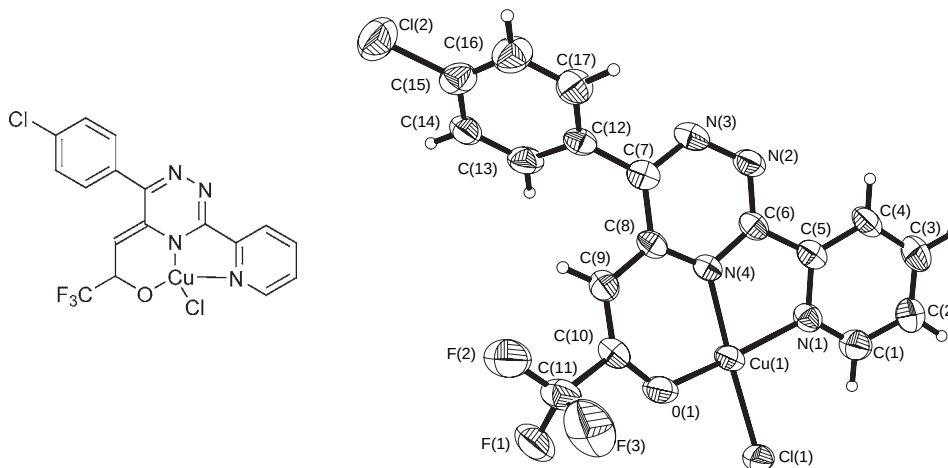


Figure 2

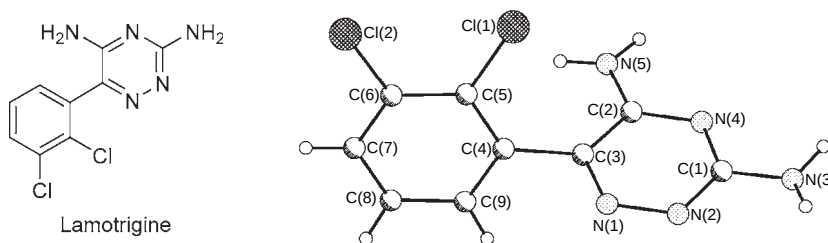


Figure 3

In addition, 1,4-diphenyl-1,4-dihydro-1,2,4-benzotriazin-4-yl radical <1996AXC3124> has been characterized by X-ray crystallography.

9.02.3.2 Neutron and Electron Diffraction Studies

No data on neutron or electron diffraction studies of 1,2,4-triazines have so far been reported in the literature.

9.02.3.3 NMR Spectroscopy

A considerable body of ^1H and ^{13}C , ^{14}N and ^{15}N NMR data, accumulated in the literature, provides an insight into electronic, structural, stereo, and conformational details for 1,2,4-triazines. ^1H and ^{13}C NMR, especially ^1H - ^1H and ^1H - ^{13}C correlation spectroscopy (COSY) and nuclear Overhauser enhancement spectroscopy (NOESY) spectra, provide valuable spectral data which usually enable one to distinguish between isomeric compounds and, finally, to establish the structure. A great deal of NMR data accumulated during the last decade concerns metal complexes of 1,2,4-triazines <1998ICA46, 1998ICA165, 1999IJA956, 2000H(53)1737, 2001CC1512, 2001JCD1326, 2002JCD3265, 2003JCR1307, 2003JCD325, 2004JCR1099, 2004ZFA627, 2004POL815, 2005ICA3430, 2005CR1087, 2005SAA1853>, and this can be illustrated, for instance, by the structural elucidation of a palladium(II) complex with the oxime of (L)-3-acetyl-5-benzyl-1-phenyl-4,5-dihydro-1,2,4-triazin-6-one <2000H(53)1737>.

9.02.3.3.1 Proton spectra

The ^1H NMR spectrum of the parent 1,2,4-triazine was first reported in 1966 <1966JOC1720>. Since that time, a considerable body of ^1H NMR spectral data has been accumulated in the literature <B-1988MI95, 1989AHC(46)73, 1996CHEC-II(6)507, 2001H(55)127, 2002AHC(82)261, 2003TL2421>.

In the ^1H NMR spectra of 1,2,4-triazines, the chemical shifts of H-3, H-5, and H-6 are in the range of 8.1–9.7 ppm (Table 4). Low values of the vicinal coupling constants $^3J(\text{H}^5\text{--H}^6) = 1.8\text{--}2.5\text{ Hz}$ are quite characteristic for this heterocyclic system, and this has been discussed in earlier review articles <B-1988MI95, 1989AHC(46)73>. The ^1H NMR spectral data accumulated during the last decade follow the same features.

Table 4 ^1H chemical shifts for selected 1,2,4-triazines and their *N*-oxides^a in CDCl_3

Compound	H-3	H-5	H-6	Reference
1,2,4-Triazine	9.63	8.53	9.24	1977JOC546
1-Oxide	9.00	8.57	8.04	1971JOC787
	(−0.63)	(+0.04)	(−1.20)	
2-Oxide	8.82	8.00	8.42	1977JOC546
	(−0.81)	(−0.53)	(−0.82)	
3-Methyl-1,2,4-triazine		8.57	9.14	1969TL3147
3-Methoxy-1,2,4-triazine		8.56	9.16	1970JHC767
1-Oxide		8.37	7.83	1966JOC3917
		(−0.19)	(−1.33)	
2-Oxide		7.70	8.12	1977JOC546
		(−0.86)	(−1.04)	
3-Methylthio-1,2,4-triazine		8.46	9.00	1970JHC767
3-Phenyl-1,2,4-triazine		8.64	9.13	1977JME723
3-Morpholino-1,2,4-triazine		8.14	8.54	1986KGS1535
2-Oxide		7.81	8.02	1977JOC546
		(−0.33)	(−0.52)	
6-Methyl-1,2,4-triazine	9.55	8.55		1971LA12
4-Oxide	9.28	8.22		1971LA12
	(−0.27)	(−0.33)		
6-Phenyl-1,2,4-triazine	9.52	8.91		1971LA12
4-Oxide	9.31	8.60		1971LA12
	(−0.21)	(−0.31)		

^aValues in parentheses refer to shielding (−) or deshielding (+) effects of the *N*-oxide function.

The ^1H NMR technique is of diagnostic value for estimation of N-protonation, N-alkylation, N-acylation, or N-oxidation sites. In particular, the ^1H NMR spectra of 1,2,4-triazine *N*-oxides exhibit upfield shifts for the H- α signals, which are of diagnostic value. Indeed, due to the back-donation effect of the *N*-oxide function, the H-6 resonance signals in the ^1H NMR spectra of 1,2,4-triazine 1-oxides are observed at significantly higher fields ($\Delta\delta = 1.2\text{--}1.4\text{ ppm}$) relative to those for the corresponding 1,2,4-triazines (Table 4). The same situation pertains to 1,2,4-triazine 2- and 4-oxides, although the electronic effects of the *N*-oxide function at positions 2 and 4 upon the chemical shifts of the α -protons are much lower ($\Delta\delta = 0.2\text{--}0.8\text{ ppm}$) (Table 4) <B-1988MI95, 1989AHC(46)73, 2002AHC(82)261>.

In addition, the ^1H NMR technique has proven to be very successful in detection and structural characterization of various σ -adducts which are derived from nucleophilic mono- and diaddition reactions on the 1,2,4-triazine ring <B-1988MI95, 2001H(55)127, 2001JHC901, 2002MC27, 2002AHC(82)261, 2003TL2421>.

9.02.3.3.2 Carbon-13 spectra

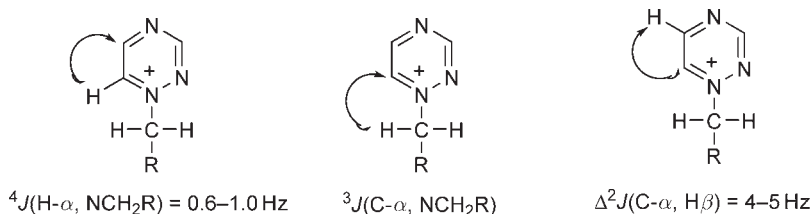
The ^{13}C chemical shifts for a number of 1,2,4-triazines indicate that the resonance of the C-3 carbon is observed at the lowest field because of the deshielding effects of the two adjacent nitrogen atoms (Table 5). The parent 1,2,4-triazine has the following chemical shifts and coupling constants: $\delta = 158.1\text{ ppm}$ (C-3), $^1J(\text{C}^3\text{--H}^3) = 207.1$, $^3J(\text{C}^3\text{--H}^5) = 9.1$, and $^4J(\text{C}^3\text{--H}^6) = 1.3\text{ Hz}$; $\delta = 149.6\text{ ppm}$ (C-5), $^1J(\text{C}^5\text{--H}^5) = 188.0$, $^2J(\text{C}^5\text{--H}^6) = 9.0$, and $^3J(\text{C}^5\text{--H}^3) = 7.5\text{ Hz}$; and $\delta = 150.8\text{ ppm}$ (C-6), $^1J(\text{C}^6\text{--H}^6) = 187.5$, $^2J(\text{C}^6\text{--H}^5) = 9.5$, and $^4J(\text{C}^6\text{--H}^3) = 2.0\text{ Hz}$ <1975OMR194>.

Table 5 ^{13}C chemical shifts for selected 1,2,4-triazines and their *N*-oxides^a in CDCl_3

Compound	C-3	C-5	C-6	Reference
1,2,4-Triazine	158.1	149.6	150.8	1975OMR194
1-Oxide	158.5	152.7	129.7	1986H(24)951
	(−0.4)	(+3.1)	(−21.1)	
2-Oxide	143.5	132.5	146.0	1986H(24)951
	(−14.6)	(−17.1)	(−4.8)	
3-Methyl-1,2,4-triazine	167.7	148.8	147.7	1975OMR194
3-Methoxy-1,2,4-triazine	166.1	151.6	145.5	1988RTC273
1-Oxide	166.5	154.0	124.5	1977JOC546
	(+0.4)	(+2.4)	(−21.0)	
2-Oxide	152.5	130.0	135.5	1977JOC546
	(−13.6)	(−21.6)	(−11.0)	
3-Methylthio-1,2,4-triazine	174.3	148.0	145.2	1988KGS525
3-Phenyl-1,2,4-triazine	164.0	148.7	147.7	1975OMR194
3-Morpholino-1,2,4-triazine	161.1	148.6	140.1	1986KGS1535
5-Methyl-1,2,4-triazine	157.0	160.5	150.9	1975OMR194
1-Oxide	158.7	166.1	129.1	1986H(24)951
	(+1.7)	(+5.6)	(−21.8)	
6-Methyl-1,2,4-triazine	155.8	149.6	159.3	1975OMR194
5-Phenyl-1,2,4-triazine	157.5	155.5	146.8	1975OMR194
6-Phenyl-1,2,4-triazine	156.1	146.6	157.8	1975OMR194
4-Oxide	149.9	132.0	157.5	1986H(24)951
	(−6.2)	(−14.6)	(−0.3)	

^aValues in parentheses refer to shielding (−) or deshielding (+) effects of the *N*-oxide function.

^1H and ^{13}C NMR spectral data have proven to be of diagnostic value to establish *N*-alkylation sites. Indeed, the formation of *N*₁-alkyl 1,2,4-triazinium salts is characterized by the following spectral features: a strong upfield shift of 6–10 ppm for the C-6 (C- α) resonance signal in the ^{13}C NMR spectra and a decrease in the geminal coupling constants between C- α and H- β of 4–5 Hz (Figure 4). Further, in the ^1H NMR spectra, the H-6 (H- α) resonance signal is either broadened or split due to the long-range coupling constant ^4J between H-6 (H- α) and the protons of the *N*-alkyl group <1992H(33)931, 2001JHC901>.

**Figure 4**

Comparison of the ^{13}C NMR spectra of 1,2,4-triazines with those of isomeric *N*-oxides reveals a great influence of the *N*-oxide function on the C- α and C- γ resonance signals. Indeed, the data presented in Table 5 show that oxidation at N-1 results in strong upfield shifts (21–22 ppm) for the C-6 resonance signals, which is diagnostic for elucidation of the structure of *N*-oxides. In addition, oxidation at N-2 causes upfield shifts for the C-3 (13–15 ppm) and C-5 (17–22 ppm) carbon resonances (Table 5) <1989AHC(46)73, 1998RCR633, 2002AHC(82)261>.

^{13}C NMR spectroscopy proved to be an efficient tool for structural elucidation of σ^{H} -adducts, derived from addition of ammonia, amines <2001H(55)127>, cyanamide <2000RCB1122>, and other nucleophiles <2002MC27, 2003TL2421>, to monitor the formation of 2,3-dihydro-5,6-diphenyl-1,2,4-triazines from the corresponding 1,2,4-oxadiazolium salts <1997J(P1)2919>, and for the identification of condensed systems obtained on the basis of 1,2,4-triazines <2001JHC901, 2002MC27, 2002T8559, 2003OL4595, 2003TL2421, 2005BMC2935>.

9.02.3.3.3 Nitrogen-15 and nitrogen-14 spectra

Both ^{15}N and ^{14}N NMR spectral data for a number of simple 1,2,4-triazines are available in the literature <1984SAA637, 1988KGS525, 1989AHC(46)73, 1992H(33)931, 1998RCR633, 2002AHC(82)261>. According to both methods, the observed nitrogen shielding increases in the order N-1 < N-2 < N-4 for all triazines studied (Table 6).

Table 6 ^{15}N and ^{14}N chemical shifts^a for selected 1,2,4-triazines

Compound	Nuclei	N-1	N-2	N-4	Reference
1,2,4-Triazine	^{15}N	420.0	382.0	318.0	1984SAA637
1-Oxide	^{15}N	337.0			1984SAA637
3-Methoxy-1,2,4-triazine	^{15}N	416.0	322.0	253.6	1984SAA637
	^{14}N	435	335	260	1988KGS525
1-Oxide	^{15}N	330.0	282.9	232.0	1984SAA637
3-Methylthio-1,2,4-triazine	^{15}N	412.0	351.0	282.0	1984SAA637
	^{14}N	430	366	288	1988KGS525
3-Phenyl-1,2,4-triazine	^{15}N				
	^{14}N				
3-Amino-1,2,4-triazine	^{15}N	415.7	319.0	250.0	1984SAA637
1-Oxide	^{15}N	328.9	273.0	228.0	1984SAA637
2-Oxide	^{15}N	341.0	243.0	227.0	1984SAA637
3-Morpholino-1,2,4-triazine	^{14}N	432	338	265	1988KGS525
1,2,4-Benzotriazine	^{15}N	448.3	403.4	281.9	1984OMR210

^a ^{15}N NMR measurements were made in DMSO- d_6 solutions, while ^{14}N chemical shifts were obtained in CDCl_3 .

In addition, 6-hydroxy-2-methyl-3-thioxo-2*H*-1,2,4-triazin-5-one, the subunit fragment of antibiotic ceftriaxone, was characterized by ^{15}N NMR spectroscopy <1996SC2075>.

In the ^{15}N NMR spectra of 1,2,4-triazine 1-oxides, the N-1 resonance signal undergoes a strong upfield shift ($\Delta\delta = -83$ to -87 ppm). Although the N-2 and N-4 resonances are also moved to a higher field, the changes in their chemical shifts are considerably less: $\Delta\delta$ (N-2) = -39 to -46 ppm and $\Delta\delta$ (N-4) = -22 to -24 ppm. Further, the back-donation effect of the *N*-oxide group at N-2 in 3-amino-1,2,4-triazine *N*-oxides causes upfield shifts of both the N-1 and N-2 resonance signals: $\Delta\delta$ (N-1) = -74.7 and $\Delta\delta$ (N-2) = -76.0 ppm (Table 6) <1998RCR633, 2002AHC(82)261>.

9.02.3.4 Mass Spectrometry

A mass spectrometric method was used to study protonation of 3-amino-1,2,4-benzotriazine and its *N*-oxides, such as the 1-oxide, 2-oxide, 4-oxide, and 1,4-dioxide (tirapazamine) <2001JOC107, 2003JAM881>. Protonation of tirapazamine in both the gas and liquid phases was shown to occur exclusively at the oxygen in the 4-position. The activation energy for loss of OH radical from O-protonated tirapazamine was estimated to be approximately 14 kcal mol⁻¹. Quantum-chemical calculations of protonated *N*-oxides were performed to interpret the experimental results and identify intermediates <2003JAM881>.

In the mass spectra of 1,2,4-triazine *N*-oxides, molecular ion peaks M^+ and the peaks $[\text{M}-16]^+$, corresponding to elimination of an oxygen atom, have been observed. Unfortunately, the fragmentation pattern for 1,2,4-triazine *N*-oxides does not allow the position of the *N*-oxide group to be established <1998RJO393, 1998RJO393>.

In addition, the lactam–lactim tautomerism of 1,2,4-triazino[2,3-*f*]theophyllin-4*H*-3-ones has been studied by means of mass spectrometry <1998CHE488>.

9.02.3.5 UV/Vis Spectroscopy

Ultraviolet (UV) Spectra of both simple 1,2,4-triazines and their more complicated derivatives have been reported and analyzed in detail in CHEC(1984) and CHEC-II(1996) <1984CHEC-I(2)385, 1996CHEC-II(6)507>.

9.02.3.6 IR/Raman Spectroscopy

The infrared (IR) absorption spectra of a number of azauracils, such as 5-oxo-1,2,4-triazin-3-thione, 3-oxo-1,2,4-triazin-5-thione, and 1,2,4-triazin-3,5-dithione, isolated in low-temperature nitrogen matrices have been reported. These compounds exist in low-temperature matrices exclusively in the oxothione and dithione tautomeric forms. Assignments of the observed IR bands were made on the basis of comparison of the experimental spectra with those obtained by *ab initio* SCF/6-311G** calculations <1996SAA645>. Additionally, IR spectroscopy has been used to study the photoisomerization reaction of 6-methyl-5-oxo-1,2,4-triazin-3-thione <2005PCA7700>. The IR spectra revealed that before UV irradiation the matrix-isolated compound adopts exclusively the oxo-thione tautomeric form.

The IR spectra of Co(II) and Cu(II) complexes of hydrazones obtained by the reaction of 5,6-diphenyl-3-hydrazino-1,2,4-triazine with furfural <2002TML398> and 2-acetylpyridine <2004JCR105> have been studied to determine the coordination sites of these ligands. In addition, Mn(II), Ni(II), and Cu(II) complexes of hydrazones derived from 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one were elucidated by IR spectra <2000SRI979>.

A few complexes of La(III), Ce(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III), and Y(III) perchlorates with 4-salicylideneamino-3-mercapto-6-methyl-1,2,4-triazine(4*H*)-5-one were isolated and characterized by IR spectra <1999IJA1297>.

The IR spectral data were used successfully to identify 1,2,4-triazine-3,6-diones derived from reactions of hydrazines with α -lactams <1998JOC9128>.

9.02.3.7 Photoelectron Spectroscopy

Photoelectron spectra of 1,2,4-triazines have been considered thoroughly in CHEC(1984) <1984CHEC-I(2)385>.

9.02.3.8 ESR Spectroscopy

A number of stable 1-aryl-3-phenyl-1,4-dihydro-1,2,4-benzotriazin-4-yl radicals have been registered by electron spin resonance (ESR) <1996AXC3124, 2002RCB1796>. In particular, the ^1H and ^{14}N hyperfine structure constants for the stable 1-(4-nitrophenyl)-3-phenyl-1,4-dihydro-1,2,4-benzotriazin-4-yl free radical, obtained by the oxidation of 1-(4-nitrophenyl)-3-phenyl-1,4-dihydro-1,2,4-benzotriazine, were determined by ESR and ^1H electron nuclear double resonance methods <2002RCB1796>.

9.02.4 Thermodynamic Aspects

For a series of 1,2,4-triazines, protonation constants for the first and second stages (pKBH^+ , pKBH_2^+) were determined in aqueous solution using a spectrophotometric procedure <2003CHE616>. Thermodynamic aspects for N-protonation and N-alkylation of 1,2,4-triazines are discussed in detail in Section 9.02.5.5.

Complexes of a number of metal ions, viz. Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Pr(III), Nd(III), Sm(III), and Yb(III), with 3-(α -benzoylbenzylidenehydrazino)-5,6-diphenyl-1,2,4-triazine have been studied by potentiometric, spectrophotometric, and electrochemical methods. The standard thermodynamic parameters, ΔG° , ΔH° , and ΔS° , terms for dissociation and for the stepwise formation of metal-ligand complexes were evaluated <2001SRI205>.

9.02.5 Reactivity of Fully Conjugated Rings

9.02.5.1 Introduction

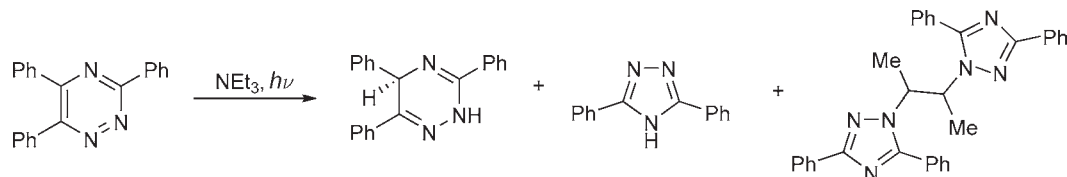
Fully conjugated 1,2,4-triazines belong to the family of azaaromatic compounds, and the presence of several nitrogen atoms makes the pattern of reactivity of 1,2,4-triazines not only specific, but a rather complicated one. Indeed, all nitrogen atoms N-1, N-2, and N-4 in 1,2,4-triazines are vulnerable for N-protonation, N-alkylation, N-acylation, and other electrophilic reactions, while carbon atoms (C-3, C-5, and C-6) are a part of π -deficient aromatic systems with a profound tendency to react with nucleophilic reagents to give either adducts, or substitution products. Besides that, low aromatic 1,2,4-triazines are rather sensitive to oxidation, reduction, cycloaddition, and ring transformation reactions.

9.02.5.2 Unimolecular Thermal and Photochemical Reactions

Photophysical and photochemical properties of several 1,2,4-triazines have been studied <2000J(P2)1723, 2000MI57>.

The triplet state characteristics for 3,5,6-triphenyl-1,2,4-triazine, 3-phenyl-1,2,4-benzotriazine, and 3-phenyl-1,2,4-phenanthro[9,10-*e*]triazine in several solvents have been obtained <2000J(P2)1723>.

Broad band irradiation of 3,5,6-triphenyl-1,2,4-triazine in neat triethylamine as solvent leads to rapid degradation of the starting material and N-dealkylation of triethylamine to give 2,5-dihydro-3,5,6-triphenyl-1,2,4-triazine, as well as ring-contraction products, 3,5-diphenyl-1,2,4-triazole and 2,3-di(3,5-diphenyl-1,2,4-triazol-1-yl)butane, as a mixture of stereomeric compounds (Scheme 1) <2000MI57>.



Scheme 1

Laser flash photolysis (400 nm excitation) of the anticancer drug tirapazamine (3-amino-1,2,4-benzotriazine 1,4-dioxide) in acetonitrile produces the singlet excited state with $\lambda_{\max} = 544$ nm. The lifetime of this state is 130 ps, which is in good agreement with the reported fluorescence lifetime. Laser flash photolysis of tirapazamine also produces the first excited singlet state; however, in the case of desoxytirapazamine, the fluorescence quantum yield and lifetime (5.4 ns) of the singlet excited state are much higher than the corresponding values for tirapazamine <2005PCA1491>.

9.02.5.3 Reduction

Electrochemical reduction of 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one, known as the herbicide metamitron, in acidic media has been studied <1998JEC177>. The first step has been shown to be reduction of the 1,6-azomethine bond by means of transfer of two electrons to the protonated form of 1,2,4-triazinone, while the second step is reduction of the 2,3-azomethine bond. The 1,6-double bond is reduced at potentials approximately 0.5 V more positive than that of the 2,3-azomethine bond <1998JEC177>. It is interesting to note that in the chemical reaction of the same triazin-5(4*H*)-one with sodium borohydride the 2,3-C=N bond is reduced first <1996JHC2063>.

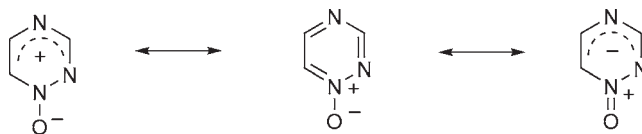
Similarly, in 4-amino-6-*tert*-butyl-3-methylthio-1,2,4-triazin-5(4*H*)-one, which is known as the widely used weed-controlling agent metribuzin <1998MI869>, as well as in all 4-amino-1,2,4-triazin-5-ones studied, the 1,6-C=N bond is reduced first electrochemically, followed by reduction of the 2,3-C=N bond <2004MI777>.

4-Amino-6-methyl-3-thio-1,2,4-triazin-5-one and 6-methyl-3-thio-1,2,4-triazin-5-one exhibit similar electrochemical behavior. Both compounds display two cathodic peaks. The first one is one-electron reduction of thiol, thus initiating dimerization and the formation of disulfides, while the second two-electron wave corresponds to reduction of the 1,2,4-triazine ring <2005JEC245>.

Also, it should be noted that a great number of nucleophilic addition or diaddition reactions at carbon atoms of the 1,2,4-triazine ring result in the formation of either dihydro or tetrahydro derivatives of 1,2,4-triazines (for details, see Sections 9.02.5.7.1–9.02.5.7.3).

9.02.5.4 Oxidation

The oxidation of 1,2,4-triazines may result in the formation of three isomeric *N*-oxides. 1,2,4-Triazine *N*-oxides are still electron-deficient aromatic compounds and, due to the electron-withdrawing character of the *N*-oxide function, the ring carbon atoms are activated for nucleophilic attack. On the other hand, the electron deficiency of the 1,2,4-triazine ring is partially compensated by the back-donation effect of the *N*-oxide moiety (Scheme 2), which is clearly reflected in ^1H , ^{13}C , and ^{15}N NMR spectra (for a detailed discussion, see Section 9.02.3.3) <1989AHC(46)73, 1998RCR633, 2002AHC(82)261>.



Scheme 2

9.02.5.5 Electrophilic Attack at Ring Nitrogen

Reactions of monocyclic 1,2,4-triazines with simple electrophiles, leading to N-protonation, N-alkylation, N-acylation, or N-oxidation, have been well studied [<1984CHEC-I\(2\)385, 1989AHC\(46\)73, 1992H\(33\)931, 1996CHEC-II\(6\)507, 2002AHC\(82\)261>](#).

9.02.5.5.1 N-Protonation

All nitrogen atoms in the 1,2,4-triazine ring, N-1, N-2, and N-4, are potential sites for proton attack. Calculations for the parent 1,2,4-triazine and some of its derivatives show that the $(\sigma+\pi)$ negative charge on the nitrogen atoms decreases in the following order: N-4 > N-2 > N-1 ([Table 1](#)). This sequence is in full agreement with ^{15}N chemical shifts for the nitrogen atoms in ^{15}N NMR spectra (see [Section 9.02.3.3.3, Table 6](#)) [<1979MR227, 1984SAA637, 1988KGS525, 1992H\(33\)931, 2003CHE616>](#). According to the $(\sigma+\pi)$ distribution over the ring nitrogens, the formation of the $\text{N}_4\text{-H}$ triazinium cations is first expected to occur [<2003CHE616>](#).

On the other hand, σ -charges in aromatic systems usually have a smaller influence on the proton attack than the π -charge densities, which decrease in the order N-2 > N-4 > N-1 ([Table 1](#)), thus indicating that the N-2 atom is the most likely protonation center.

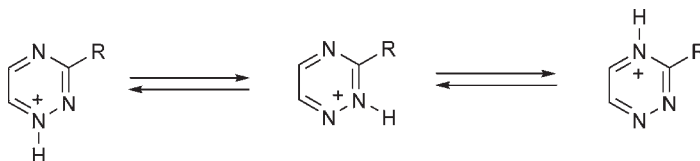
The thermodynamic stability of 1,2,4-triazinium salts is also an important factor. The *ab initio* calculations performed for the parent 1,2,4-triazine show that energies for $\text{N}_1\text{-}$ and $\text{N}_2\text{-}$ protonation are less than that for the formation of the $\text{N}_4\text{-H}$ triazinium salt [<1987JST135, 1988JCC784, 2003CHE616>](#). Recent data, obtained by *ab initio* calculations with $\text{HF}/6\text{-}31\text{G}^{**}$ basis set, have shown that the $\text{N}_2\text{-H}$ triazinium cation is the most stable one thermodynamically. This is also true for the series of phenyl-substituted NH -1,2,4-triazinium salts, with the exception of 6-phenyl-1,2,4-triazine, for which the existence of both $\text{N}_1\text{-}$ and $\text{N}_2\text{-H}$ 1,2,4-triazinium salts may be equally possible [<2003CHE616>](#).

One of the reasons why the formation of $\text{N}_1\text{-H}$ and $\text{N}_2\text{-H}$ triazinium salts is favored thermodynamically, is that N-protonation of one of the two neighboring nitrogen atoms eliminates repulsion of their electron pairs. Besides that, $\text{N}_1\text{-H}$ or $\text{N}_2\text{-H}$ protonation is stabilized by intramolecular hydrogen-bond formation, as shown in [Figure 5](#) [<1992H\(33\)931>](#).



Figure 5

Protonation of 1,2,4-triazines has been studied experimentally [<1972LA111, 1988KGS525, 1992H\(33\)931, 2003CHE616>](#). The ^1H , ^{13}C , ^{14}N , and ^{15}N NMR spectral data provided convincing arguments that a mixture of three interconverting prototropic isomers is formed in solution on treatment of 1,2,4-triazines with acids ([Scheme 3](#)). The preferential contribution of the $\text{N}_1\text{-H}$ and $\text{N}_2\text{-H}$ 1,2,4-triazinium forms to the prototropic equilibria is also an experimental fact which has been noted in a number of publications [<1988KGS525, 1992H\(33\)931, 2003CHE616>](#).



Scheme 3

As far as 1,2,4-benzotriazines are concerned, the sites of protonation of 3-amino-1,2,4-benzotriazine 1,4-dioxide (tirapazamine), and its metabolites, including 3-amino-1,2,4-benzotriazine 1-oxide, 3-amino-1,2,4-benzotriazine 4-oxide, 3-amino-1,2,4-benzotriazine, and 3-amino-1,2,4-benzotriazine 2-oxide, have been studied <2001JOC107, 2003JAM881>. Protonation of tirapazamine in both gas and liquid phases was shown to occur exclusively at the oxygen in the 4-position <2003JAM881>.

9.02.5.5.2 N-Alkylation and dequaternization

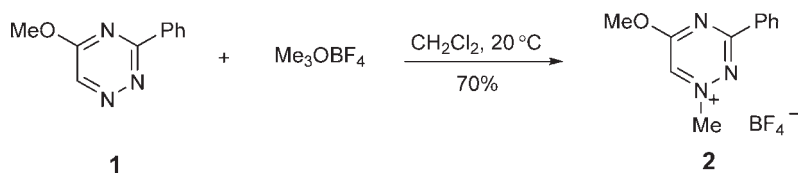
In principle, three types of *N*-alkyl-1,2,4-triazinium salts can be obtained from *N*-alkylation of 1,2,4-triazines. As already mentioned, the basic character of nitrogen atoms in 1,2,4-triazines is changed as follows: $N-4 > N-2 > N-1$ <1988KGS525, 1992H(33)931>; however, according to the CNDO/2 molecular orbital calculations, the formation of N_1 - and N_2 -alkyl-1,2,4-triazinium salts is more favored thermodynamically <1988KGS525>. Experimental data show that *N*-alkylation of 1,2,4-triazines is governed predominantly by steric effects of bulky substituents <1988KGS1535, 1989T6499, 1992H(33)931, 1997RJO1033>.

Alkylation of 3-substituted- and 3,5-disubstituted-1,2,4-triazines bearing a bulky substituent at C-3, such as 3-phenyl, 3-morpholino, and 3-piperidino, with alkyl iodides or trialkyloxonium tetrafluoroborates occurs predominantly at *N*-1 (Table 7). For instance, methylation of 5-methoxy-3-phenyl-1,2,4-triazine **1** with trimethyloxonium tetrafluoroborate is a site-selective process, yielding the N_1 -methyl-1,2,4-triazinium salt **2** (Scheme 4) <2001JHC901>.

Table 7 *N*-Alkylation of selected 1,2,4-triazines on treatment with trialkyloxonium (Me_3O^+ or Et_3O^+) tetrafluoroborates in CH_2Cl_2 at 25 °C

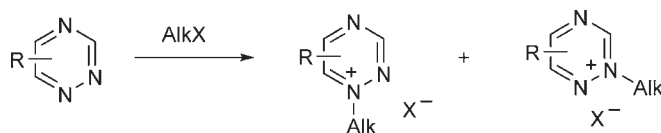
Starting 1,2,4-triazine	Ratio of isomers		Reference
	<i>N</i> -1	<i>N</i> -2	
3-Methoxy-1,2,4-triazine	100	0	1992H931
3-Methylthio-5-phenyl-1,2,4-triazine	92	8	1988KGS525
3-Amino-5-phenyl-1,2,4-triazine	80	20	1988KGS525
3-Amino-5-phenyl-6-methyl-1,2,4-triazine ^a	0	100	1987AJC1979
3-Amino-5,6-dimethyl-1,2,4-triazine ^a	30	70	1987AJC1979
3-Amino-5,6-diphenyl-1,2,4-triazine ^a	0	100	1987AJC1979
3-Dimethylamino-1,2,4-triazine	100	0	1987AJC1979
3-Morpholino-1,2,4-triazine	100	0	1992H(33)931
3-Phenyl-1,2,4-triazine	100	0	1992H(33)931
3-Phenyl-5-methoxy-1,2,4-triazine	100	0	2001JHC901
3-Morpholino-5-phenyl-1,2,4-triazine	100	0	1992H(33)931

^aReflux with methyl iodide.



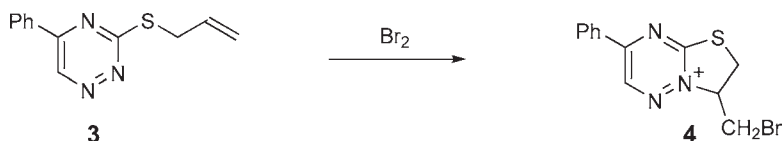
Scheme 4

In other cases, a mixture of N_1 - and N_2 -alkyl-1,2,4-triazinium salts is formed (Scheme 5; Table 7).



Scheme 5

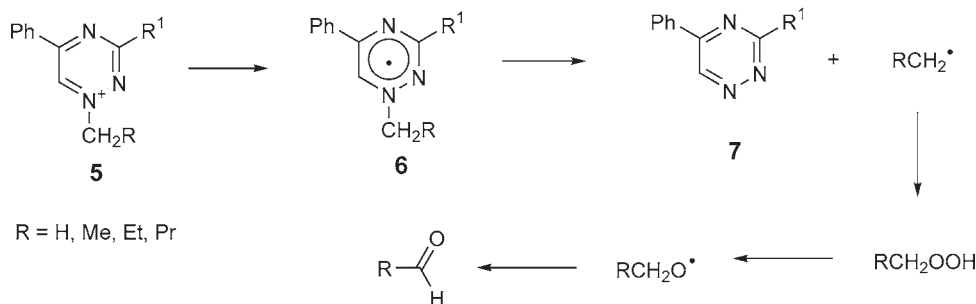
Intramolecular N-alkylation of 3-allylthio-5-phenyl-1,2,4-triazine **3** has been found to occur on treatment with bromine, and it is directed exclusively at N-2, thus giving 3-bromomethyl-7-phenyl-2,3-dihydrothiazolo[3,2-*b*]-1,2,4-triazinium bromide **4** (Scheme 6) <1997RJO1033>.



Scheme 6

The ^1H and ^{13}C NMR spectra of *N*-alkyl-1,2,4-triazinium salts usually enable one to distinguish isomeric structures (see Sections 9.02.3.3.1 and 9.02.3.3.2).

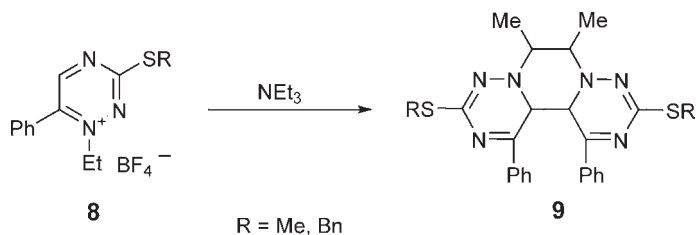
It is well recognized that N-alkylation of aza-aromatic compounds is usually an irreversible process <1978AHC(22)71>. However, a feature of 1-alkyl-1,2,4-triazinium salts **5** is an unusual dequaternization reaction which has been found to occur under very mild conditions on treatment of **5** with triethylamine in methanol, ethanol, or acetone solutions (Scheme 7) <1995MC104>.



Scheme 7

The mechanism suggested on the basis of ^1H NMR and ESR studies of the reaction mixtures and kinetic measurements involves the formation of intermediate radical species **6** (Scheme 7). The reaction is very fast in comparison with dequaternization of *N*-alkylpyridinium cations. Indeed, the observed pseudo-first-order rate constants k_{obs} for dequaternization of a number of 1-alkyl-1,2,4-triazinium salts proved to be approximately 10^{-3} s^{-1} at 25°C , while *N*-alkylpyridinium salts are dequaternized much more slowly ($k_{\text{obs}} = 10^{-5} \text{ s}^{-1}$ at 100°C) <1995MC104>.

Another feature of 1-alkyl-1,2,4-triazinium salts is their ability to undergo an unusual dimerization reaction, which takes place on treatment with triethylamine in methanol or ethanol solution (Scheme 8) <1990TL7665>.

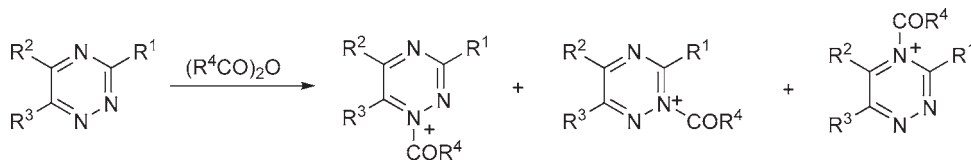


Scheme 8

9.02.5.5.3 N-Acylation

Since *N*-acyl-1,2,4-triazinium salts are very unstable, all attempts to register their formation in solutions by NMR have failed. Nevertheless, these reactive species are undoubtedly formed on treatment of 1,2,4-triazines with acyl anhydrides or acyl halogenides, and N-acylation has proved to be a very effective procedure for activation of

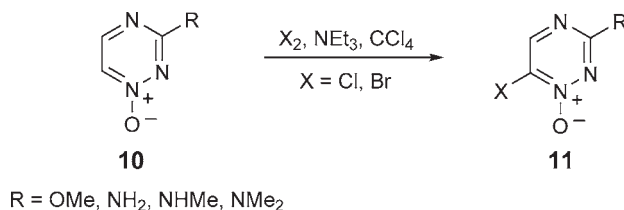
1,2,4-triazines toward nucleophilic attack <1997JHC573, 1997JHC1013, 1998RJO297, 1998RJO452, 2001H(55)2349, 2001MC77, 2003TL2421, 2003RCB1740, 2004RCB1279, 2004RCB1351, 2006JOC8272, 2006MC95>. As far as the site selectivity is concerned, N-acylation of 1,2,4-triazines appears to take place predominantly at the nitrogen N-1, and to a lesser extent at N-2, as follows from the structure of adducts derived from nucleophilic addition reactions (see Sections 9.02.5.7), although the formation of *N*₄-acyl-1,2,4-triazinium cations cannot be excluded (Scheme 9).



Scheme 9

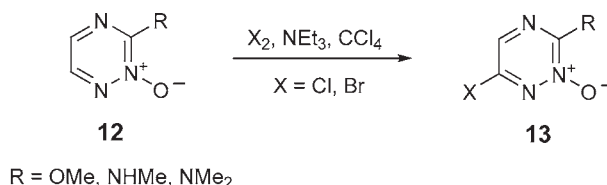
9.02.5.6 Electrophilic Attack at Ring Carbon

Due to the strong electron-deficient character of the 1,2,4-triazine system, the ring carbon atoms in a vast majority of derivatives are resistant toward electrophilic attack. However, electron-donating substituents and, especially, the *N*-oxide function with its back-donation effect (see Sections 9.02.5.4 and 9.02.3.3.1), may activate the 1,2,4-triazine ring to such an extent, that electrophilic substitution becomes possible. Indeed, 3-methoxy- and 3-amino-substituted 1,2,4-triazine 1-oxides react easily with chlorine or bromine to form the corresponding 6-halo-1,2,4-triazine 1-oxides (Scheme 10) <1977JOC3498, 1978JOC2514, 2002AHC(82)261>.



Scheme 10

Halogenation of 3-methoxy-, 3-methylamino-, and 3-dimethylamino-1,2,4-triazine 2-oxides was shown to proceed in a similar manner, resulting in 6-halo-1,2,4-triazine 2-oxides (Scheme 11) <2002AHC(82)261>.



Scheme 11

9.02.5.7 Nucleophilic Attack at Ring Carbon

Being a part of a π -deficient system, carbon atoms in 1,2,4-triazines are vulnerable to nucleophilic attack, resulting in the displacement of either a hydrogen atom (S_N^H) or a good leaving group (S_N^{ipso}) <B-1988MI95, 1989AHC(46)73, 1992H(33)931, B-1994MI1, 1998RJO297, 1998RCR633, 2002AHC(82)261>.

9.02.5.7.1 Addition reactions

It is well recognized that many reactions between electron-deficient aza-aromatic substrates and nucleophilic reagents are initiated by an addition step, leading to the formation of σ -adducts <1988T1, B-1994MI1>. As far as 1,2,4-triazines are concerned, the formation of σ -adducts at C-5 is especially favored in this series due to: (1) a low aromatic character of the 1,2,4-triazine ring; (2) effective delocalization of the negative charge at N-2 (Figure 6) <1989AHC(46)73>.

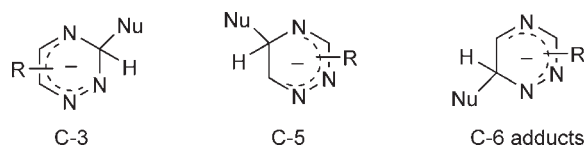
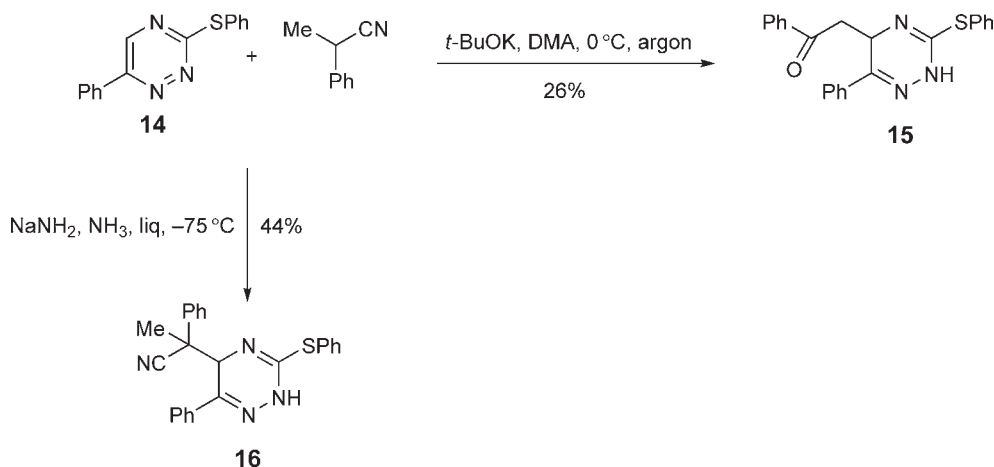


Figure 6

9.02.5.7.1(i) Adducts with C-nucleophiles

The formation of C-adducts **14** and **15** at C-5 of the 1,2,4-triazine ring is illustrated by the reaction of 3-phenylthio-6-phenyl-1,2,4-triazine with phenylpropionitrile in the presence of potassium *t*-butoxide or sodium amide (Scheme 12) <2001CHE1418>.



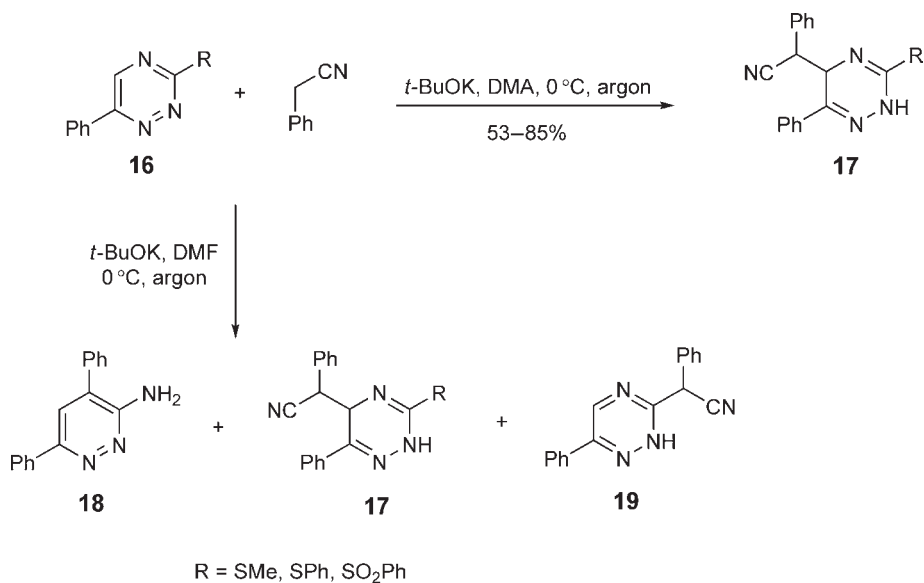
Scheme 12

The reaction of 1,2,4-triazine **16** with phenylacetone in dimethylacetamide (DMA) leads to the formation of σ^H -adducts **17**, while in dimethylformamide (DMF) these σ^H -adducts are transformed into 3-aminopyridazine **18** along with **17** and **19** (Scheme 13) <2001CHE1418>. It is worth noting that similar transformations of the ANRORC-type (addition of the nucleophile, ring opening, and ring closure) have been observed to occur on reacting **16** (R = Cl) with ethyl cyanoacetate, malonodinitrile, and phenylsulfonylacetonitrile <2000JHC879>.

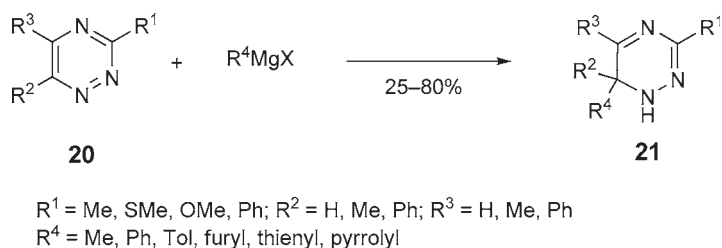
Grignard reagents are effective C-nucleophiles for the incorporation of alkyl, aryl, or hetaryl substituents into the 1,2,4-triazine ring. The formation of exclusively C-5 adducts **21** on treatment of 1,2,4-triazines **20** with Grignard reagents in tetrahydrofuran (THF) at -50°C has been determined by ^1H NMR (Scheme 14) <1998RJO297>.

Treatment of 1,2,4-triazine **22** with organolithium compounds results in the formation of adducts **23** (yields 8–18%), whereas the reaction of **22** with *tert*-butyl- or *n*-butyllithium as C-nucleophiles affords the hexahydrotriazine **24** (Scheme 15) <2002J(P1)2549>.

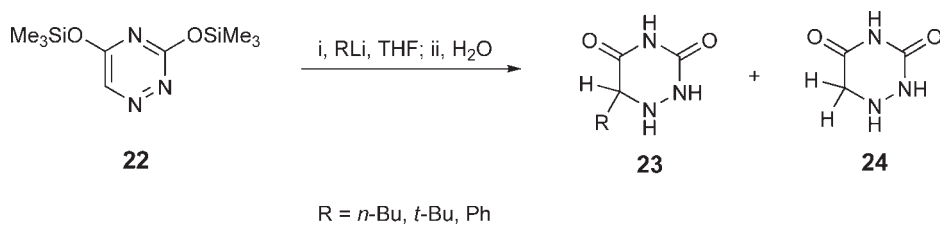
3-Amino- and 3-methylthio-substituted 1,2,4-triazines react with calixpyrroles in the presence of acids to give the corresponding C-adducts **25** in 60% yields (Scheme 16) <2004RCB1351>.



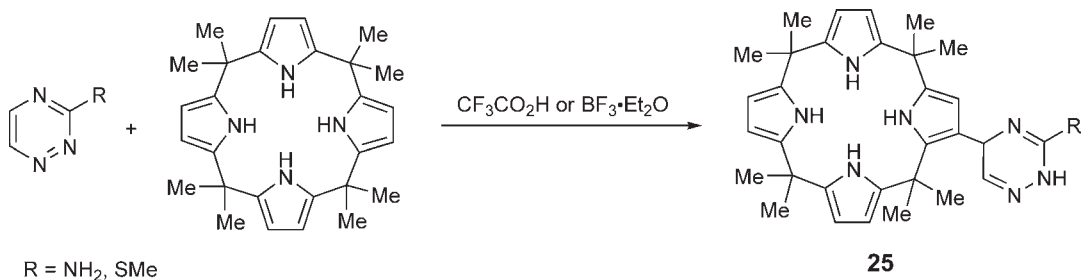
Scheme 13



Scheme 14

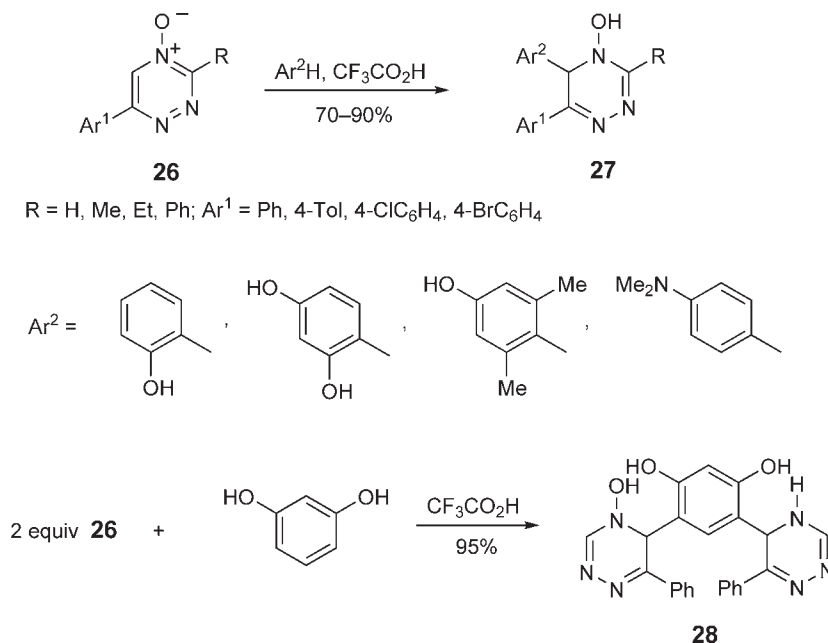


Scheme 15



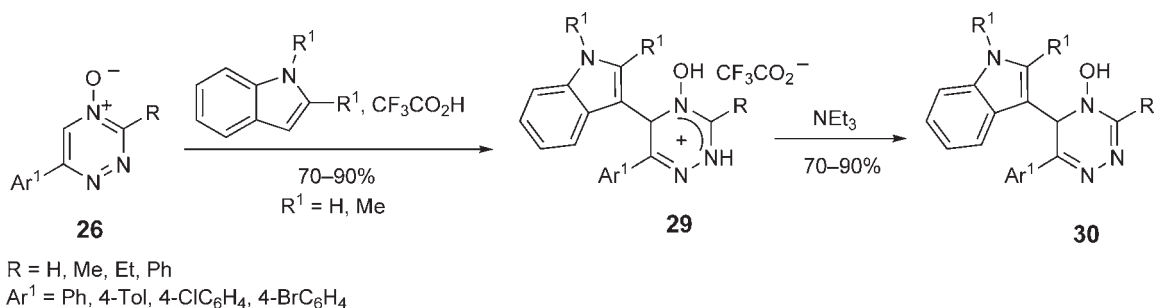
Scheme 16

Upon reaction with C-nucleophiles, such as phenol, 2,6-dimethylphenol, resorcinol, or *N,N*-dimethylaniline, in the presence of trifluoroacetic acid (TFA), 1,2,4-triazine 4-oxides **26** give rise to relatively stable C-5 adducts, for example, 5-aryl-4-hydroxy-4,5-dihydro-1,2,4-triazines **27** (Scheme 17) <1997MC116, 1998RJO297, 2002AHC(82)261>. It is worth noting that resorcinol reacts with 2 equiv of 5-phenyl-1,2,4-triazine 4-oxide **26** (Ar=Ph; R=H) to give the corresponding 4,6-bis(4-hydroxy-6-phenyl-1,2,4-triazin-5-yl)resorcinol **28** (Scheme 17).



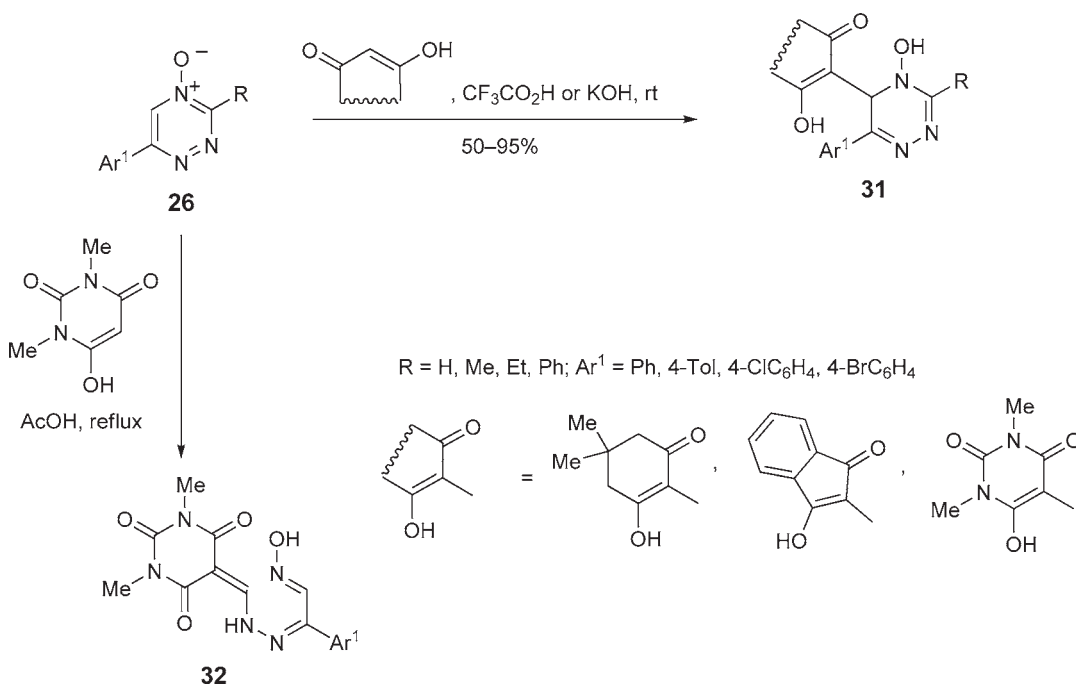
Scheme 17

In a similar manner, 1,2,4-triazine 4-oxides **26** react with indole and its methyl derivatives in TFA to give 6-aryl-5-(indolyl-3)-4,5-dihydro-4-hydroxy-1,2,4-triazines, which have been isolated as protonated trifluoroacetates **29**, and also as neutral compounds **30** (Scheme 18) <1996MC116, 1998RJO297, 1998RJO400, 2002AHC(82)261>.



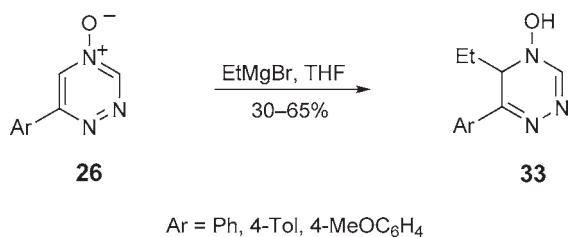
Scheme 18

Rather stable C-5 adducts **31** are formed in the reaction of 1,2,4-triazine 4-oxides **26** with cyclic 1,3-dioxo compounds, such as dimedone, 1,3-indandione, and 1,3-dimethylbarbituric acid, under either acidic or basic conditions (Scheme 19) <1998RJO297, 1998RJO400, 2001CHE520, 2001CHE1136, 2002AHC(82)261, 2004CHE911>. In contrast, in the reaction of 3-unsubstituted triazines **26** (R=H) with dimethylbarbituric acid in refluxing acetic acid (or in dimethyl sulfoxide (DMSO) at 50 °C), nucleophilic attack takes place at C-3, thus initiating opening of the 1,2,4-triazine ring and the formation of open-chain products **32** (Scheme 19) <2001CHE520, 2001CHE1136, 2004CHE911>.



Scheme 19

The addition of ethylmagnesium bromide at C-5 of 6-aryl-1,2,4-triazine 4-oxides results in the formation of 4-hydroxy-5-ethyl-4,5-dihydro-1,2,4-triazines **33** (Scheme 20) <2004CHE911>.

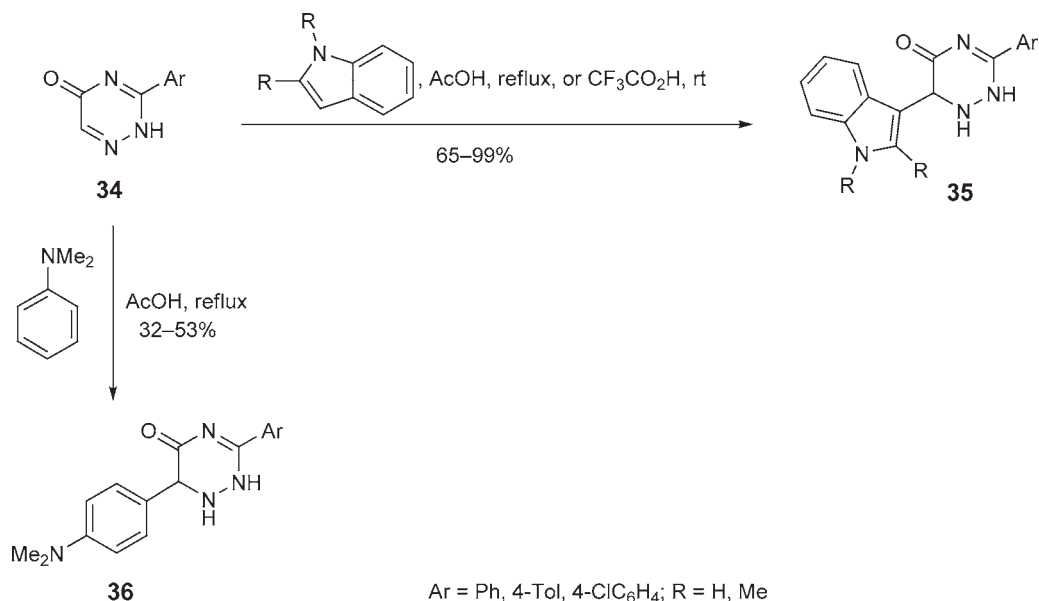


Scheme 20

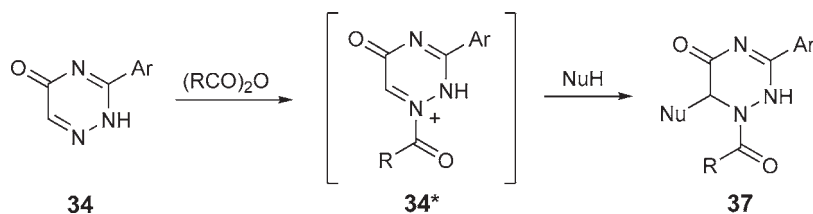
There are many examples of the formation of σ^{H} -adducts derived from nucleophilic attack by C-nucleophiles at an unsubstituted carbon atom of the 1,2,4-triazine ring. For instance, the reaction of 3-aryl-1,2,4-triazin-5-ones **34** with indole and its methyl derivatives affords 3-aryl-6-(indolyl-3)-1,6-dihydro-1,2,4-triazin-5(2H)-ones **35** (Scheme 21) <1997JHC1013, 1998RJO297>. In a similar way, adducts of **34** with *N,N*-dimethylaniline, viz. **36**, are formed (Scheme 21) <1997JHC573, 1998RJO297, 2001H(55)2349>.

The addition of aromatic or heteroaromatic C-nucleophiles at C-6 of 1,2,4-triazin-5-ones **34** proceeds rather smoothly when the reactions are carried out in such solvents as acyl anhydrides or formic acid. There are two reasons: (1) the formation of *N*-acyl-1,2,4-triazinium salts **34*** facilitates nucleophilic addition reactions; (2) the σ^{H} -adducts **37** are stabilized by the *N*-acyl group, as illustrated by the formation of adducts **37** with phenols, arylamines, pyrroles, and indoles (Scheme 22; Table 8) <1997JHC573, 1997JHC1013, 1998RJO297, 1998RJO452, 2001MC77, 2004RCB1351>.

It is interesting to note that the reaction of the 1,2,4-triazin-5-ones **34** with pyrroles in acetic anhydride leads exclusively to 1-acyl-3-aryl-6-(pyrrolyl-2)-1,2,4-triazin-5-ones **38**; however, when the same reaction is carried out in trifluoroacetic anhydride or formic acid, 3-substituted pyrroles, that is, 1-trifluoroacetyl- or 1-formyl-3-aryl-6-(pyrrolyl-3)-1,2,4-triazin-5-ones, **39**, are formed (Scheme 23) <1997JHC1013, 1998RJO297, 2001MC77>.



Scheme 21



Scheme 22

When reacting with 1,2,4-triazin-5-ones **34**, benzo-annulated crown ethers **40** and their open-chain analogs, the podands **42**, behave like phenol ethers, thus yielding C-adducts **41** and **43** (Scheme 24) <2001H(55)2349>.

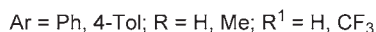
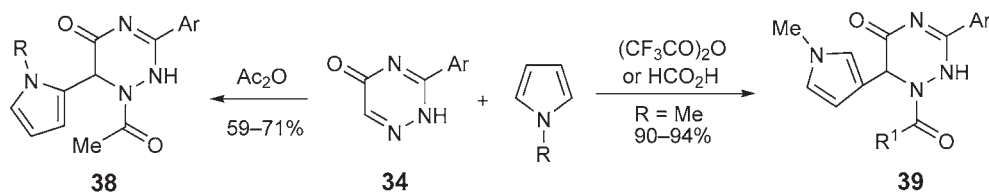
In addition, the C–C coupling reaction between calixarene **44** and triazinones **34** can be performed in TFA solution in the presence of acetic or trifluoroacetic anhydrides. The electrophilicity of the protonated 1,2,4-triazin-5(2*H*)-one is not sufficient to cause the reaction with calixphenols; however, treatment of triazinones **34** with acetic anhydride results in the corresponding 2-acyl derivatives, the protonated forms of which proved to be active enough to react with calix[4]arene **44**. Nucleophilic addition of calix[4]arene **44** at C-6 of 1,2,4-triazin-5-ones **34** results in the formation of the corresponding σ^H -adducts. The reaction is accompanied by the rearrangement of the *N*-2-acyl derivatives into more stable adducts **45** and **46**, bearing an acyl group at the N-1 atom which is adjacent to the reaction center (Scheme 25) <2006JOC8272>.

New estrone derivatives **47** and **48** containing 1,2,4-triazin-5-one **34** moieties were synthesized through direct C–C coupling of estrone 3-methyl ether with triazinones (Scheme 26) <2006MC95>.

Interesting results have been obtained from the study of the reaction of 1,2,4-triazin-5-ones **34** with indoles and *N*-substituted aminoacids as acylating agents (Scheme 27) <2006TL7485>. On reacting **34** with indole and *N*-Bz-aminocaproic acid in the presence of dicyclohexylcarbodiimide (DCC), compounds **49** have been obtained. Also, natural α -aminoacids can be used as acylating agents, as illustrated by the stereoselective addition of indoles at C-6 of **34** in the presence of *N*-acetyl-L-valine or *N*-acetyl-L-tryptophan **50**, activated by DCC. The products **51** proved to have the *S,S*-configuration with >95% de (Scheme 27). In contrast, *N*-formyl- or *N*-acetyl-D-alanine **52** in the same reaction with **34** and indoles affords the *R,R*-compounds **53**. It is quite natural that racemic mixtures of *N*-benzyl-D,L-leucine or *N*-acetyl-D,L-phenylalanine give rise to the corresponding diastereomeric *S,S*- and *R,R*-products.

Table 8 Yields of compounds **37** on reacting of 3-aryl-1,2,4-triazin-5-one **34** with C-nucleophiles in $(\text{CH}_3\text{CO})_2\text{O}$ (reflux), $(\text{CF}_3\text{CO})_2\text{O}$ (rt), or 80% aqueous HCOOH (reflux)

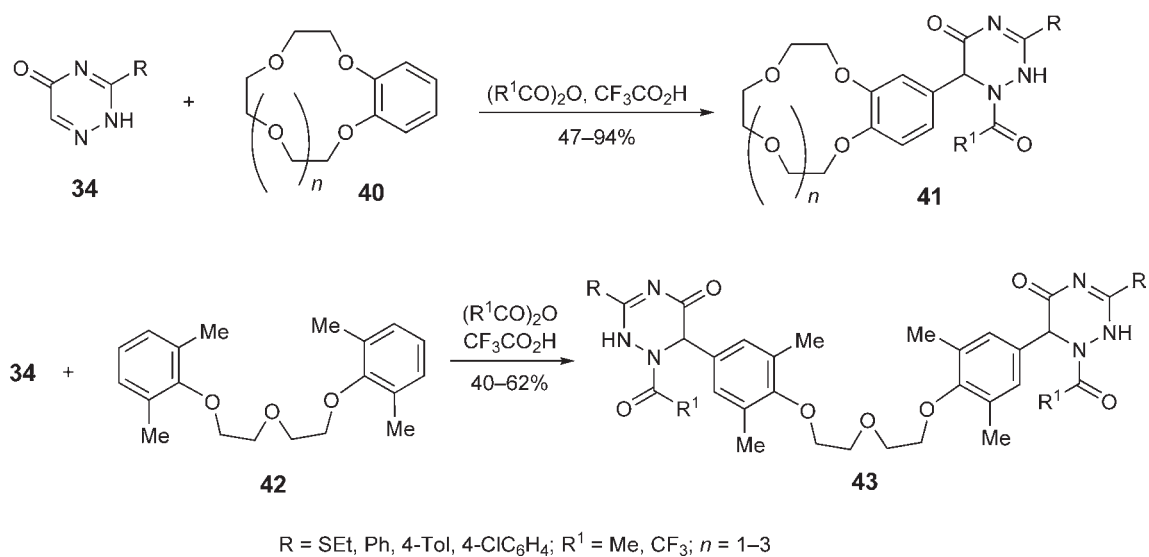
<i>Aryl</i>	<i>Nucleophile</i>	<i>R</i>	<i>Yield (%)</i>	<i>Reference</i>
Ph	4-Me ₂ NC ₆ H ₄	Me	88	1997JHC1013
4-Tol	4-Me ₂ NC ₆ H ₄	Me	90	1997JHC1013
4-Cl-C ₆ H ₄	4-Me ₂ NC ₆ H ₄	Me	90	1997JHC1013
Ph	4-OH-C ₆ H ₄	CF ₃	93	1997JHC573
4-Tolyl	4-OH-C ₆ H ₄	CF ₃	91	1997JHC573
4-Cl-C ₆ H ₄	4-OH-C ₆ H ₄	CF ₃	92	1997JHC573
Ph	4-OMe-C ₆ H ₄	CF ₃	71	1997JHC573
4-Tol	4-OMe-C ₆ H ₄	CF ₃	76	1997JHC573
4-Cl-C ₆ H ₄	4-OMe-C ₆ H ₄	CF ₃	74	1997JHC573
Ph	4-OH-3,5-Me ₂ C ₆ H ₂	CF ₃	98	1997JHC573
4-Tolyl	4-OH-3,5-Me ₂ C ₆ H ₂	CF ₃	97	1997JHC573
4-ClC ₆ H ₄	4-OH-3,5-Me ₂ C ₆ H ₂	CF ₃	99	1997JHC573
Ph	2,4-(OMe) ₂ C ₆ H ₃	CF ₃	62	1997JHC573
4-Tolyl	2,4-(OMe) ₂ C ₆ H ₃	CF ₃	50	1997JHC573
Ph	3-Indolyl	Me	88	1997JHC1013
4-Tolyl	3-Indolyl	Me	85	1997JHC1013
4-ClC ₆ H ₄	3-Indolyl	Me	80	1997JHC1013
Ph	3-(1-Me-indolyl)	Me	90	1997JHC1013
4-Tol	3-(1-Me-indolyl)	Me	97	1997JHC1013
Ph	3-(2-Me-indolyl)	Me	72	1997JHC1013
4-Tol	3-(2-Me-indolyl)	Me	86	1997JHC1013
Ph	2-Pyrrolyl	Me	65	1997JHC1013
4-Tolyl	2-Pyrrolyl	Me	60	1997JHC1013
Ph	2-Pyrrolyl	CF ₃	90	2001MC77
Ph	2-(1-Me-pyrrolyl)	Me	59	1997JHC1013
4-Tolyl	2-(1-Me-pyrrolyl)	Me	71	1997JHC1013
Ph	3-(1-Me-pyrrolyl)	CF ₃	90	2001MC77
Ph	3-(1-Me-pyrrolyl)	H	94	2001MC77
4-Tol	3-(1-Me-pyrrolyl)	H	92	2001MC77
Ph	3-(Octamethylcalix[4]pyrrolyl)	Me	71	2004RCB1351

**Scheme 23**

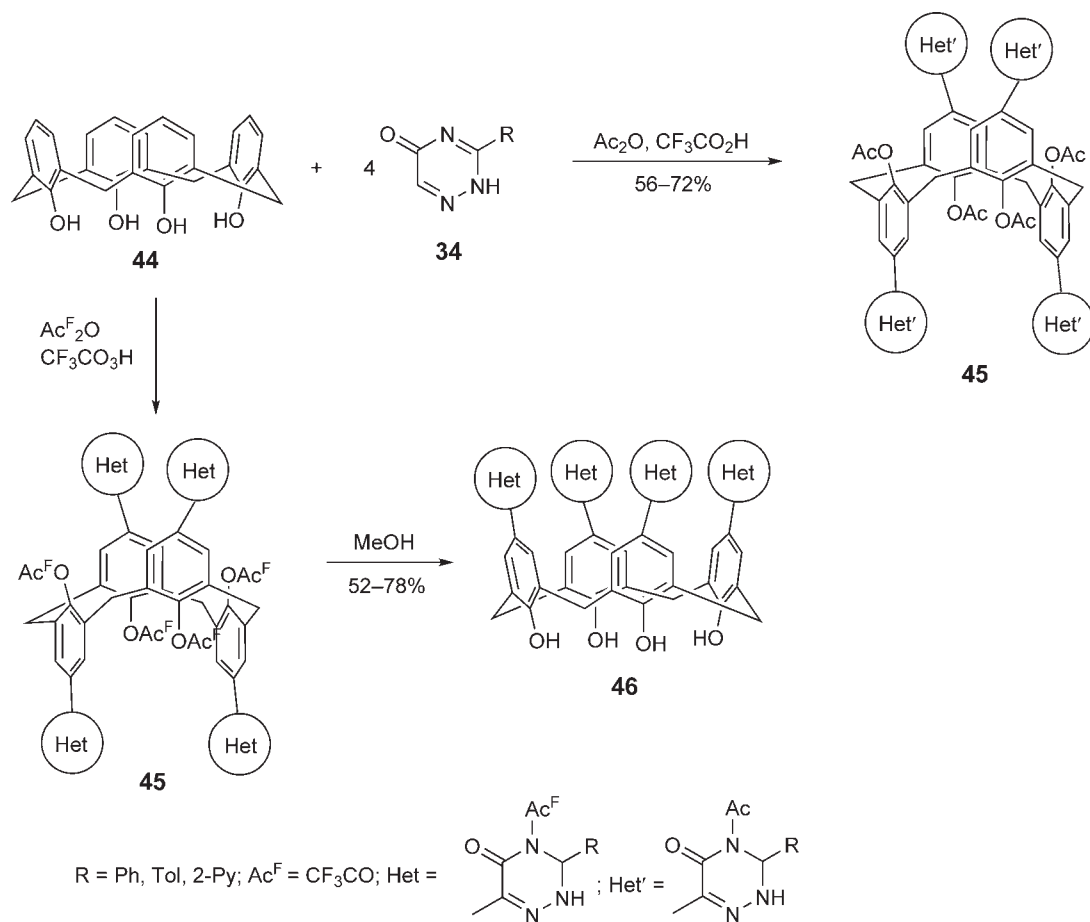
In spite of steric hindrance, interaction of 5-phenyl-1,2,4-triazine-3-one **54** with indole or 2-methylindole in the presence of hydrochloric acid takes place at C-5 of the 1,2,4-triazine ring to form 5-(3-indolyl)-5-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **55** (Scheme 28) <1996MC115>.

Nitro derivatives of azolo-annulated 1,2,4-triazines **56** react with resorcinol or indoles without any additional activation to give the corresponding 7-substituted-6-nitro-4,7-dihydro[5,1-*c*]-1,2,4-triazines **57** and **58** (Scheme 29) <1997MI103, 1998RJO297>.

Under similar conditions, fervenulin-3-one and fervenulin-3-one 4-oxide give rise to the C-adducts with arylamines (cf. **59**) and indoles (cf. **60** and **61**) (Figure 7) <1998RJO297, 2000SRI979>.

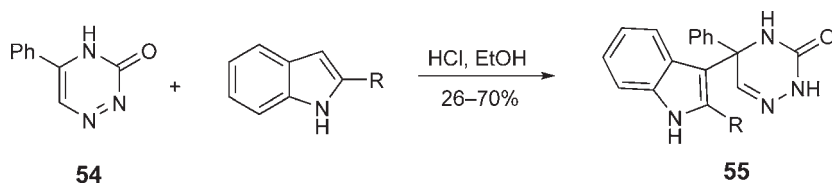


Scheme 24

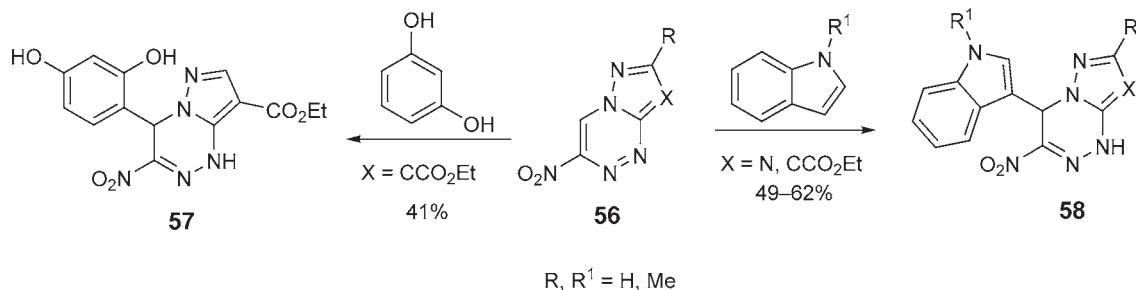


Scheme 25





Scheme 28



Scheme 29

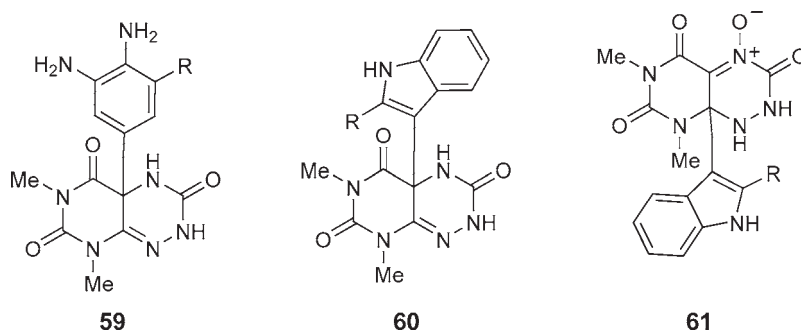
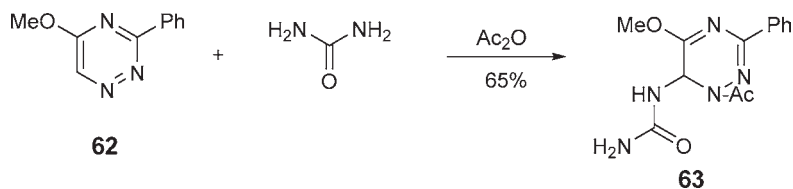


Figure 7

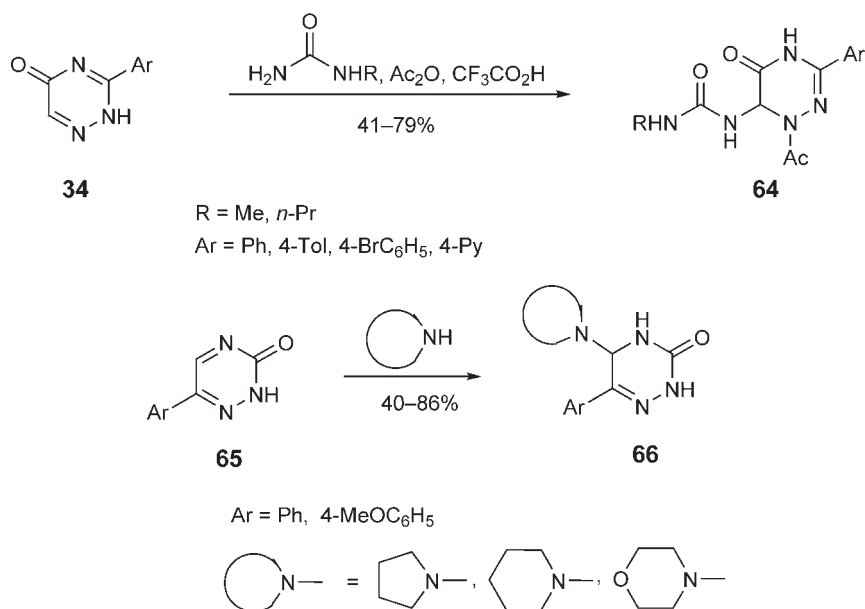
9.02.5.7.1(ii) Adducts with N-nucleophiles

The electron-deficient character of the triazine ring facilitates addition of ammonia and other N-nucleophiles. Indeed, 1,2,4-triazines bearing substituents at C-3 and/or C-6 react easily with liquid ammonia yielding the C-5 amino adducts, which can be registered by low-temperature ^1H NMR [\[1989AHC\(46\)73\]](#). If the 1,2,4-triazine ring contains substituents at C-3 and C-5, position 6 has to be attacked by nucleophiles; however, the C-6 adducts are usually not very stable. An exception is the N-adduct **63**, derived from the reaction of 3-phenyl-5-methoxy-1,2,4-triazine **62** with urea, which appears to be stabilized by an intermolecular hydrogen bond between NH of the triazine ring and C=O of the urea fragment ([Scheme 30](#)) [\[2000MC58\]](#).



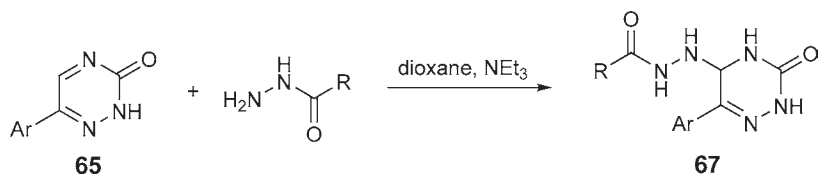
Scheme 30

Further, the reaction of 3-aryl-1,2,4-triazin-5-ones **34** with urea derivatives affords N-adducts **64** at C-6 of the 1,2,4-triazine ring (Scheme 31) <2003RCB2161>, while on heating of 6-aryl-1,2,4-triazin-3-ones **65** with an excess of cycloalkylimines the N-addition of nucleophiles takes place at C-5 to give the corresponding 5-amino-6-aryl-4,5-dihydro-1,2,4-triazin-3-ones **66** (Scheme 31) <2000RJO602>.



Scheme 31

In contrast, heating of 6-aryl-1,2,4-triazin-3-ones **65** with acylhydrazides affords N-adducts **67** (Scheme 32; Table 9) <2004RJO94>.



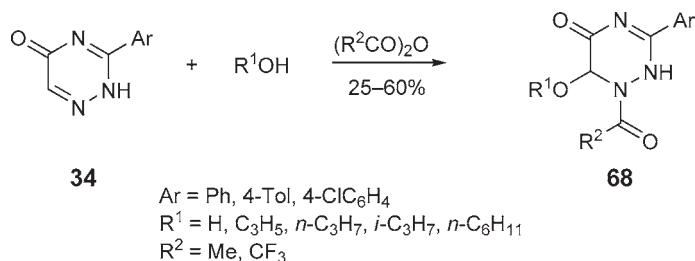
Scheme 32

Table 9 Yields of C-5 amino adducts derived from the reaction of 6-aryl-1,2,4-triazin-3-ones with acylhydrazides

Ar	R	Yield (%)
Ph	Me	58
Ph	Ph	55
4-BrC ₆ H ₄	Ph	48
Ph	3-NO ₂ C ₆ H ₄	76
4-BrC ₆ H ₄	3-NO ₂ C ₆ H ₄	60
Ph	4-Py	55
4-BrC ₆ H ₄	4-Py	38
Ph	3-Py	54
4-BrC ₆ H ₄	3-Py	50

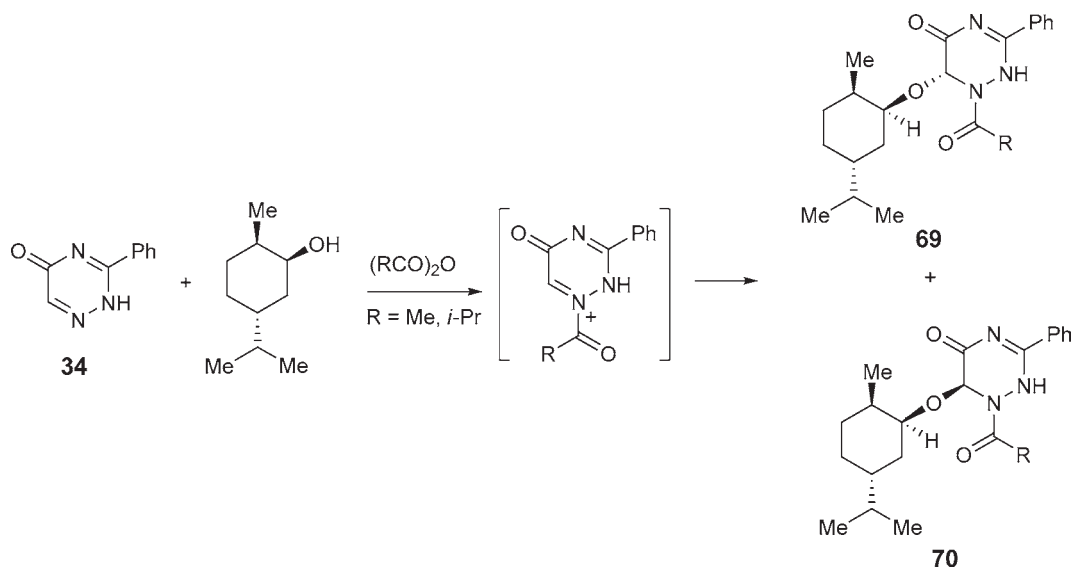
9.02.5.7.1(iii) Adducts with O-nucleophiles

Treatment of 1,2,4-triazin-5-ones **34** with primary or secondary alcohols, or water in the presence of acetic or trifluoroacetic anhydride, results in the corresponding 6-alkoxy- or 6-hydroxy-1-acyl-1,6-dihydro-1,2,4-triazin-5-ones **68** (Scheme 33) <2004MI26>.



Scheme 33

Interaction of 3-phenyl-1,2,4-triazin-5-one **34** with L-menthol in the presence of acyl anhydrides gives rise to a mixture of 1-acyl-6-[(1'*R*,3'*R*,4'*S*)-menthyl-3']-3-phenyl-(6*S*)-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **69** and 1-acyl-6-[(1'*R*,3'*R*,4'*S*)-menthyl-3']-3-phenyl-(6*R*)-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **70**. The reaction proceeds stereoselectively with predominant formation of (6*S*)-isomers (Scheme 34) <2001TL2393, 2004RCB1290>. The diastereomeric excess can be enhanced when a substituent located in the vicinity of the reactive center is able to hinder sterically the formation of one of the isomers. Indeed, for compounds with $R^1 = \text{CH}_3$, the ratio of stereoisomers **69** and **70** proved to be 60:40, 20% de, while in the case $R^1 = i\text{-C}_3\text{H}_7$ the ratio was 85:15, and 70% de.



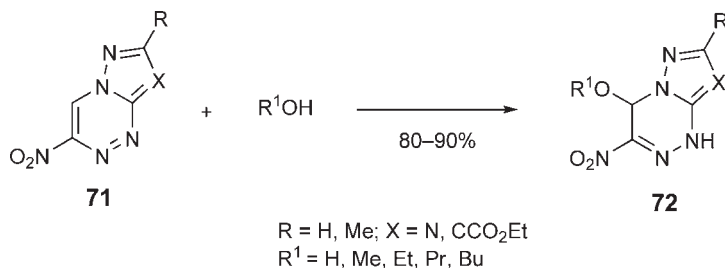
Scheme 34

Rather stable O-adducts **72** are formed on heating 6-nitroazolo[5,1-*c*][1,2,4]-triazines **71** with water or alcohols (Scheme 35) <1997MI103>.

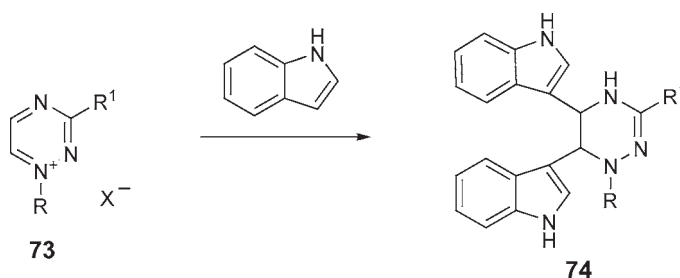
9.02.5.7.2 Diaddition reactions

It has been discussed in Section 9.02.5.7.1 that upon reaction with simple nucleophiles, 1,2,4-triazines generally participate in monoaddition reactions at C-5. However, the nucleophilic addition process is not complete at this stage, and a subsequent addition of a nucleophile may occur, resulting in the formation of diadducts at C-5 and C-6. This mode of nucleophilic diaddition usually requires as prerequisite that the 1,2,4-triazine ring is strongly activated either

by a positive charge or electron acceptors. Indeed, it has been shown that 1-alkyl-1,2,4-triazinium salts **73** add two molecules of indole at C-5 and C-6 to afford 5,6-diindolyl-substituted 1,4,5,6-tetrahydro-1,2,4-triazines **74** in good yields (**Scheme 35**) <1986KGS1535>.

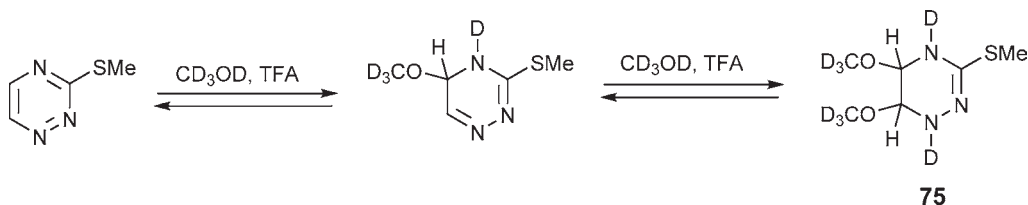


Scheme 35



Scheme 36

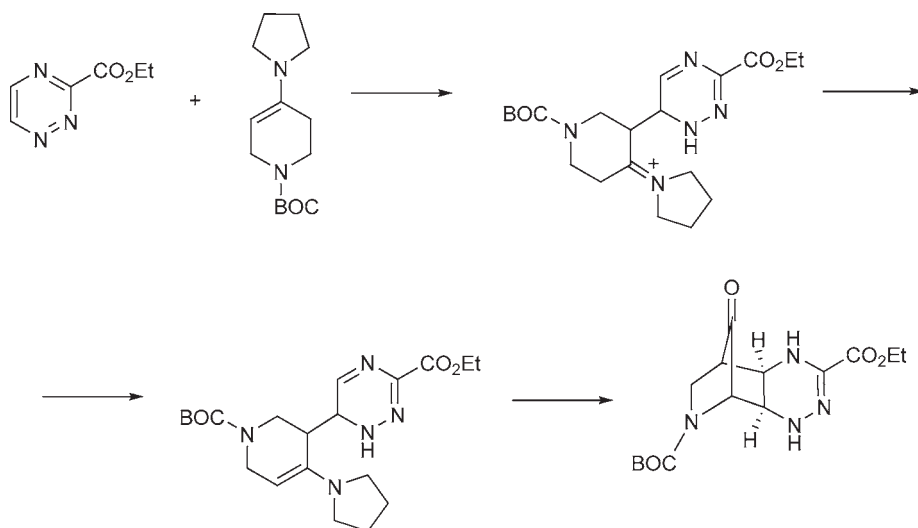
An attempt to extend this diaddition reaction to NH-triazinium salts failed. According to ^1H NMR spectra, an equilibrium mixture of mono- and diadducts resulted and, even with an excess of indole, diadducts **74** were present only as minor products. Similarly, in the reaction of 3-methylthio-1,2,4-triazine with CD_3OD and TFA, the 5,6-dimethoxy adduct **75** has been identified by ^1H NMR as a minor adduct, even in the case where a large excess of CF_3COOH is present in the reaction mixture (**Scheme 37**) <1989AHC(46)73>.



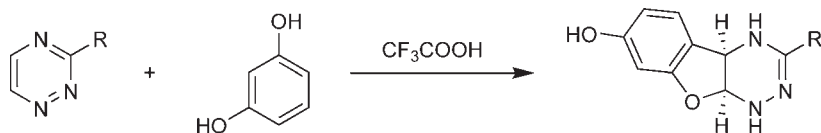
Scheme 37

9.02.5.7.3 Tandem $\text{A}_\text{N}-\text{A}_\text{N}$ reactions

The synthesis of fused derivatives by the double addition of bifunctional reagents on two neighboring carbons of the 1,2,4-triazine ring appears to be a very constructive concept <2004PAC1621>. Indeed, the tandem reactions of bifunctional nucleophiles at C-5 and C-6 of the 1,2,4-triazine ring proved to be an efficient route to condensed 1,2,4-triazines, as illustrated by **Schemes 38–40**. Thus, ethyl 1,2,4-triazin-3-carboxylate was shown to react with the pyrrolidine enamine of *N-tert*-butoxycarbonylpiperidone at room temperature (chloroform solution) to give azabicyclo[3.2.1]octane, as result of a stepwise $\text{A}_\text{N}-\text{A}_\text{N}$ tandem reaction (**Scheme 38**) <1998CC983>.



Scheme 38



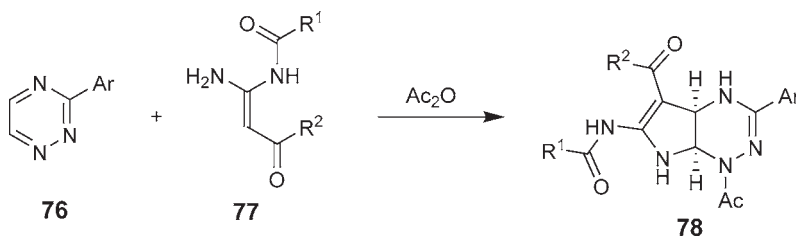
Scheme 39



Scheme 40

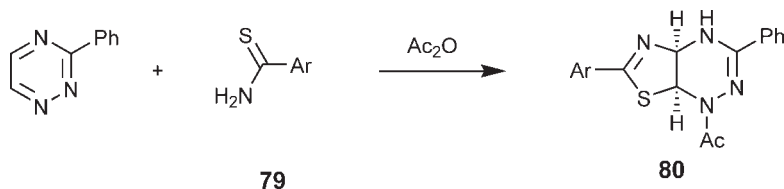
When activated by N-protonation (**Scheme 39**) <1988TL1431, 1989AHC(46)73, 2001JHC901>, N-alkylation (**Scheme 40**) <1989AHC(46)73, 1992H(33)931, 2001JHC901>, or N-acylation (**Scheme 41**) <2001JHC901, 2002MC28, 2003TL2421, 2993RCB1749>, 1,2,4-triazines are very prone to form cycloadducts with a variety of bifunctional nucleophiles.

In particular, it has been found that the reaction of 3-aryl-1,2,4-triazines **76**, activated by acetic anhydride, with β -aminovinyl ketones or β -aminocrotonate **77** in acetic anhydride proceeds at room temperature very smoothly and regioselectively, leading to 3a,4,7,7a-tetrahydro derivatives **78** of the 1*H*-pyrrolo[3,2-*e*]-1,2,4-triazine ring system (**Scheme 41**) <2003RCB1740>.



Scheme 41

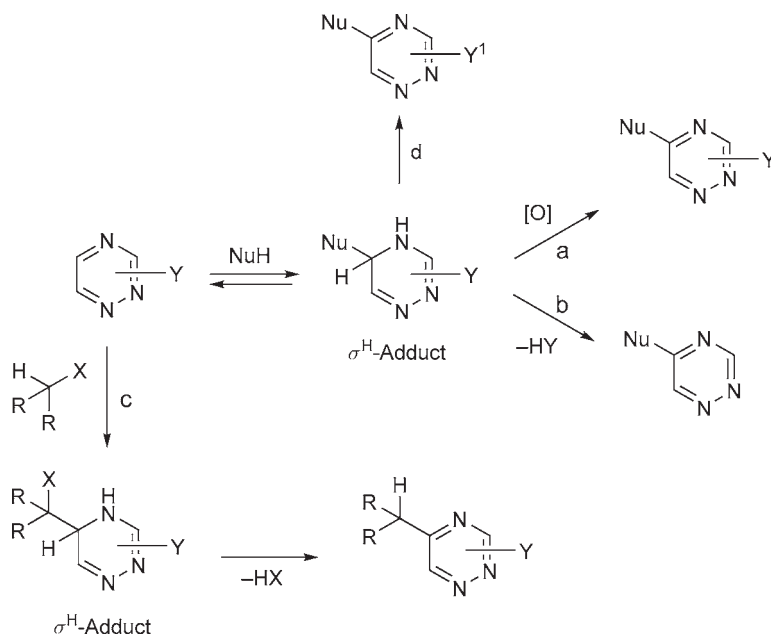
In a similar manner, a tandem N,S-addition reaction takes place at C-5 and C-6 of the 1,2,4-triazine ring. Thus, 3-phenyl-1,2,4-triazine reacts with thioamides **79** in the presence of acetic anhydride to give 1,4,4a,7a-tetrahydrothiazolo[4,5-*e*]-1,2,4-triazines **80** (Scheme 42) <2004RCB1279>.



Scheme 42

9.02.5.7.4 Nucleophilic substitution of hydrogen ($\text{S}_{\text{N}}^{\text{H}}$ reactions)

During the last two decades, the $\text{S}_{\text{N}}^{\text{H}}$ methodology has become one of the most advanced tools of organic synthesis. Indeed, $\text{S}_{\text{N}}^{\text{H}}$ reactions enable one to form a variety of C–C, C–N, C–O, C–P, C–S, and other bonds with an aromatic ring <B-1994MI1>. Nucleophilic displacement of hydrogen in the series of aza-aromatics, including 1,2,4-triazines, has been a subject of a number of reviews and monographs <1988AHC(43)301, B-1988MI95, 1988T1, 1989AHC(46)73, 1992H(33)931, B-1994MI1, 1996ZK663, 1998RJO297, 2002AHC(82)261, 2004PAC1621, B-2005MI19>. The $\text{S}_{\text{N}}^{\text{H}}$ reactions proceed according to the ‘addition–elimination’ scheme and involve the formation of σ^{H} -adducts followed by rearomatization by action of an oxidant (Scheme 43, route a) or through the so-called ‘auto’-aromatization process (Scheme 43, routes b and c) <B-1994MI1>.

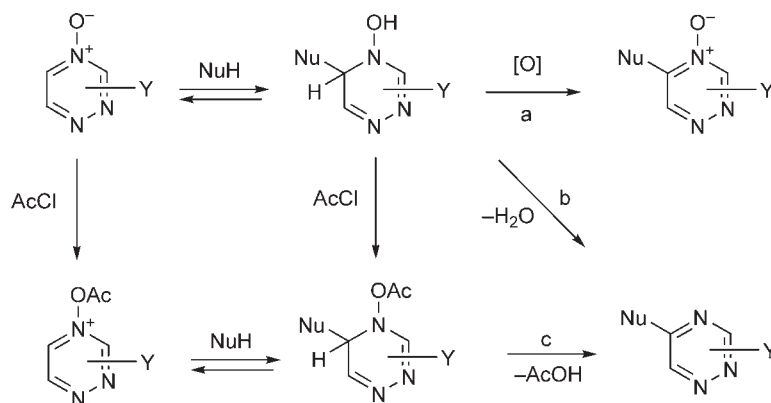


Scheme 43

1,2,4-Triazines bearing good leaving groups as side-chain substituents, for instance $\text{Y} = \text{CCl}_3$, can also undergo the ‘tele’-substitution reaction (Scheme 43, route d).

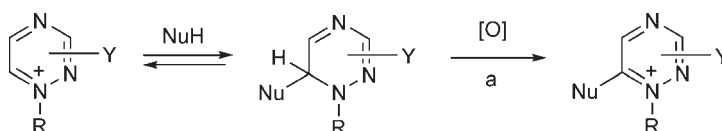
In the $\text{S}_{\text{N}}^{\text{H}}$ reactions of 1,2,4-triazine *N*-oxides, elimination of hydrogen from the sp^3 carbon C-5 is caused by departure of the hydroxy group from *N*–OH (Scheme 44, route b); however, the presence of an oxidant enables one to functionalize 1,2,4-triazines with the retention of the *N*-oxide moiety (Scheme 44, route a).

Autoaromatization can also be facilitated by an auxiliary group which is present in a nucleophile (Scheme 44, route c). This approach is commonly known as the ‘vicarious’ nucleophilic substitution of hydrogen (VNS), and it is illustrated by several examples of the displacement of hydrogen at C-5 of the 1,2,4-triazine ring by action of chloromethyl arylsulfones as C-nucleophiles <1992PJC3, 1996RCB491, 2004CRV2631>.



Scheme 44

An important feature of the reactivity of 1-alkyl-1,2,4-triazinium salts is that the C-6 carbon atom adjacent to the quaternary nitrogen appears to be more reactive toward nucleophiles than C-5, as shown in [Scheme 45](#).

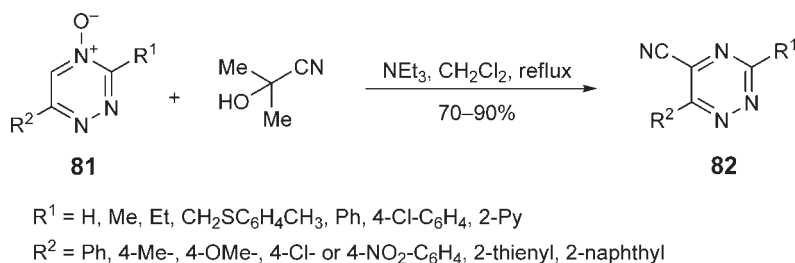


Scheme 45

9.02.5.7.4(i) Reactions with C-nucleophiles

9.02.5.7.4(i)(a) Cyanation

Direct cyanation of 1,2,4-triazin-4-oxides takes place on treatment of **81** with acetone cyanohydrin in the presence of triethylamine, thus affording the corresponding 5-cyano-1,2,4-triazines **82** in high yields [<1997MC66, 2002RJO744, 2002TL4923, 2003JOC2884, 2006TL869>](#). Addition of the cyanide ion at C-5 of the 1,2,4-triazine ring is accompanied by aromatization of the intermediate σ^H -adducts through elimination of water to give the S_N^H products **82** in 70–90% yields ([Scheme 46](#)).

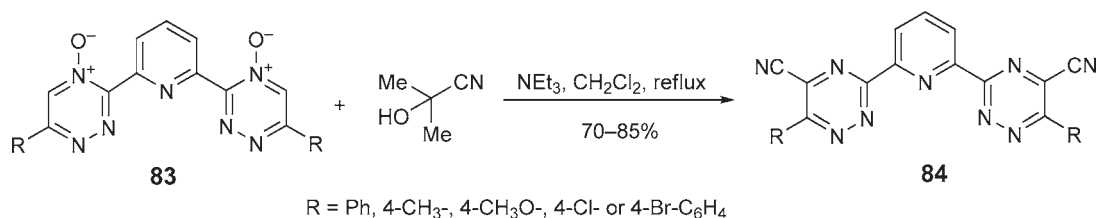


Scheme 46

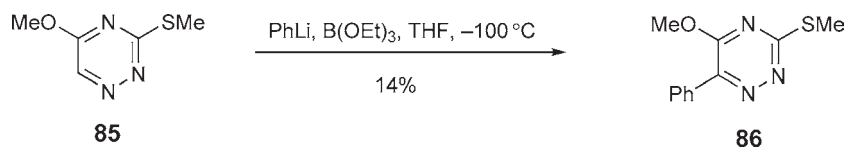
In a similar way, cyanation of two triazine *N*-oxide fragments in 2,6-disubstituted pyridine **83** affords the corresponding dicyano derivatives **84** in 70–85% yields ([Scheme 47](#)) [<2002TL4923, 2003JOC2884, 2003S2400>](#).

9.02.5.7.4(i)(b) Reactions with organolithium compounds

Organolithium compounds are widely used to modify 1,2,4-triazines by means of the S_N^H methodology [<2002J\(P1\)2549, 2004S2893>](#), as exemplified by the reaction of 3-methylthio-5-methoxy-1,2,4-triazine **85** with phenyllithium leading to 3-methylthio-5-methoxy-6-phenyl-1,2,4-triazine **86** ([Scheme 48](#)) [<2002J\(P1\)2549>](#).

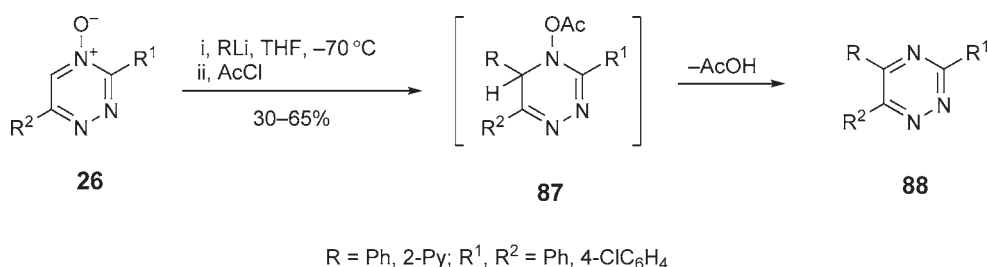


Scheme 47



Scheme 48

Organolithium derivatives of arenes and heteroarenes have been shown to react smoothly with 1,2,4-triazine-4-oxides **26** in the presence of acetyl chloride to give 5-aryl- or 5-hetaryl substituted 1,2,4-triazines **88**, as the $\text{S}_{\text{N}}^{\text{H}}$ products. In this case, aromatization of the intermediate σ^{H} -adducts **87** takes place due to O-acetylation of the 1,2,4-triazine *N*-oxides and elimination of OAc as the auxiliary group (Scheme 49).



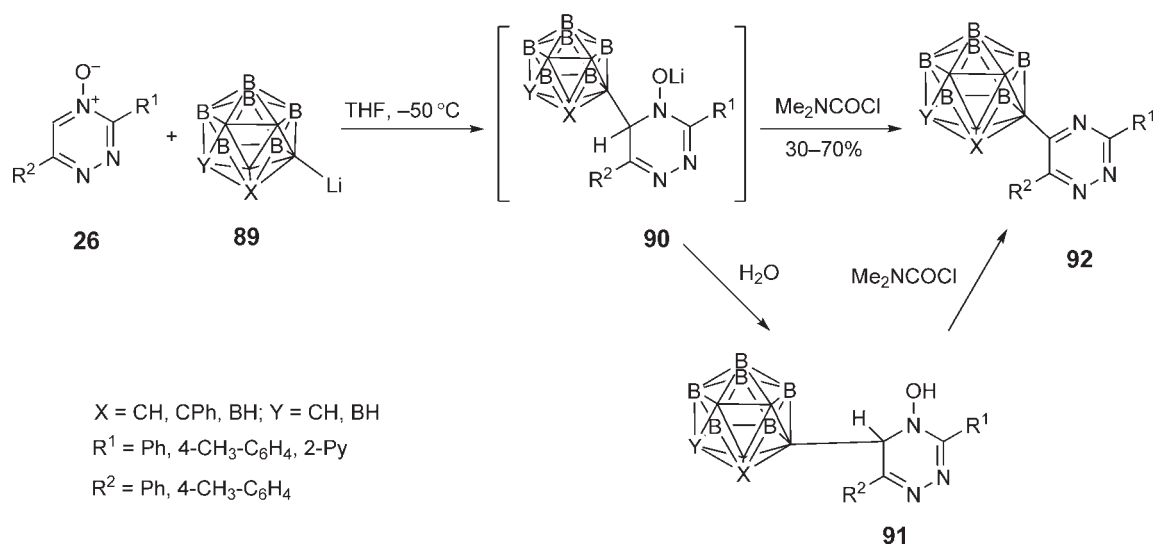
Scheme 49

Direct incorporation of organoboron compounds into the 1,2,4-triazine ring through C–C coupling at C-5 appears to be a new approach to modify the structure of 1,2,4-triazines <2003MC165; 2004RCB1223, 2006TL869, 2006OM2972>. In particular, 1,2,4-triazine-4-oxides **26** have been shown to react with 1-lithiated *ortho*-carboranes **89** ($\text{X} = \text{CH}$, CPh ; $\text{Y} = \text{BH}$) in THF at low temperatures to give σ^{H} -adducts **90**, which undergo aromatization into compounds **92** on treatment of the reaction mixture with acetic anhydride or *N,N*-dimethylaminocarbonyl chloride. Also, 3,6-diphenyl-1,2,4-triazine-4-oxide and C-lithiated *meta*-carborane **89** ($\text{X} = \text{BH}$, $\text{Y} = \text{CH}$) can be transformed easily under these conditions into 1-(3,6-diphenyl-1,2,4-triazinyl-3)-1,7-dicarba-*closo*-dodecaborane **92** <2003MC165, 2004RCB1175, 2004RCB1223>. The intermediate adducts **90** can be characterized by NMR and isolated in some cases. For instance, compound **91** has been isolated; however, it easily loses water to give the corresponding 1,2,4-triazine **92** (Scheme 50).

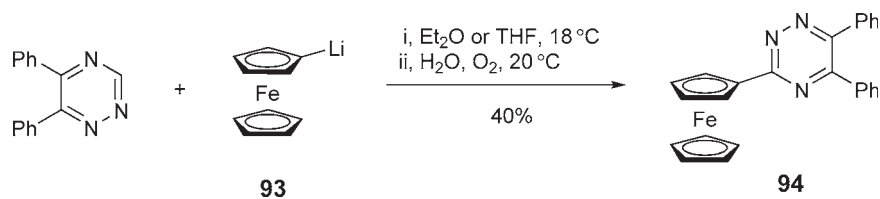
The last decade has brought a number of interesting new examples of the $\text{S}_{\text{N}}^{\text{H}}$ reaction in the 1,2,4-triazine series. For instance, 5,6-diphenyl-1,2,4-triazine was found to react with ferrocenyl lithium **93** under oxidative conditions to give the corresponding 3-ferrocenyl-1,2,4-triazine **94** (Scheme 51) <2007EJO857>.

9.02.5.7.4(i)(c) Reactions with organomagnesium compounds

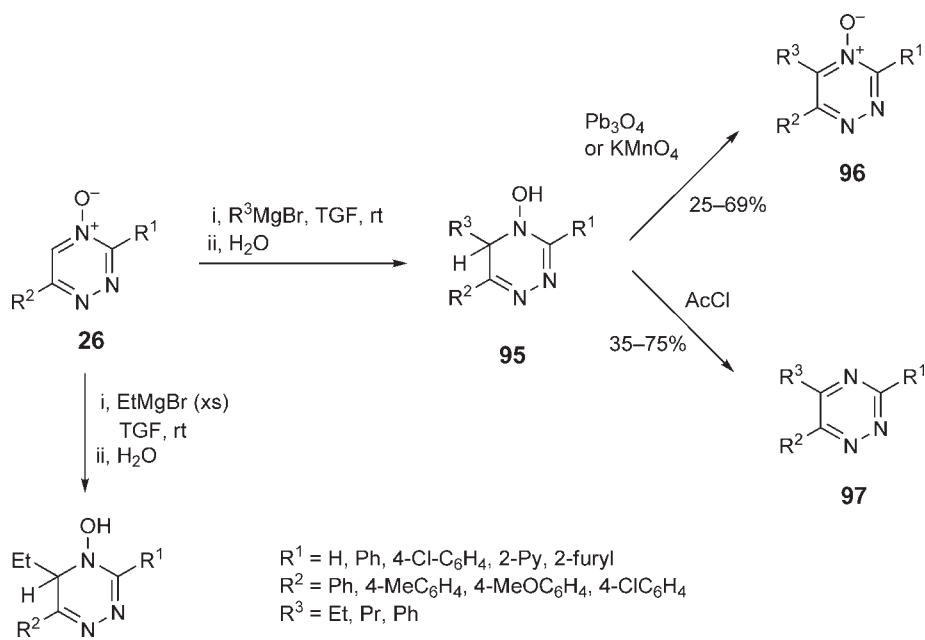
Grignard reagents are a well-known class of C-nucleophiles, which proved to be appropriate compounds for direct incorporation of alkyl, aryl, or hetaryl fragments into the 1,2,4-triazine ring. The reaction of 1,2,4-triazine 4-oxides **26** with organomagnesium compounds proceeds smoothly at C-5 to give the adducts **95**, which undergo aromatization into *N*-oxides **96** by means of oxidation with potassium permanganate (Scheme 52), or an autoaromatization takes place in the presence of an acyl chloride, thus resulting in the formation of 1,2,4-triazines **97** (Scheme 52) <2003PJC1157>.



Scheme 50



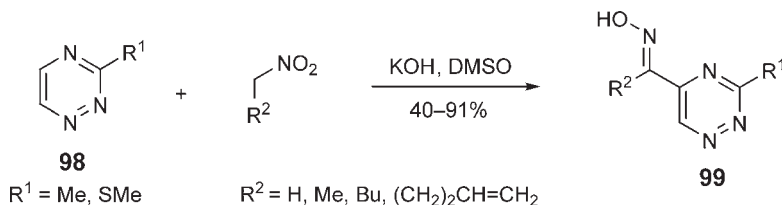
Scheme 51



Scheme 52

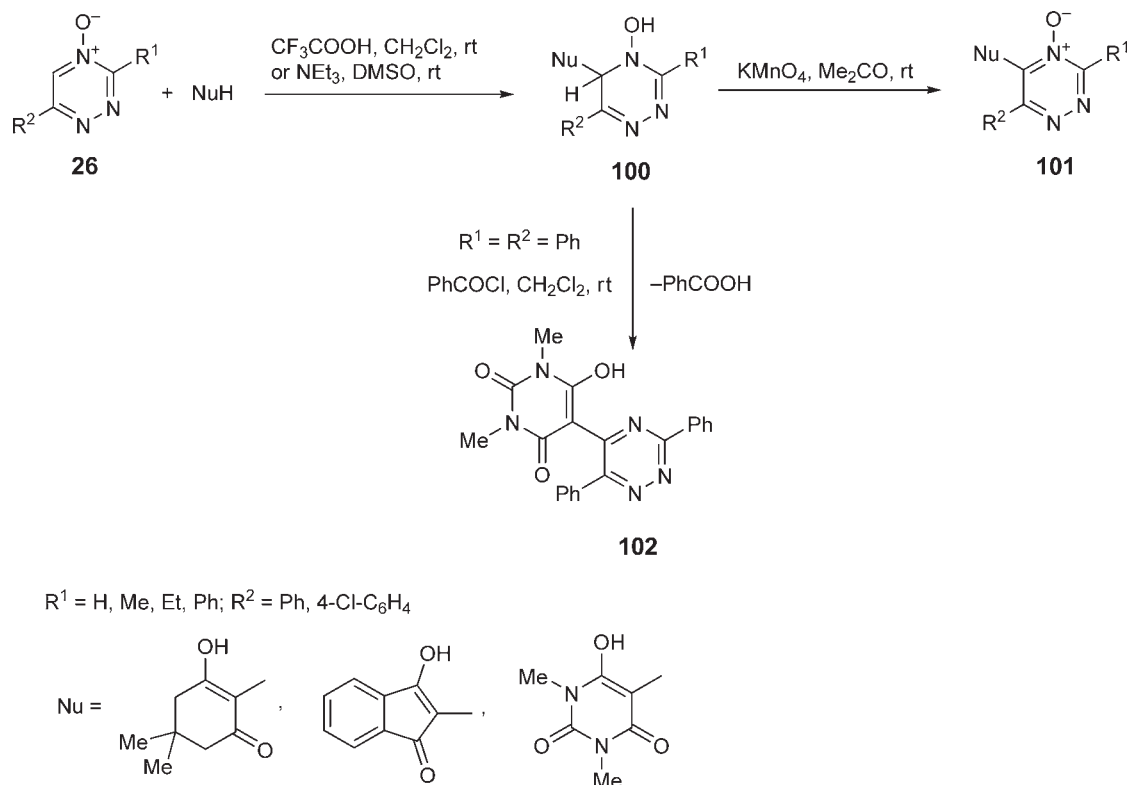
9.02.5.7.4(i)(d) Reactions with CH-active compounds

3-Methyl- and 3-methylthio-1,2,4-triazines **98** react with nitroalkanes in a solution of KOH in DMSO to yield oximes **99** (Scheme 53) <1996JHC1567, 2001CHE231, 2004CRV2631>.



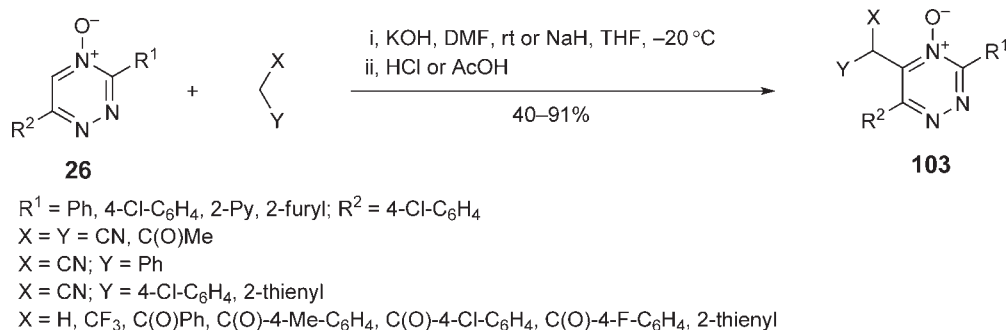
Scheme 53

1,2,4-Triazin-4-oxides **26** were found to react with cyclic β -diketones under acidic or basic conditions to give rather stable σ^{H} -adducts **100** and finally $\text{S}_{\text{N}}^{\text{H}}$ products **101** or **102** <2001KGS1239, 2004KGS911, 2001CHE1136, 2004CHE911>. Oxidative aromatization of the adducts **100** or their autoaromatization with benzoyl chloride, through elimination of benzoic acid, results in the formation of either 1,2,4-triazin-4-oxides **101** or the 1,2,4-triazine **102** (Scheme 54).



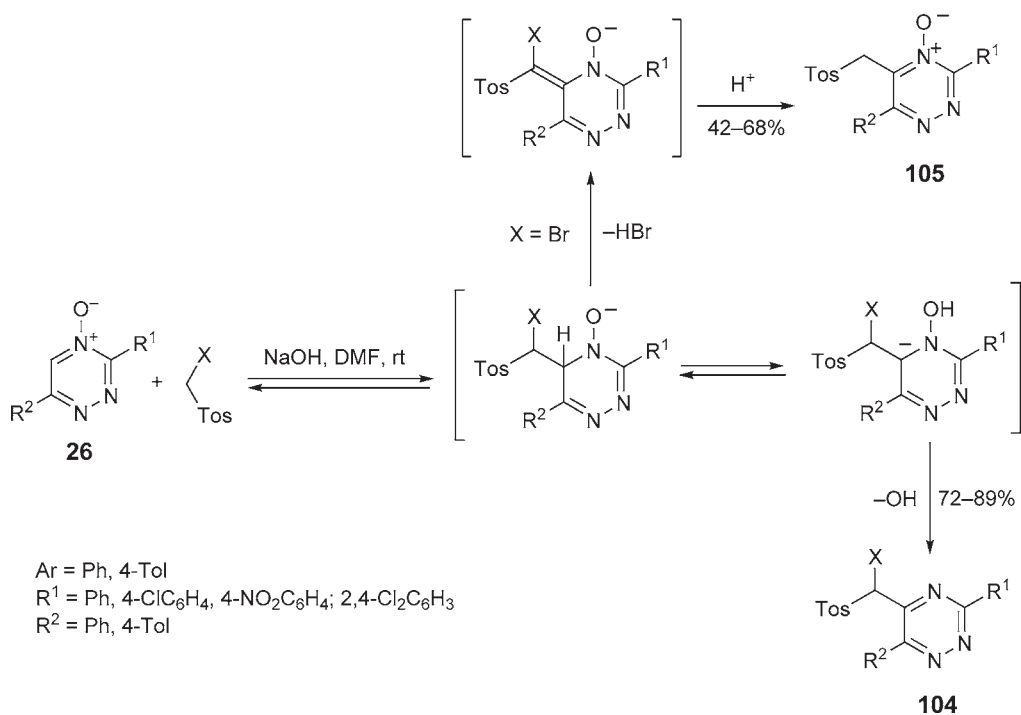
Scheme 54

Reactions of 1,2,4-triazin-4-oxides **26** with carbanions, generated from CH-active compounds, usually give rise to fully aromatic 1,2,4-triazines **103**, since aromatization of intermediate dihydro-1,2,4-triazines takes place simultaneously. Indeed, 1,2,4-triazin-4-oxides react with a variety of CH-active compounds, such as acetophenone, malonodinitrile, acetoacetone, and arylacetonitriles, thus giving the corresponding 5-substituted-1,2,4-triazines (Scheme 55) <1996MC116, 2000MC227, 2002EJO1412, 2003RCB1588>.



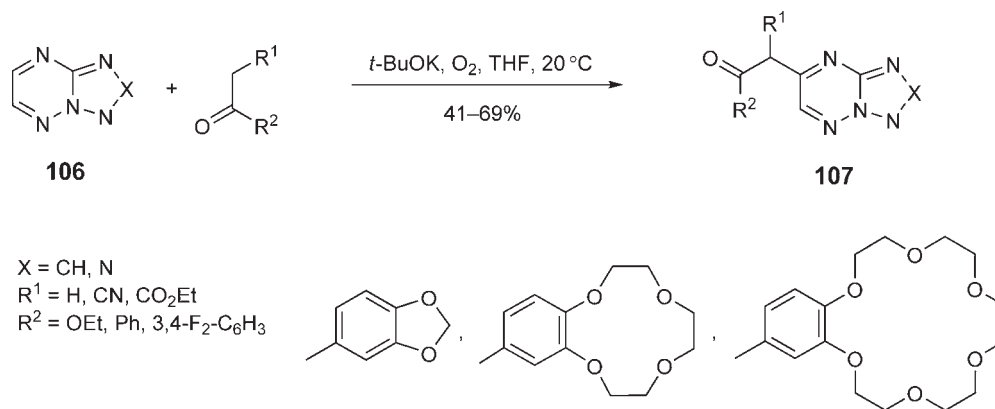
Scheme 55

Carbanions of α -halomethylarylsulfones, well known as vicarious agents for nucleophilic substitution of hydrogen (VNS), have also been used in 1,2,4-triazine chemistry [<1996RCB491, 2004CRV2631, 2002EJO1412>](#). These nucleophiles were found to react with 1,2,4-triazine 4-oxides **26** predominantly according to pathway c ([Scheme 44](#)) to give the corresponding 5-arylsulfonylchloromethyl-1,2,4-triazines **104** ([Scheme 56](#)) [<1996H\(43\)2095, 2002EJO1412>](#). The expected VNS products, 5-arylsulfonylmethyl-1,2,4-triazine 4-oxides **105**, have been registered by NMR only as minor products and isolated in poor yields (4–6%). It is evident that in this case aromatization of σ^{H} -adducts by means of dehydration proceeds faster than β -elimination of HCl. However, if arylbromomethylsulfone is used instead of the chloro compound, the pathway e, leading to 5-tosylmethyl-1,2,4-triazine 4-oxides **105**, becomes the major one ([Scheme 56](#)).



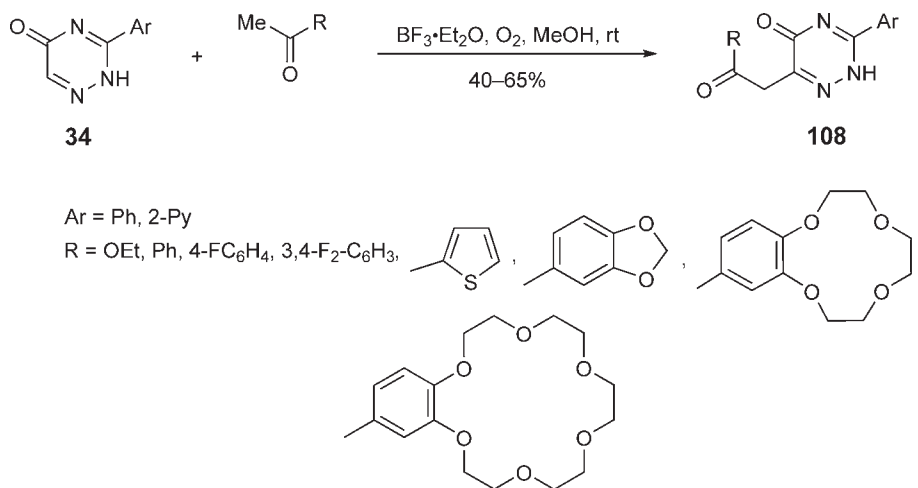
Scheme 56

Azolo[4,3-*b*][1,2,4]-triazines **106** can be regarded as compounds which are isosteric to 1,2,4-triazin-3-one. Indeed, they react with carbanions of CH-active compounds, such as malonic ester and ethyl cyanoacetate, and acetophenone in the presence of air oxygen, according to the oxidative $\text{S}_{\text{N}}^{\text{H}}$ procedure to give the nucleophilic displacement products **107** ([Scheme 57](#)) [<2001RCB2183>](#).



Scheme 57

Upon activation with $\text{BF}_3\cdot\text{Et}_2\text{O}$, 3-substituted-1,2,4-triazin-5-ones **34** are capable of reacting with a variety of acetophenones to give the $\text{S}_{\text{N}}^{\text{H}}$ products at C-6 of the triazine ring, viz. **108** (Scheme 58) <2002HCO75>.



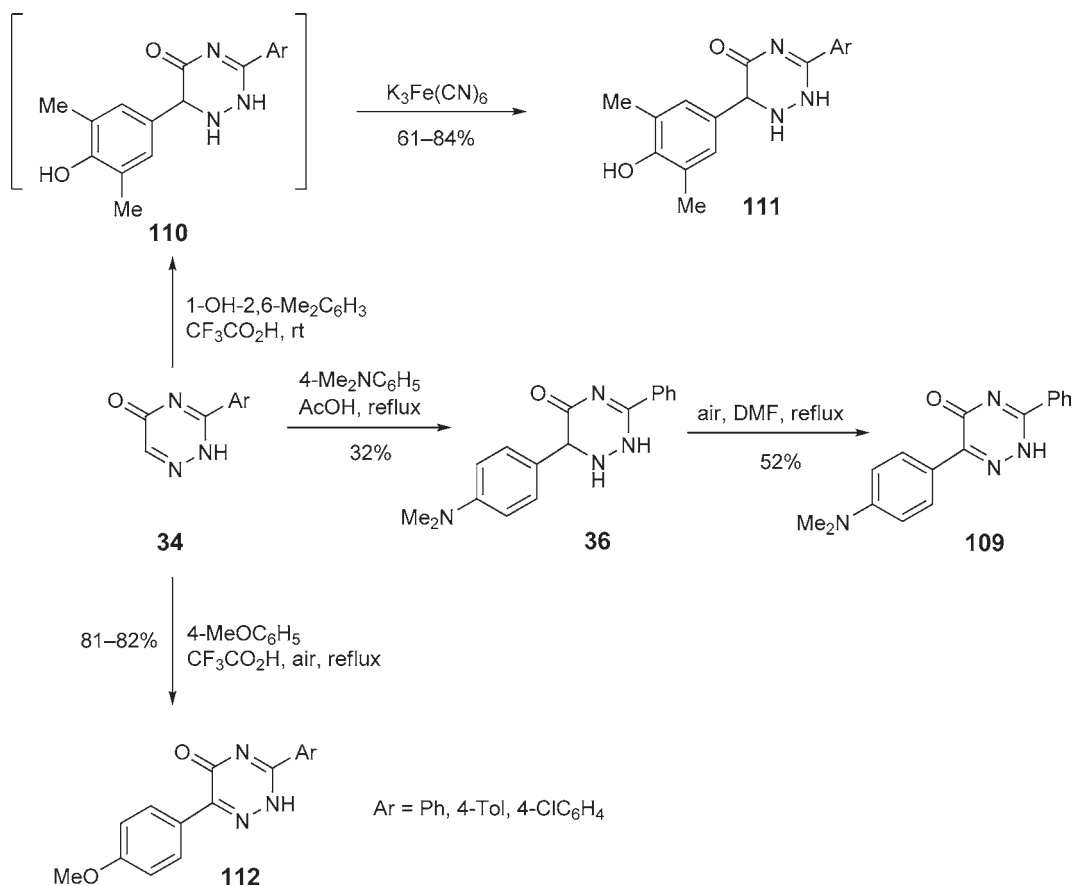
Scheme 58

9.02.5.7.4(i)(e) Reactions with aromatic C-nucleophiles

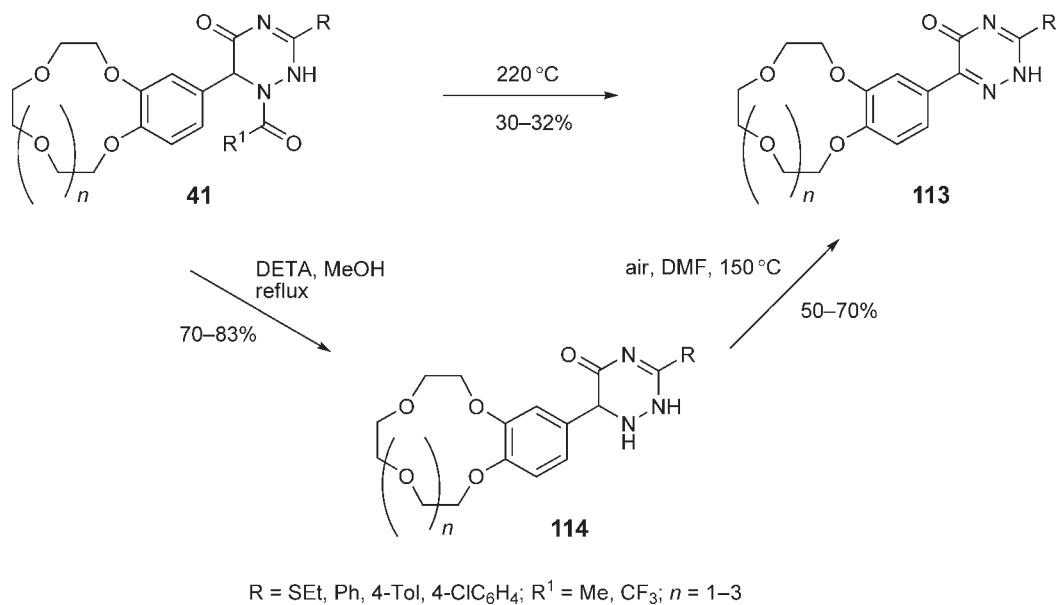
3-Phenyl-1,2,4-triazin-5-one reacts with *N,N*-dimethylaniline on heating in acetic acid to give rather stable 3-phenyl-6-(4-*N,N*-dimethylaminophenyl)-1,6-dihydro-1,2,4-triazin-5(2*H*)-one **36** <97JHC537>. Oxidative aromatization takes place on bubbling air through a solution of **36** in DMF, thus affording 3-phenyl-6-(4-*N,N*-dimethylaminophenyl)-1,6-dihydro-1,2,4-triazin-5-one **109** (Scheme 59).

The σ^{H} -adducts **110** derived from the reaction of 3-aryl-1,2,4-triazin-5(2*H*)-ones **34** with 2,6-dimethylphenol in TFA can be characterized by ^1H NMR; however, if potassium hexacyanoferrate is added to the reaction mixture, the adducts **110** are transformed into 3-aryl-6-hydroxyphenyl-1,2,4-triazin-5-ones **111** (Scheme 59) <97JHC537>. In addition, the reaction of **34** with anisole on reflux in TFA affords 3-aryl-6-(4-methoxyphenyl)-1,2,4-triazin-5-ones **112**, through oxidation of the intermediate σ^{H} -adducts by air oxygen (Scheme 59) <1997JHC537>.

In a similar fashion, compounds **34** react with benzo-annulated crown ethers, which contain the phenol moiety, to form adducts **41**, which can be transformed into $\text{S}_{\text{N}}^{\text{H}}$ products through elimination of aldehyde <B-1994M11> (see also Section 9.02.5.7.1(i)). Indeed, thermolysis of the σ^{H} -adducts **41** affords 1,2,4-triazin-5-ones **113** (Scheme 60) <2001H(55)2349>. Yields of **113** are poor, but can be improved when the reaction is carried out in an argon atmosphere <2001H(55)2349>.



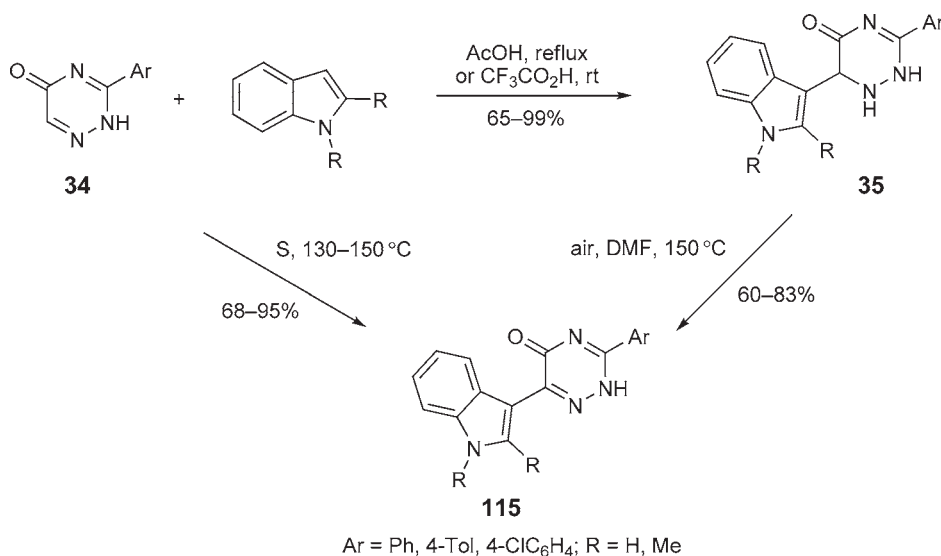
Scheme 59



Scheme 60

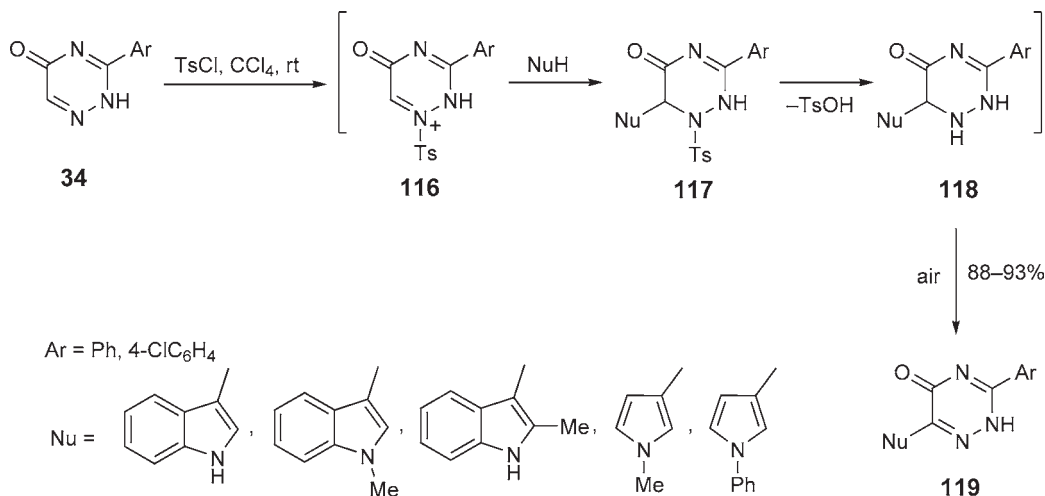
Use of a two-step procedure, which involve deacylation of compounds **41** by action of diethylenetriamine and oxidation of tetrahydro-1,2,4-triazines **114**, enables one to perform aromatization of **41** under milder conditions and to enhance yields of the final products (Scheme 60).

As mentioned previously, the reaction of 3-aryl-1,2,4-triazin-5-ones **34** with indole or its methyl derivatives in acetic acid or TFA provides 3-aryl-1,6-dihydro-1,2,4-triazin-5(2*H*)-ones **35** <1997JHC1013> (see Section 9.02.5.7.1(i)). Aromatization of compounds **35** by air oxygen in DMF affords 3-aryl-6-(indolyl-3)-1,2,4-triazin-5-ones **115**. Also, the S_N^H products **115** can be obtained through oxidative substitution of hydrogen in **34** by indoles in a melt with sulfur (Scheme 61) <2000RJO602>.



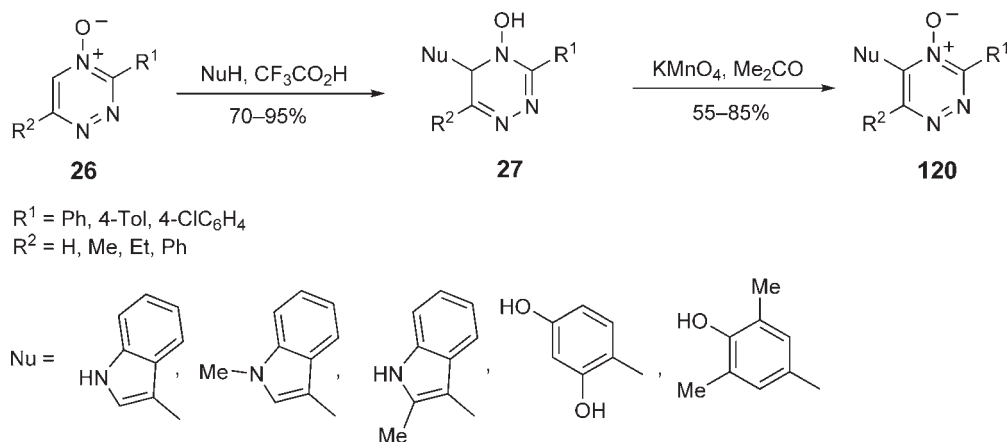
Scheme 61

Heating compounds **34** with indoles in acetic anhydride gives 1-acetyl-3-aryl-6-(indolyl-3)-1,2,4-triazin-5(2*H*)-ones (see Section 9.02.5.7.1(i)) <1997JHC1013>, while use of tosyl chloride provides high yields of 6-substituted-3-aryl-1,2,4-triazin-5(2*H*)-ones **119** (Scheme 62) <2002RCB1042>. An ¹H NMR study has revealed that this reaction is realized as an oxidative S_N^H process (Scheme 43, route a) involving N-acylation of triazinone **34**, nucleophilic addition at C-6 of the salts **116**, the formation of σ^H -adducts **117**, deacylation of **117**, and oxidation of the intermediate **118** by air oxygen (Scheme 62) <2002RCB1042>.



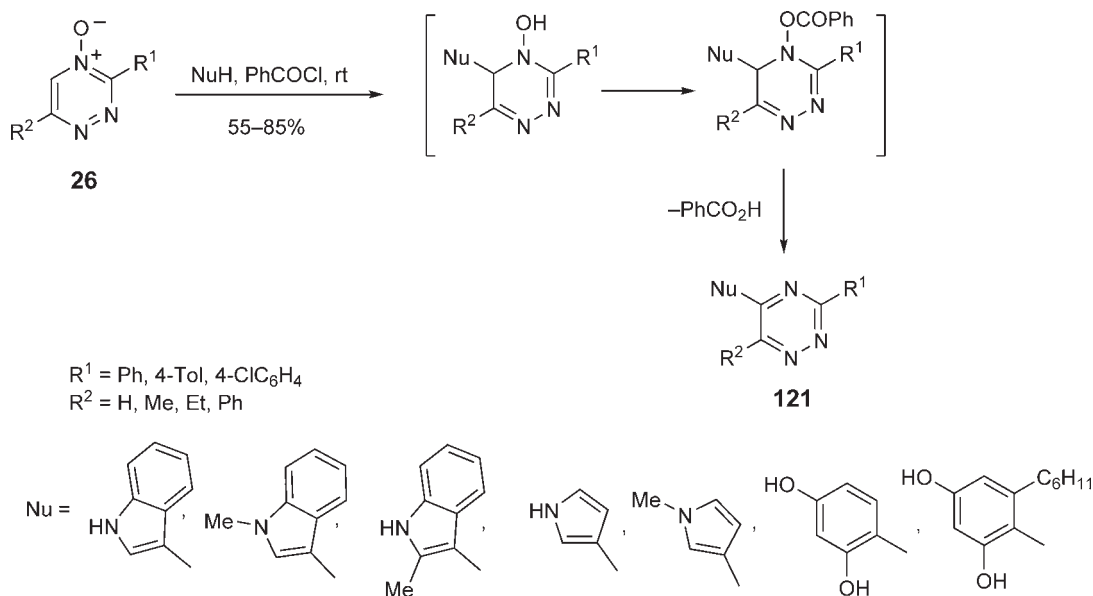
Scheme 62

The formation of σ^H -adducts in the S_N^H reactions of 1,2,4-triazine *N*-oxides with nucleophiles has been shown first by isolation of dihydro compounds **27** and **30** derived from the reaction of 1,2,4-triazine 4-oxides **26** with indoles and phenols (see **Schemes 17** and **18**, Section 9.02.5.7.1(i)) <1997MC116, 1998RJO429, 2002AHC(82)261>. Dihydro-1,2,4-triazines **27** are stable enough to avoid thermal dehydration on reflux in butanol, DMF, or TFA according to the pathway c (**Scheme 44**). On the other hand, oxidative aromatization by pathway a (**Scheme 44**) takes place easily to give 5-substituted-1,2,4-triazine *N*-oxides **120** (**Scheme 63**) <1997MC116, 1998RJO400, 2002AHC(82)261>.



Scheme 63

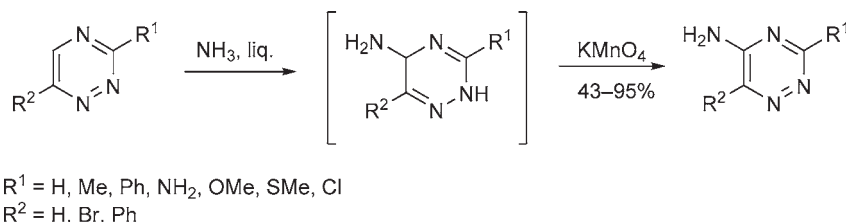
1,2,4-Triazine 4-oxides **26** react with aromatic (phenols, anilines) and heteroaromatic (indoles, pyrroles) C-nucleophiles in the presence of benzoyl chloride to form the corresponding S_N^H products **121** by means of autoaromatization with elimination of benzoic acid (**Scheme 64**) <2000RJO1050, 2002AHC(82)261, 2005RCB2187, 2006TL869>.



Scheme 64

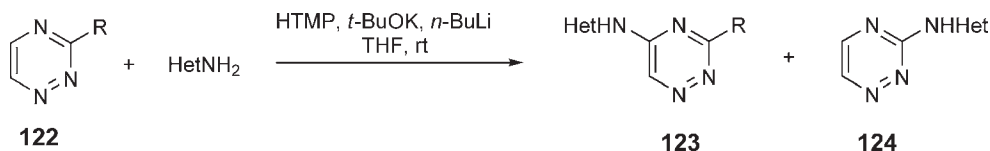
9.02.5.7.4(ii) Reactions with N-nucleophiles

A new version of the Chichibabin amination of azaaromatics in liquid ammonia in the presence of potassium permanganate, suggested by H. C. van der Plas, has been applied successfully in the series of 1,2,4-triazines (**Scheme 65**) <1985S884, 2001H(55)127, 2004SOS(17)357>. The low-temperature amination reaction always takes place at the position 5, even in those cases where the 1,2,4-triazine ring bears a good leaving group at position 3.



Scheme 65

The reaction of 1,2,4-triazines **122** with heterocyclic amines under basic conditions affords both S_N^H , **123**, and S_N^{ipso} , **124**, products (Scheme 66; Table 10) <2004JOC7809>.

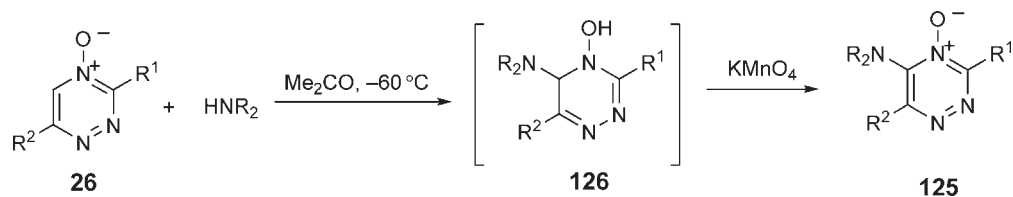


Scheme 66

Table 10 Yields of amino-1,2,4-triazines derived from the S_N^H and S_N^{ipso} reactions

R	HetNH_2	S_N^H product	Yield (%)	S_N^{ipso} product	Yield (%)
SMe			71		
SMe			65		21
SMe			75		5
$S\text{-}t\text{-Bu}$			43		39
OMe			8		30
SMe			48		15
SMe			64		

Amination of 1,2,4-triazine 4-oxides **26** by the action of primary and secondary alkylamines, as well as cycloalkylamines, takes place smoothly in acetone solution at -60 to -40°C through the intermediacy of the σ^H -adducts **126**, which are easily oxidized by potassium permanganate into the corresponding 5-amino-1,2,4-triazine 4-oxides **125** (Scheme 67; Table 11) <B-2003MI2>.

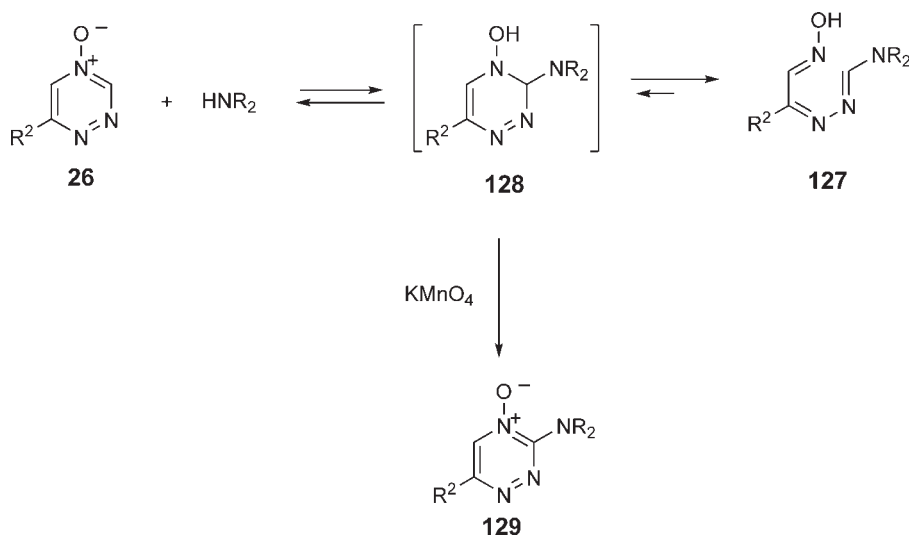


Scheme 67

Table 11 Yields of 5-amino-1,2,4-triazine 4-oxides derived from the Chichibabin amination reaction in liquid ammonia at -60°C <B-2003MI2>

R^1	R^2	NR_2	Yield (%)
H	Ph	NH_2	42
H	Ph	NHMe	65
H	Ph	NMe_2	56
H	Ph	NEt_2	41
H	Ph	Pyrrolidino	51
H	Ph	Piperidino	63
H	Ph	Morpholino	40
Ph	Ph	Morpholino	65
Ph	Ph	Piperidino	70
3-Br- C_6H_4	Ph	NHMe	50
4- NO_2 - C_6H_4	Ph	NMe_2	48
4- NO_2 - C_6H_4	Ph	NCHMe_2	40
H	4- FC_6H_4	NH_2	40
H	4- ClC_6H_4	NH_2	30
H	4-Tol	NH_2	72

In the amination of 6-R-substituted 1,2,4-triazine 4-oxides bearing two unsubstituted carbons (C-3 and C-5), the site selectivity depends on the reaction conditions, thus enabling one to obtain selectively both 5-amino **125** or 3-amino compounds **129** through the intermediacy of the corresponding amino adducts **126** or **128** (Schemes 67 and 68; Tables 11 and 12).

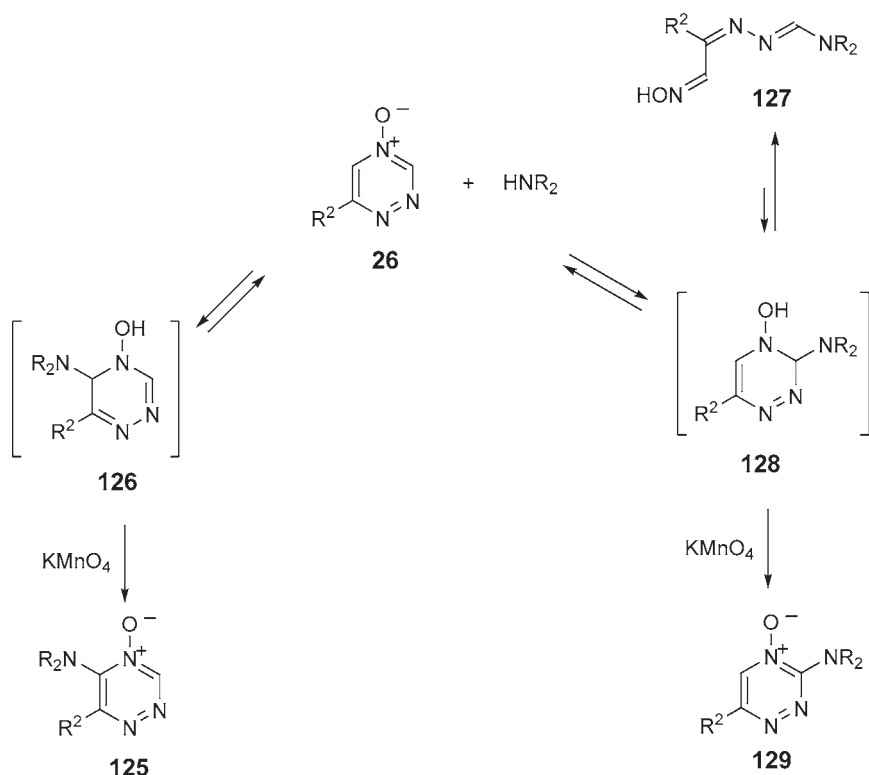


Scheme 68

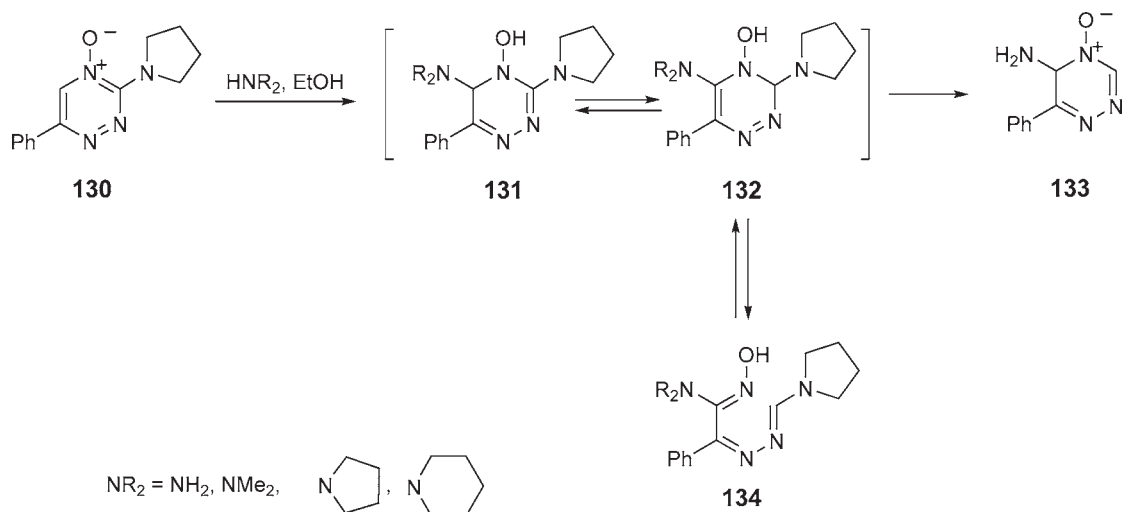
Table 12 Yields of 3-amino-1,2,4-triazine 4-oxides derived from the Chichibabin amination reaction at room temperature <B-2003MI2>

R^2	NR_2	Yield (%)
Ph	NMe ₂	36
Ph	NEt ₂	43
Ph	Pyrrolidino	34
Ph	Piperidino	35
Ph	Morpholino	30
4-FC ₆ H ₄	NMe ₂	47
4-FC ₆ H ₄	Pyrrolidino	43
4-FC ₆ H ₄	Piperidino	44
4-FC ₆ H ₄	Morpholino	40
4-ClC ₆ H ₄	NMe ₂	60
4-ClC ₆ H ₄	Pyrrolidino	61
4-BrC ₆ H ₄	Pyrrolidino	40
4-BrC ₆ H ₄	Piperidino	38
4-Tol	Morpholino	60
2-Thienyl	NMe ₂	41
4-Py	NMe ₂	28
4-Py	Pyrrolidino	35

¹H NMR studies have shown that the C-5 adducts **126**, which are formed at -50°C , undergo a ring-opening reaction at temperatures above 0°C to give open-chain 1-hydroxy-6-dimethylamino-3-phenyl-1,4,5-triazahexatriene **127** <2001H(55)127>, while oxidation of **126** affords 5-amino-1,2,4-triazine 4-oxides **125** <1998RJO388>. An increase in temperature shifts the equilibrium to the triazahexatrienes **127**; however, the presence of an oxidant causes aromatization of the intermediate amino adducts **128** into 3-amino-1,2,4-triazine 4-oxides **129** (Scheme 69).

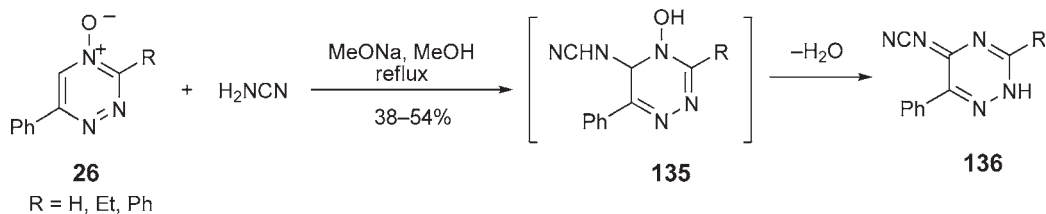
**Scheme 69**

The telesubstitution process has been found to occur when 3-pyrrolidino-6-phenyl-1,2,4-triazine 4-oxide **130** reacts with ammonia on heating in an alcohol solution to give 5-amino-6-phenyl-1,2,4-triazine 4-oxide **133** in 70% yield. The reaction mechanism suggests addition of ammonia at C-5 of the 1,2,4-triazine ring and a 1,5-sigmatropic hydrogen shift which transforms the σ^H -adduct **131** into **132**, followed by elimination of pyrrolidine (**Scheme 70**) <1999TL6099, 2004SOS(17)357>. The scheme is substantiated by the synthesis of ^{15}N -labeled 5-amino-6-phenyl-1,2,4-triazine 4-oxide from **130** and ^{15}N -labeled ammonia, as well as by the reaction of **130** with amines at room temperature leading to 1-hydroxy-1,4,5-triazahexatrienes **134**. Heating of **134** (R = H) in ethanol affords 5-amino-6-phenyl-1,2,4-triazine 4-oxide **133**, which is also in agreement with **Scheme 70**.



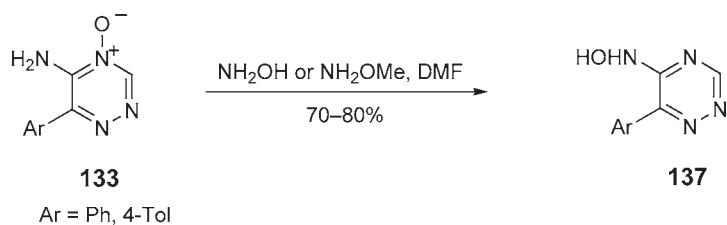
Scheme 70

The reaction of 1,2,4-triazine 4-oxides **26** with cyanamide under basic conditions results in 4,5-dihydro-5-cyanamino-1,2,4-triazines **135** followed by autoaromatization with the loss of water to yield **136** (**Scheme 71**; see also pathway b in **Scheme 44**) <2000RCB1122>.



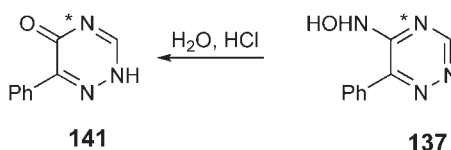
Scheme 71

Amination of 5-amino-6-aryl-1,2,4-triazine 4-oxides **133** with hydroxylamine hydrochloride or O-methylhydroxylamine in DMF results in 5-hydroxylamino-6-aryl-1,2,4-triazines **137** in 70–80% yields, thus indicating that the Dimroth rearrangement is involved (**Scheme 72**) <2000TL7379>.



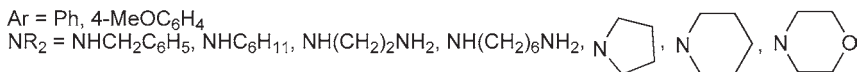
Scheme 72

experiments with the labeled 5-¹⁵N]-amino-6-phenyl-1,2,4-triazine **133** (Scheme 73) <2000TL7379>.



Scheme 73

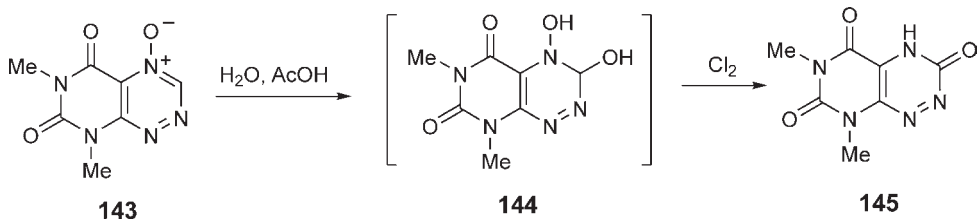
outer oxidant has also been described (**Scheme 74**) <1997RJO554, 2000TL7379>.



Scheme 74

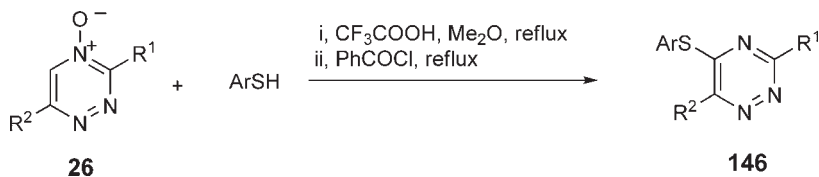
9.02.5.7.4(iii) Reactions with O- and S-nucleophiles

fervenulin-3-one 4-oxide **145**. The reaction takes place on bubbling of chlorine through an aqueous solution of fervenulin-4-oxide **143** and involves addition of water followed by oxidation of the σ^H -adduct **144** (Scheme 75) <1997KFZ47>.



Scheme 75

Treatment of 1,2,4-triazine 4-oxides **26**, activated by TFA, with thiophenol or its derivatives affords 5-arylthio-1,2,4-triazines **146** (Scheme 76; Table 13) <2001RCB1068>.

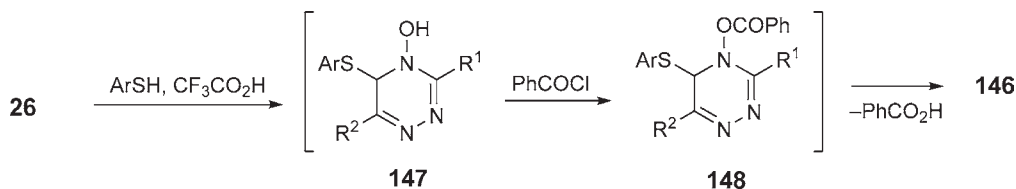


Scheme 76

Table 13 Yields of 5-arylthio-1,2,4-triazines **146**

R^1	R^2	Ar	Yield (%)
Ph	Ph	Ph	81
Ph	4-NO ₂ C ₆ H ₄	Ph	85
4-Tol	Ph	Ph	71
Ph	Ph	4-Cl-C ₆ H ₄	68
Ph	Ph	4-OH-C ₆ H ₄	65
Ph	Ph	3-MeO-C ₆ H ₄	87

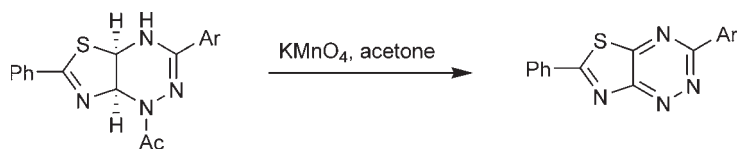
When reacting with 1,2,4-triazine 4-oxides **26**, thiophenols act as S-nucleophiles, and that is in contrast with a similar reaction of **26** with phenols <1997MC116>, in which the latter behave exclusively as C-nucleophiles. The reaction mechanism involves the S-addition of thiophenols leading to adducts **147**, followed by acylation of the *N*-oxide moiety, thus facilitating autoaromatization of **148** according to pathway c (see Scheme 44) <2000RCB1122>. Elimination of benzoic acid is the final step on the pathway to products of nucleophilic substitution of hydrogen in the triazine ring **146** (Scheme 77) <2001RCB1068>.



Scheme 77

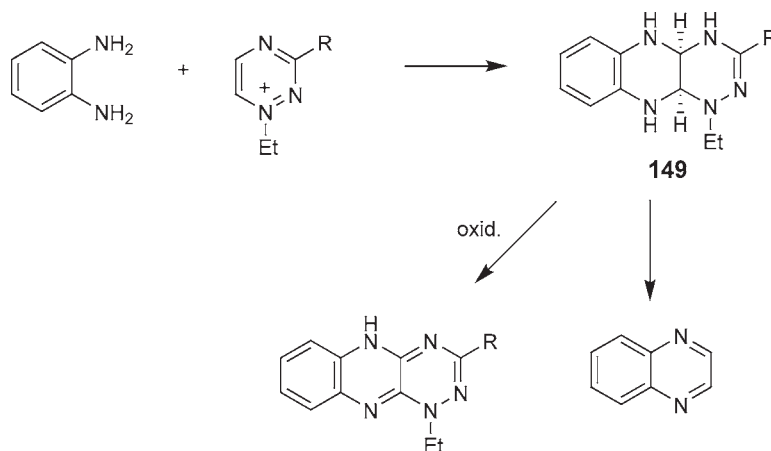
9.02.5.7.5 Tandem $\text{S}_\text{N}^\text{H}$ - $\text{S}_\text{N}^\text{H}$ reactions

Some condensed tetrahydro-1,2,4-triazines, derived from the A_N - A_N tandem reactions, can be oxidized into the corresponding aromatic systems, and these oxidation products are regarded as products of the tandem $\text{S}_\text{N}^\text{H}$ - $\text{S}_\text{N}^\text{H}$ reactions <B-1994MI1, 2004PAC1621>. For instance, aromatization of 3a,4,7,7a-tetrahydrothiazolo[4,5-*e*]-1,2,4-triazines with potassium permanganate in acetone proceeds smoothly at room temperature, and the oxidation process is accompanied by elimination of the *N*-acetyl group (Scheme 78).



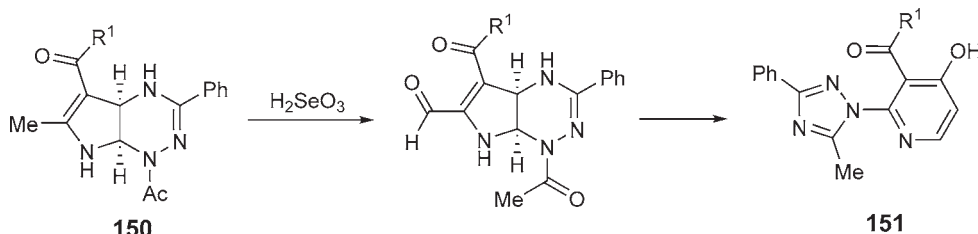
Scheme 78

In addition, there are other examples where oxidation of cycloadducts resulting from the A_N-A_N tandem reactions is the only constructive way to avoid degradation of their cyclic structure. For instance, the adducts **149** of 1,2,4-triazinium salts with 1,2-diamines are unstable and can be registered by NMR only at low temperatures (from -40 to -20 °C). However, these adducts **149** are easily transformed into 1,2,4-triazino[5,6-*b*]quinoxalines under oxidative conditions (potassium permanganate, DMF, -20 °C). Upon heating in DMF to room temperature without an oxidant, 1-ethyl-1,4,4a,5,10,10a-hexahydro-1,2,4-triazino[5,6-*b*]quinoxalines undergo elimination of the corresponding amidrazones to give fully aromatic quinoxaline (**Scheme 79**) <B-1994MI1>.



Scheme 79

Attempts to cause the $S_N^H-S_N^H$ reaction by oxidation of tetrahydro derivatives of pyrrolo[2,3-*e*]-1,2,4-triazines **150** with selenic acid failed. Instead, oxidation of the exocyclic methyl group initiated expansion of the pyrrole ring into the pyridine system, while the triazine ring was transformed into triazole derivative **151** (**Scheme 80**) <2003RCB1740>.



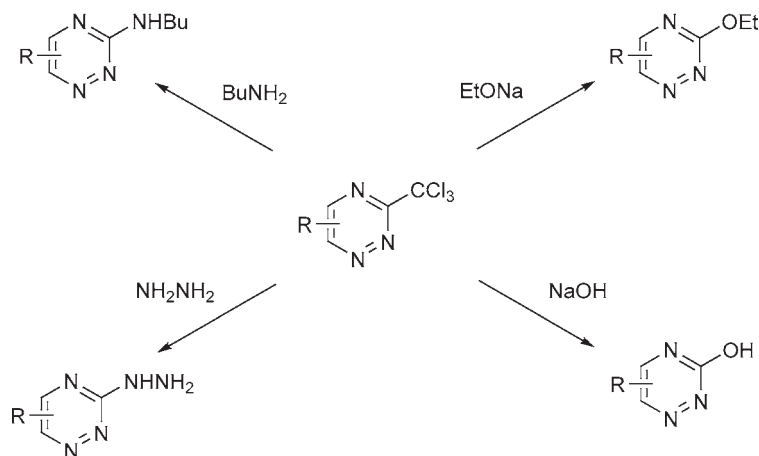
Scheme 80

9.02.5.7.6 Nucleophilic substitution of good leaving groups

Nucleophilic displacement of good leaving groups $S_N(AE)^{ipso}$ in the series of 1,2,4-triazines has been the subject of a number of reviews and monographs <1978MI191, 1984CHEC-I(2)385, 1989AHC(46)73, 1992H(33)931, 1996CHEC-II(6)507, 1997MI103, 1998HOU(E9c)582, 1998RCR633, 1998RJO297, 2002AHC(82)261, B-2004MI(3)185, 2004SOS(17)357>.

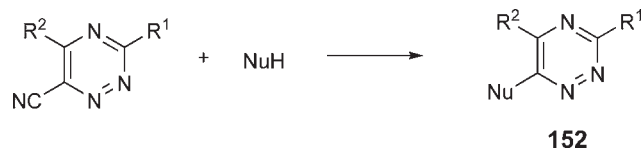
9.02.5.7.6(i) The $S_N(AE)^{ipso}$ substitutions

The displacement of nucleofugal groups is usually realized through the addition–elimination two-step mechanism $S_N(AE)^{ipso}$. For instance, the trichloromethyl group in 1,2,4-triazines is displaced easily by the action of hydrazine, butylamine, sodium hydroxide, and alkoxides (**Scheme 81**) <2004SOS(17)357>; however, in the reaction of 6-aryl-3-trichloromethyl-1,2,4-triazines with aromatic C-nucleophiles, substitution of hydrogen takes place <2004RCB1295>.



Scheme 81

The cyano group in 6-cyano-1,2,4-triazines is activated enough to be displaced with CH-active, organomagnesium or organolithium compounds, water, alcohols, and amines to give the corresponding 6-substituted-1,2,4-triazines **152** (Scheme 82; Table 14) <1997MC66, 1998RJO297, 2000MC117, 2000MC227, 2002RJO744, 2004SOS(17)357, 2004RCB1223>. This method of modifying the structure of 1,2,4-triazines becomes especially important since the cyano group can be incorporated directly into 1,2,4-triazine 4-oxides <1997MC66, 2002RJO744>.



Scheme 82

Nucleophilic *ipso*-substitution is a characteristic feature of chloro derivatives in the series of monocyclic and fused 1,2,4-triazines <1984CHEC-I(2)385, 1989AHC(46)73, 1996CHEC-II(6)507, 1997MI103, 1998CHE488, 1998HOU(E9c)582, 1998RCR633, 1998RJO297, 1999JME730, 2002AHC(82)261, 2003BP1807, B-2004MI(3)185, 2004SOS(17)357, 2005BML4774>. The vast majority of reactions proceed in good yields (>80%), and the order of reactivity is C-5 > C-6 > C-3 toward neutral nucleophiles, and C-5 > C-3 > C-6 relative to anionic species <2004SOS(17)357>. Representative examples of nucleophilic substitution reactions are shown in Scheme 83 <1998CHE488, 1998HOU(E9c)582, 1998RCR633, 1998RJO297, 2001UKZ53, 2002AHC(82)261, 2004SOS(17)357>.

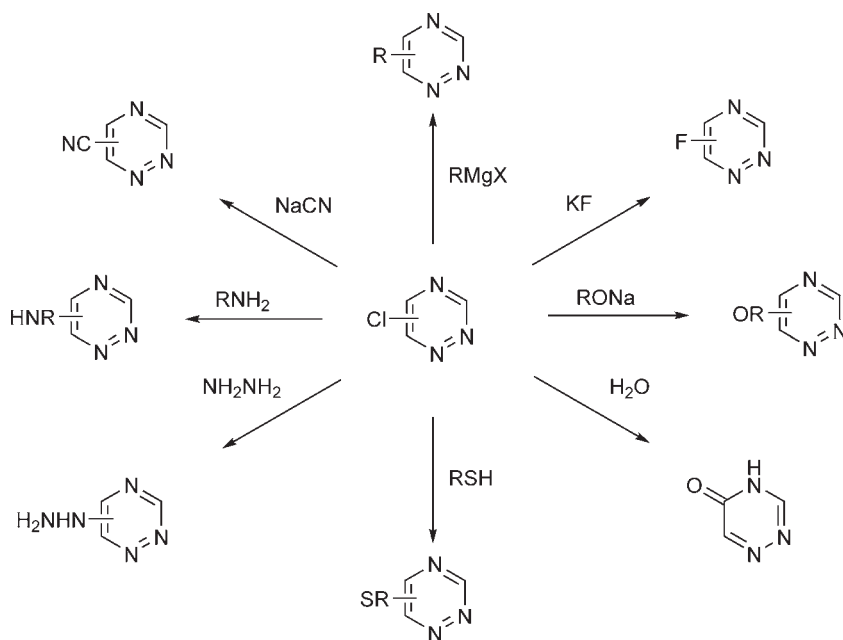
In addition, 3-chloro and 3-bromo groups in 1,2,4-triazine 2-oxides and benzo-1,2,4-triazine 1-oxides are substituted easily on treatment with amines, alcohols, phenols, sodium azide, and other nucleophiles <1998HOU(E9c)582, 1998RCR633, 1998RJO297, 2002AHC(82)261, 2003BP1807>.

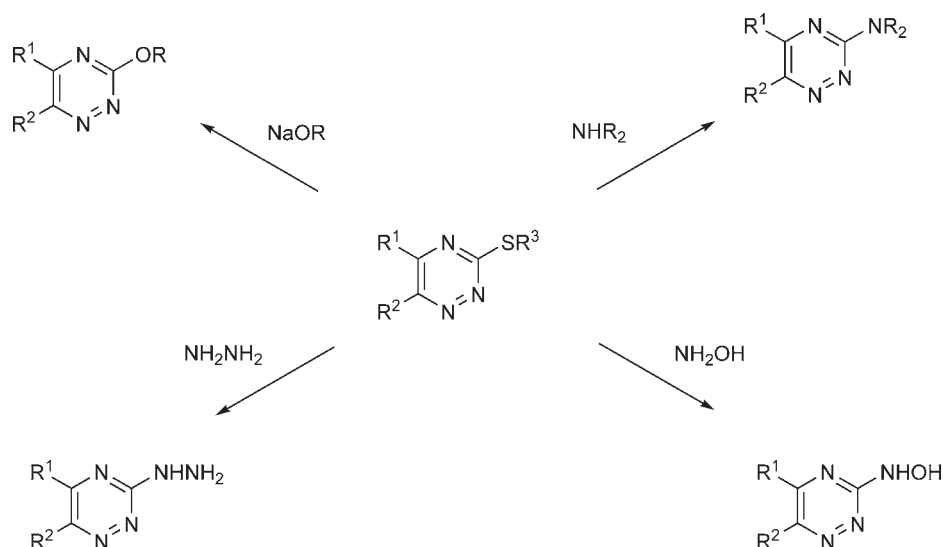
Alkoxy groups in 1,2,4-triazines also exhibit good leaving abilities, and can be displaced by amines, hydrazines, or carbanions of CH-active compounds <1998HOU(E9c)582, 1998RCR633, 1998RJO297, 2002AHC(82)261, 2004SOS(17)357>. Yields are usually high and exceed 70%. For instance, 3-hydrazino-1,2,4-triazine can be obtained from 3-methoxy-1,2,4-triazine in 82% yield <2004SOS(17)357>. A high leaving group ability of the methoxy group at C-5 in 1,2,4-triazines and 1-alkyl-1,2,4-triazinium salts has been exploited to perform the tandem A_N-S_N^{*ipso*} and S_N^H-S_N^{*ipso*} reactions (see Section 9.02.5.7.7) <2001JHC901>.

A common way to modify 3-alkylthio-1,2,4-triazines is through a nucleophilic substitution reaction at C-3 by the action of alkoxides, amines, hydrazines, and hydroxylamines, enabling one to obtain a variety of 3-substituted-1,2,4-triazines in good yields (>75%) (Scheme 84) <1996CHEC-II(6)507, 1996TL5061, 1998HOU(E9c)582, 1999JME730, 2001CHE1418, 2004SOS(17)357>.

Table 14 Displacement of the cyano group in 6-cyano-1,2,4-triazines*3-R¹-5-R²-6-cyano-1,2,4-triazine*

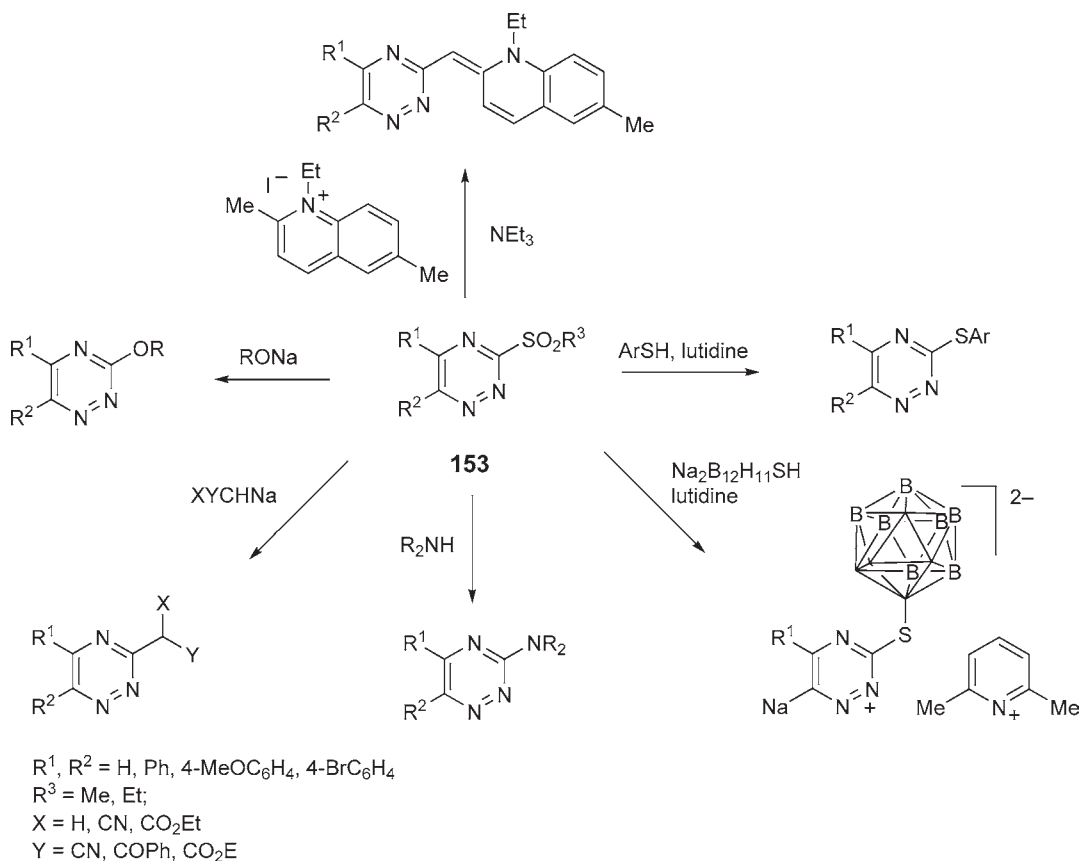
<i>R</i> ¹	<i>R</i> ²	<i>NuH/B</i>	<i>Yields of 152 (%)</i>	<i>Reference</i>
Ph	Ph	MeOH/KOH	85	2002RJO744
Ph	4-ClC ₆ H ₄	MeOH/KOH	95	2002RJO744
H	Ph	EtOH/KOH	77	2002RJO744
Me	Ph	EtOH/KOH	80	2002RJO744
Ph	Ph	EtOH/KOH	76	2002RJO744
Ph	4-ClC ₆ H ₄	EtOH/KOH	90	2002RJO744
Ph	Ph	<i>i</i> -PrOH/KOH	79	2002RJO744
Ph	Ph	<i>n</i> -BuOH/KOH	93	2002RJO744
Ph	Ph	HO(CH ₂) ₂ OH/KOH	95	2002RJO744
Ph	Ph	H ₂ O/KOH	81	2002RJO744
Ph	Ph	Ammonia	80	2002RJO744
Ph	Ph	Me ₂ NH	85	2002RJO744
Ph	Ph	Piperazine	92	2002RJO744
Ph	Ph	Pyrrolidine	93	2002RJO744
Ph	Ph	Morpholine	91	2002RJO744
Ph	Ph	PhCH ₂ NH ₂	52	2002RJO744
Ph	Ph	EtO ₂ CCH ₂ NH ₂	60	2002RJO744
Ph	Ph	HO(CH ₂) ₂ NH ₂	95	2002RJO744
Ph	Ph	HO(CH ₂) ₂ NHMe	91	2002RJO744
Ph	Ph	Me ₂ N(CH ₂) ₂ OH	94	2002RJO744
Ph	Ph	PhCOMe/NaH	61	2000MC227
Ph	Ph	CH ₂ (CN) ₂ /NaH	76	2000MC227
Ph	4-ClC ₆ H ₄	CH ₂ (CN) ₂ /NaH	70	2000MC227
Ph	Ph	CNCH ₂ Ph/NaH	60	2000MC227
Ph	Ph	CNCH ₂ CO ₂ Et/NaH	68	1998RJO297
Ph	Ph	CH ₂ (CO ₂ Et) ₂ /NaH	63	1998RJO297
Ph	Ph	MeMgI	41	1998RJO297
Ph	Ph	PhMgBr	46	1998RJO297
Ph	Ph	1-Lithium-2-phenylcarborane	40	2004RCB1223

**Scheme 83**



Scheme 84

3-Alkylsulfonyl-1,2,4-triazines **153** are convenient starting materials for the synthesis of a variety of substituted 1,2,4-triazines, due to the good leaving ability of the RSO_2- group, which is easily substituted by hydroxy and alkoxy anions, amines, and carbanions [<1998RJO297, 2004TL3249, 2004SOS\(17\)357>](#), as well as thiols, including carboranylthio derivatives (Scheme 85) [<2004TL3249>](#).

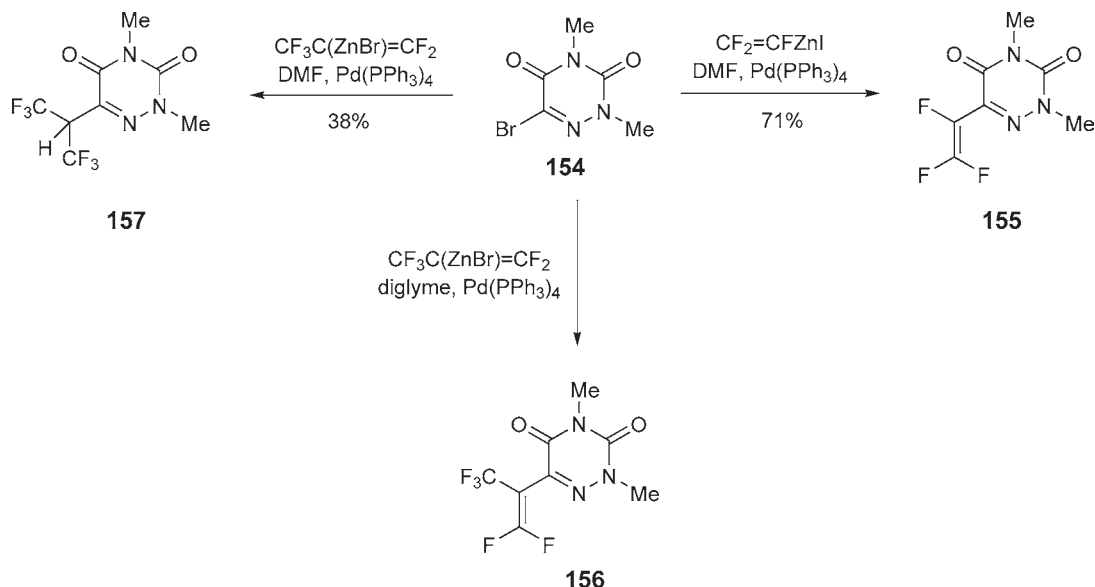


Scheme 85

In a similar way, pyrimido[4,5-*e*][1,2,4]triazin-6,8-diones, bearing the alkylsulfonyl group, undergo the nucleophilic displacement reaction by action of malonodinitrile, indole, and 1-phenyl-3-methyl-5-pyrazolone <1998RJO297, 2003KFZ20, 2003PCJ238>.

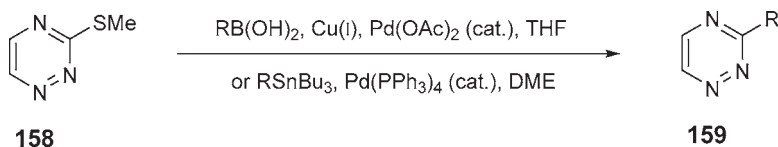
9.02.5.7.6(ii) Cross-coupling reactions

Palladium-catalyzed cross-coupling of 1,3-dimethyl-5-bromo-6-azauracil **154** with organozinc compounds $\text{CF}_2=\text{CFZnI}$ or $\text{CF}_3\text{C}(\text{ZnBr})=\text{CF}_2$ enables one to incorporate these fluorinated alkenyl and alkyl fragments into the 1,2,4-triazine ring and to obtain compounds **155–157** (Scheme 86) <2004MC63>.



Scheme 86

The Suzuki cross-coupling reaction has been applied to obtain 3-substituted-1,2,4-triazines **159** by reacting 3-methylthio-1,2,4-triazine **158** with aryl-, hetaryl-, or vinylboronic acids in the presence of a catalytic amount of palladium(II) acetate (Scheme 87; Table 15) <2002SL447, 2004SOS(17)357>. Similarly, a cross-coupling reaction takes place between 3-methylthio-1,2,4-triazine **158** and tributyl organostannyl compounds (Scheme 87; Table 15) <2003OL803>.



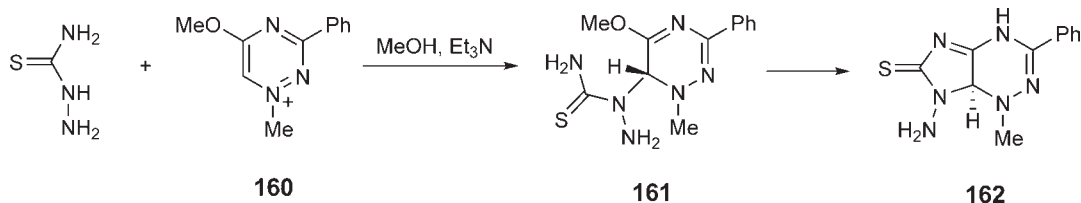
Scheme 87

9.02.5.7.7 Tandem $\text{A}_\text{N}-\text{S}_\text{N}^{\text{ipso}}$ and $\text{S}_\text{N}^{\text{H}}-\text{S}_\text{N}^{\text{ipso}}$ reactions

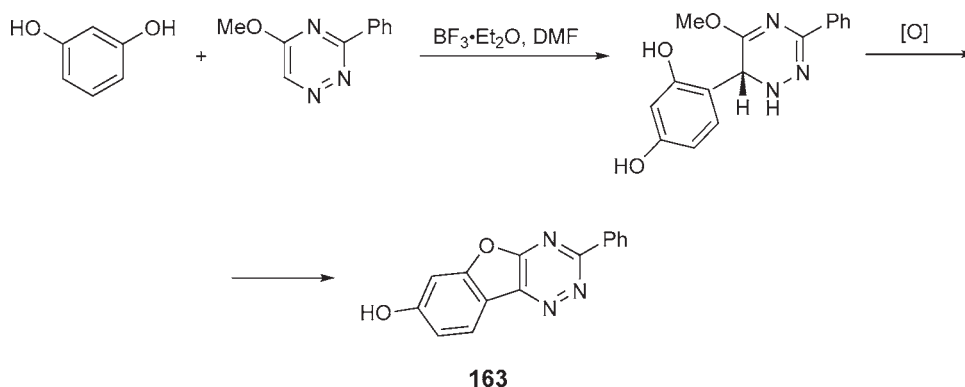
Interaction of 1-methyl-5-methoxy-3-phenyl-1,2,4-triazinium salt **160** with thio-semicarbazide leading to imidazo[4,5-*e*][1,2,4]triazin-6-thione **162** is an example of combination of the A_N and $\text{S}_\text{N}^{\text{ipso}}$ processes (Scheme 88) <2001JHC901>. Intermediate **161**, which can be isolated in 1 h after the beginning of the reaction, indicates that nucleophilic attack at the unsubstituted 6-position of the 1,2,4-triazine ring proceeds faster than the displacement of the 5-methoxy group, which requires 4–5 h for completion <2001JHC901>.

Table 15 Cross-coupling reactions of 3-methylthio-1,2,4-triazine with aryl-, hetaryl-, or vinyl-boronic acids and organostannane compounds

Nucleophile	Yields of 3-R-1,2,4-triazines 159 (%)	Reference
2-Thienyl-B(OH) ₂	80	2002SL447
2-Furyl-B(OH) ₂	70	2002SL447
4-MeOC ₆ H ₄ B(OH) ₂	85	2002SL447
3-CF ₃ C ₆ H ₄ B(OH) ₂	60	2002SL447
4-AcNHC ₆ H ₄ B(OH) ₂	60	2002SL447
PhCH=CHB(OH) ₂	83	2002SL447
1-Hexenyl-B(OH) ₂	65	2002SL447
2-Thienyl-SnBu ₃	90	2003OL803
2-Furyl-SnBu ₃	90	2003OL803
Ph-SnBu ₃	92	2003OL803
3-NO ₂ C ₆ H ₄ SnBu ₃	80	2003OL803
4-MeOC ₆ H ₄ SnBu ₃	80	2003OL803
4-Py-SnBu ₃	48	2003OL803
PhCH=CHSnBu ₃	60	2002SL447

**Scheme 88**

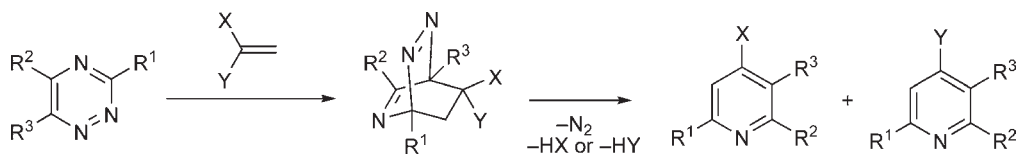
Upon activation by boron trifluoride, 5-methoxy-3-phenyl-1,2,4-triazine reacts with resorcinol at room temperature in the presence of air to give the corresponding benzofurotriazine **163** due to the tandem S_N^H and S_N^{ipso} reactions (Scheme 89) <2001JHC901>.

**Scheme 89**

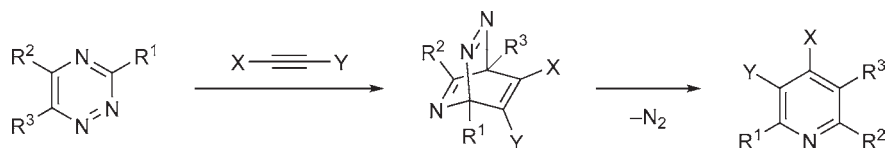
9.02.5.8 Cycloaddition Reactions

1,2,4-Triazines are known to undergo inverse electron demand Diels–Alder cycloaddition reactions with electron-rich dienophiles, such as enamines, cyclic enamines, pyrroles, indoles, imidazoles, enols, 2,3-dihydrofuran or 2,5-norbornadiene (Scheme 90), ynamines, etc. (Scheme 91), and these reactions enable one to prepare a variety of pyridine derivatives <1984CHEC-I(2)385, 1987JOC4287, 1989AHC(46)73, 1996CHEC-II(6)507, 1996SC4409, 1997PJC83,

1998TL2487, 1998TL6687, 1998TL6691, 1998TL8817, 1998TL8821, 1998TL8825, 1999EJO313, 1999KGS381, 1999CHE334, 2000T1165, 2002TL6015, 2002TL9565, 2003S2089, 2003S2096, 2003JOC2882, 2003JOC4345, 2003TL4495, 2003T8489, 2004T6021, 2004TL8331, 2004TL9565, 2004TL8607, 2004JA12260, 2004JOC7171, 2005JOC10086, 2005T8148, 2006OM2972>.



Scheme 90



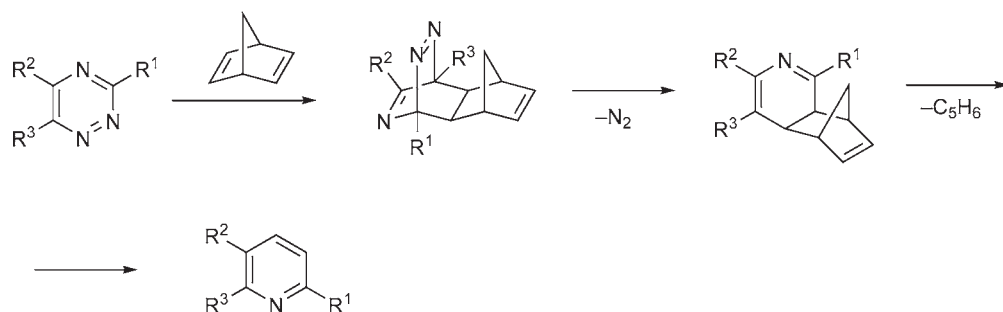
Scheme 91

These reactions usually involve cycloaddition of an electron-rich dienophile across C₃–C₆ of the 1,2,4-triazine ring followed by the loss of nitrogen and elimination of a small molecule to restore an aromatic system (**Schemes 90 and 91**).

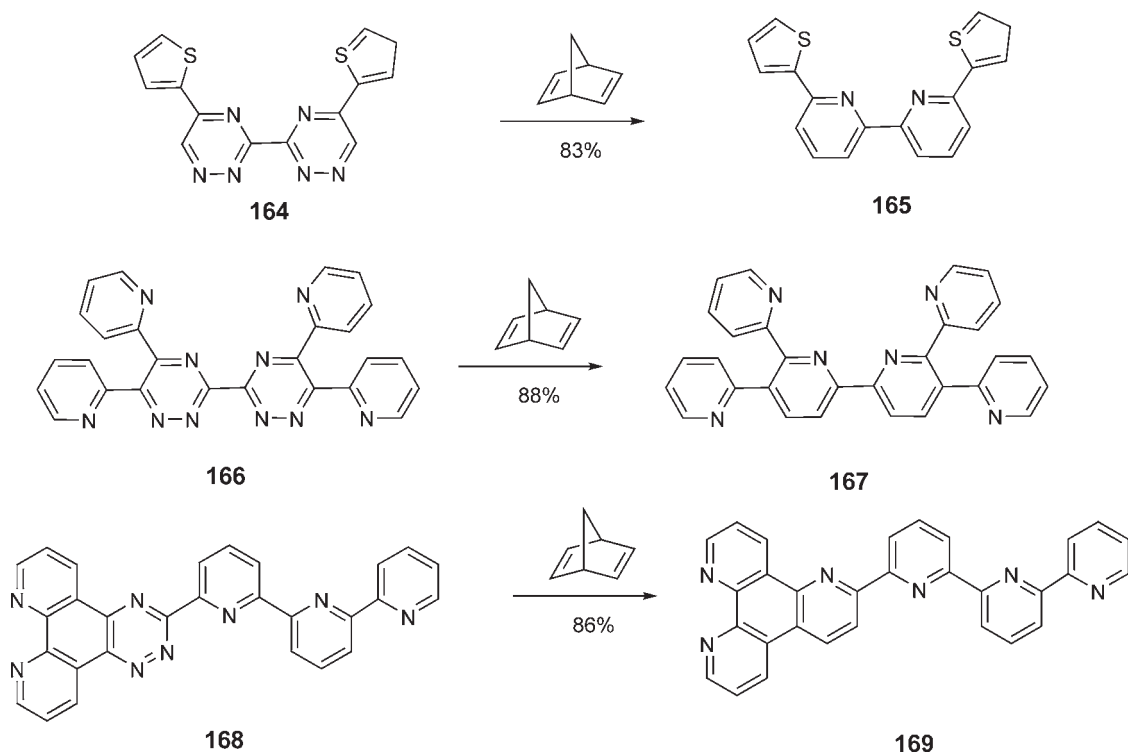
9.02.5.8.1 Intermolecular cycloadditions

The aza-Diels–Alder reaction of 1,2,4-triazines with 2,5-norbornadiene is an important synthetic route to a variety of pyridines (**Scheme 99**), especially those which contain two, three, four, and more pyridine rings (**Scheme 92**) <1998TL6687, 1998TL6691, 1998TL8817, 1998TL8821, 1998TL8825, 1999T5047, 1999EJO313, 2002TL4923, 2002MC30, 2002TL6015, 2003JOC2882, 2003S2400, 2003TL693, 2005TL1791, 2005TL6111, 2006TL869, 2006OM2972>. These reactions usually require many hours of reflux in a solvent with a high-temperature boiling point; however, yields of pyridines are good. For instance, oligopyridines **165**, **167**, and **169** were obtained from the corresponding 1,2,4-triazines **164**, **166**, and **168** in 83–88% yields (**Scheme 93**).

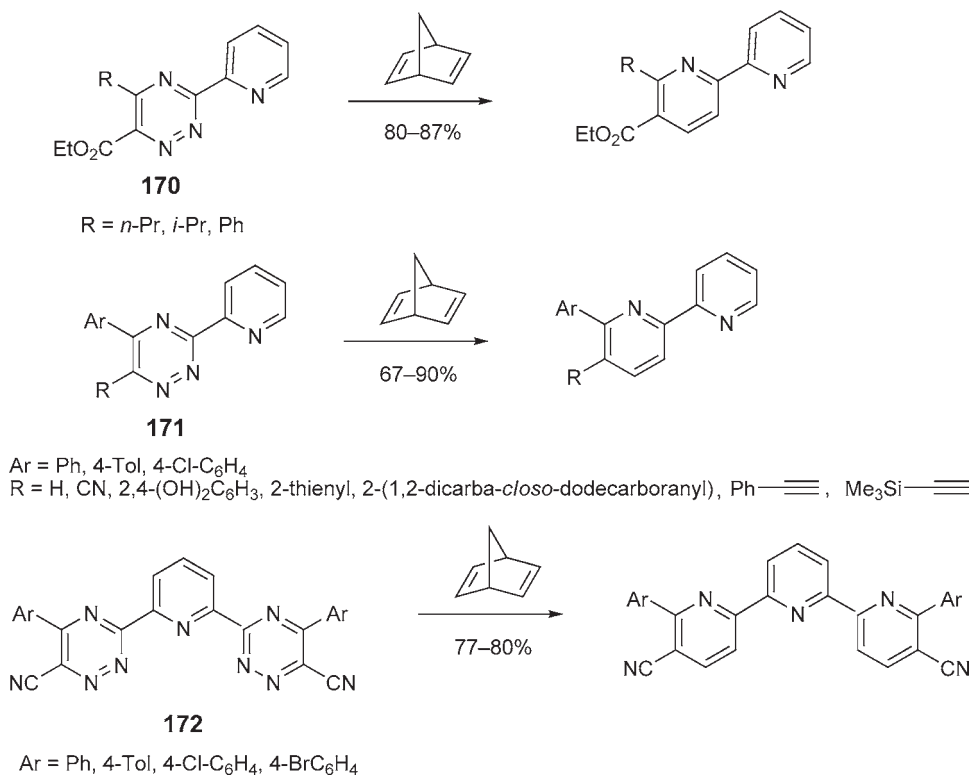
The presence of electron-withdrawing groups in the 1,2,4-triazine ring facilitates the cycloaddition reaction. Indeed, ethyl 3-(2-pyridinyl)-1,2,4-triazin-6-carboxylates **170** or 6-cyano-1,2,4-triazines **171** and **172** react with 2,5-norbornadiene on reflux in ethanol or benzene (**Scheme 94**) <2003S2400, 2003TL693, 2003JOC2882, 2005TL6111>.



Scheme 92

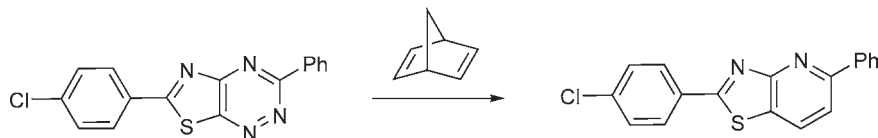


Scheme 93



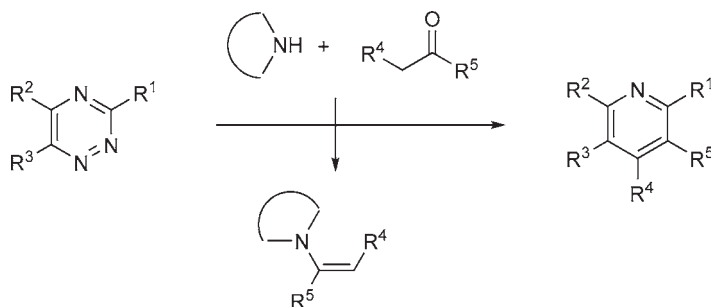
Scheme 94

A new approach to thiazolo[4,5-*b*]pyridines, based on the 1,2,4-triazine to pyridine ring-transformation reaction, has been reported recently <2005MC151>. The reaction of thiazolo[4,5-*e*][1.2.4]triazines with bicyclo[2.2.1]heptadiene was found to proceed under high-pressure conditions (15 kbar), thus yielding the corresponding thiazolo[4,5-*b*]pyridines (Scheme 95) <2005MC151>.

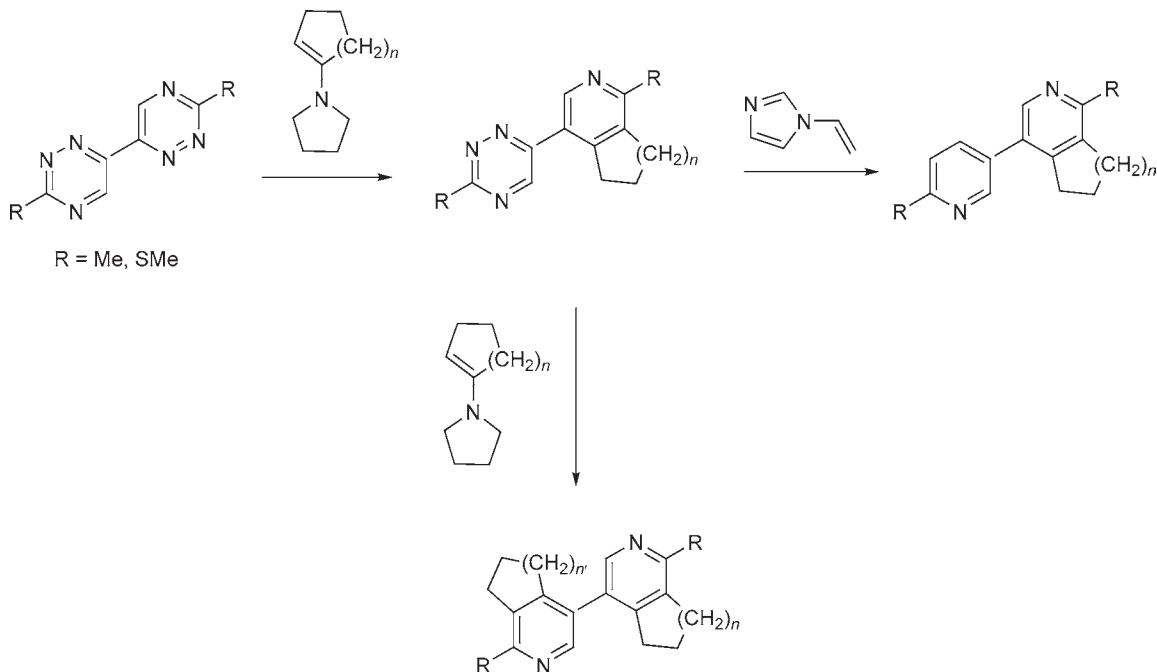


Scheme 95

Enamines of ketones, including those obtained *in situ* from cycloalkylimines and appropriate oxo compounds, are good electron-rich dienophiles, which are capable of reacting with 1,2,4-triazines under very mild conditions (Schemes 96 and 97) <2000TL3657, 2002CPB463, 2002MC30, 2002TL4923, 2002TL9565, 2002SL1892, 2003JOC2882, 2003S2400, 2003S2089, 2003S2096, 2005MOL265, 2004T6021, 2004JA12260, 2005JOC10086, 2005MOL274, 2006TL869>.

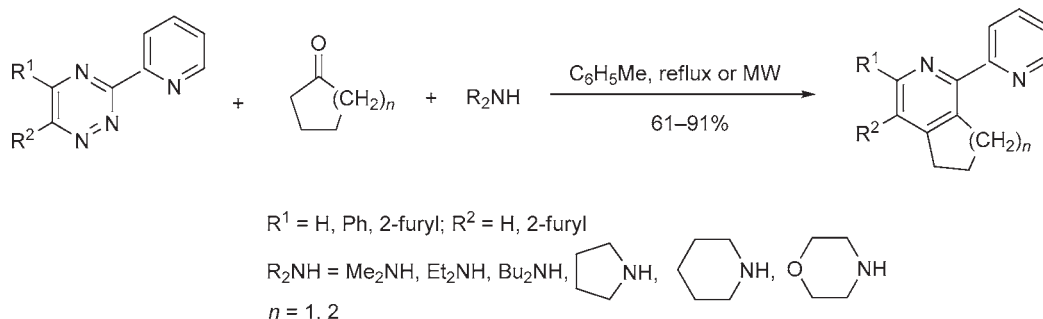


Scheme 96



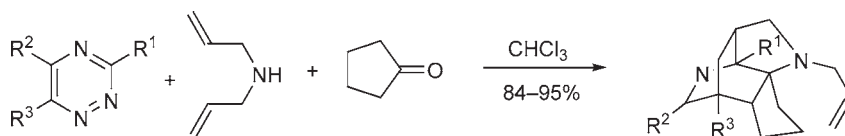
Scheme 97

Enamines generated *in situ* from secondary amines and ketones have been used widely for the synthesis of oligopyridines by means of Diels–Alder cycloaddition reactions (**Scheme 98**) <2002MC30, 2002TL4923, 2002TL9565, 2003JOC2882, 2003S2400, 2004JA12260, 2005JOC10086>.



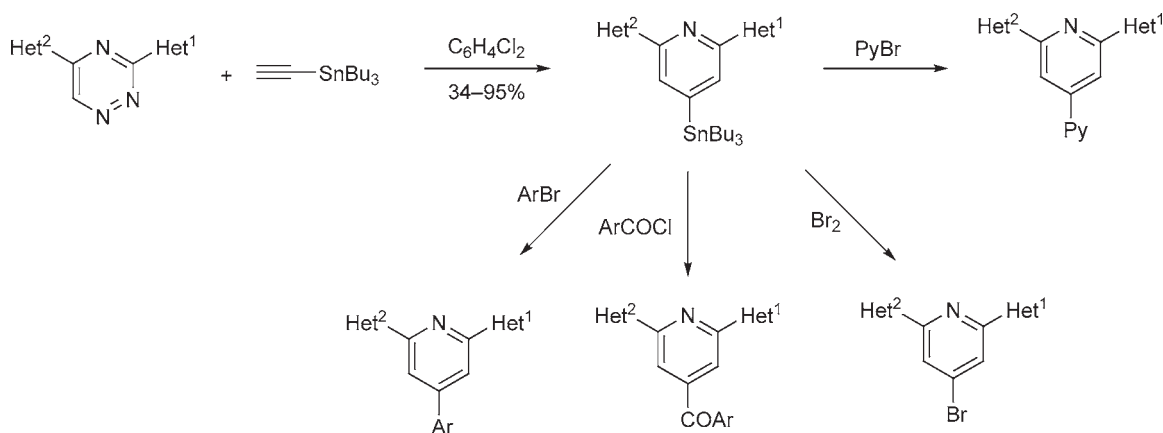
Scheme 98

Cascade reactions of substituted 1,2,4-triazines are of great interest as simple ways to a dramatic increase in molecular complexity, from planar 1,2,4-triazine unit into a polycyclic system. Indeed, in this multistep process, the diallylamine and cyclopentanone react first *in situ* to give the corresponding enamine, which undergoes an inverse electron demand cycloaddition reaction with 1,2,4-triazine to give an intermediate dihydropyridine compound. A spontaneous intramolecular Diels–Alder reaction between the allyl moiety and the dihydropyridine gives the tetracyclic compound (**Scheme 99**) <2004JA12260>.



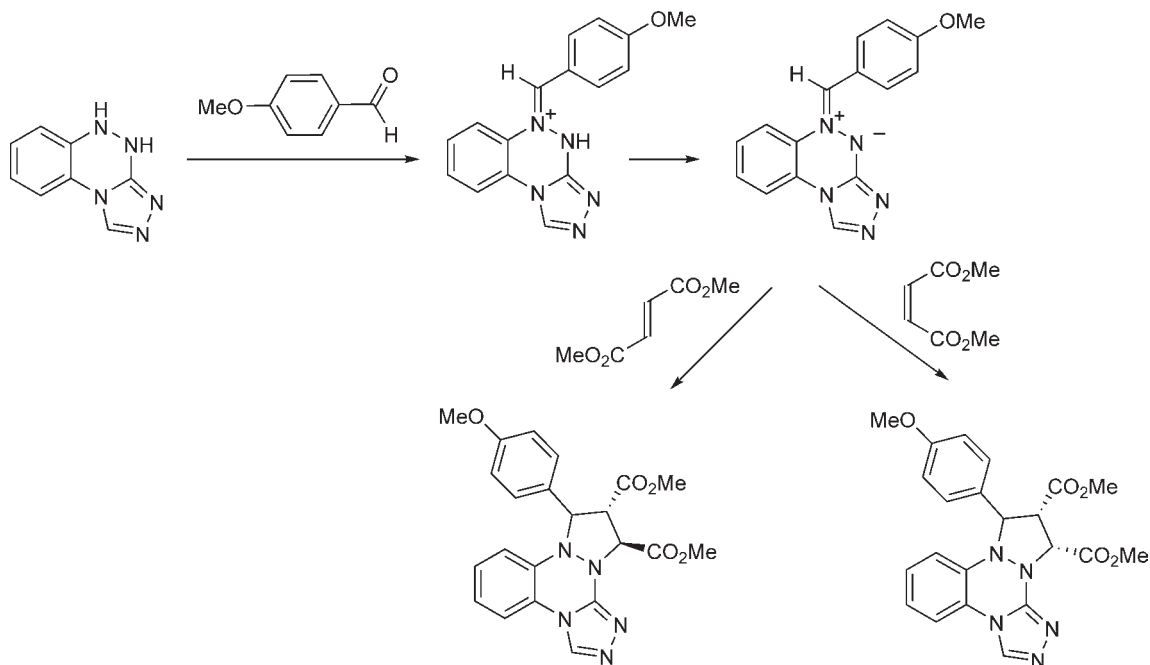
Scheme 99

Ethynylbutylstannane is also an appropriate reagent for the Diels–Alder cycloaddition with 1,2,4-triazines to give intermediate organostannyl derivatives of pyridines, which can be functionalized easily by means of nucleophilic displacement reactions (**Scheme 100**) <1998TL5047,1999EJO313>.



Scheme 100

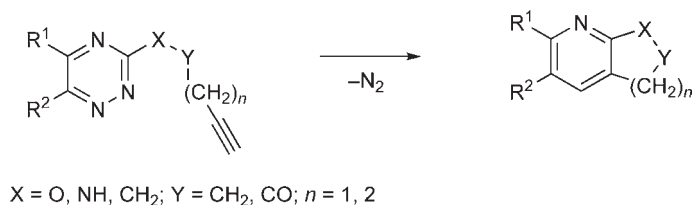
Another approach is based on using the 1,3-azomethine imines, generated by deprotonation of the corresponding triazolo[4,3-*a*][1,2,4]-triazine aryliminium salts. These 1,3-dipoles are capable of reacting with fumaric and maleic esters to give the expected 1,3-cycloadducts in a stereoselective manner (**Scheme 101**) <2005H(65)1889>.



Scheme 101

9.02.5.8.2 Intramolecular cycloadditions

Intramolecular Diels–Alder reactions have also found wide application in the chemistry of 3-substituted-1,2,4-triazines, bearing an appropriate dienophilic fragment at C-3, as efficient synthetic routes to condensed pyridines (**Scheme 102**) <2000T1165, 2000T8489, 2003TL4495, 2004JOC7171>.

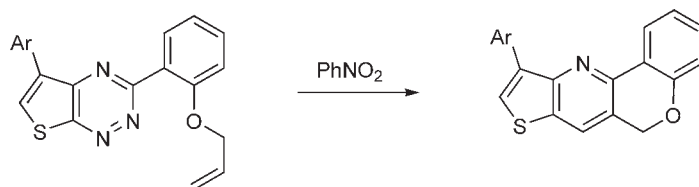


Scheme 102

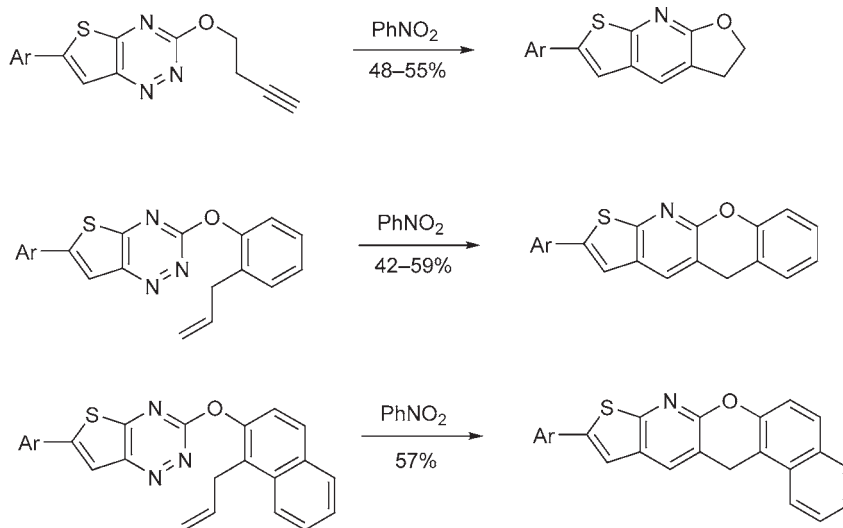
This general scheme is illustrated by intramolecular [4+2] cycloaddition reactions of suitably designed thieno[3,2-*e*]- and thieno[2,3-*b*][1,2,4]triazines tethered with alkene or alkyne terminals (**Schemes 103** and **104**) <2002JCM60, 2003T8489>.

This methodology has been applied to obtain annelated dipyridines and pyridinyl 2-substituted pyrazines (**Schemes 105** and **106**) <2004T6021>.

In a similar way, azepino[2,3-*b*]pyridines can be obtained through the intramolecular 1,2,4-triazine to pyridine ring-transformation reaction (**Scheme 107**) <1999JCD583>.

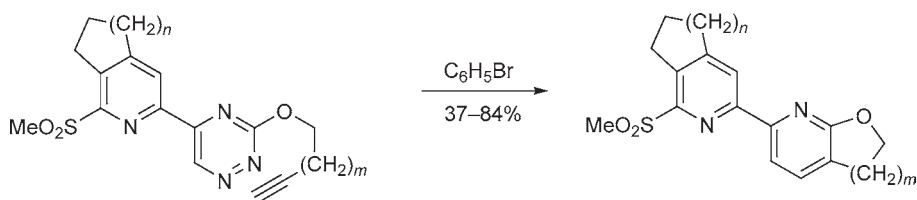


Scheme 103



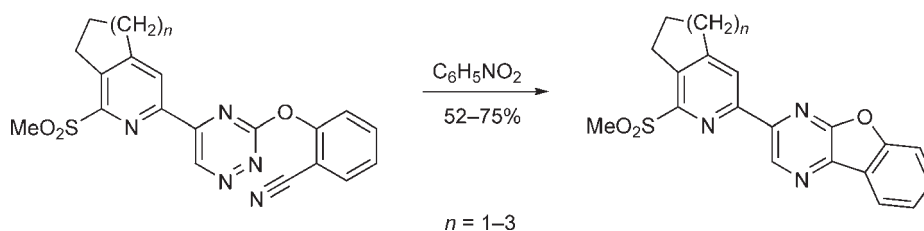
Ar = Ph, 4-MeOC₆H₄, 2-furyl, 2-thienyl

Scheme 104



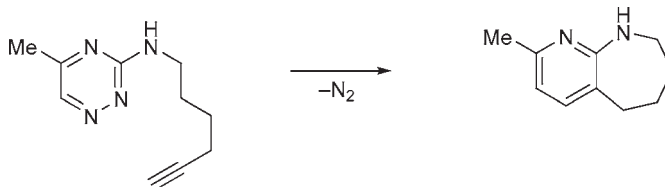
$n = 1, 2, 3, 4; m = 1, 2$

Scheme 105



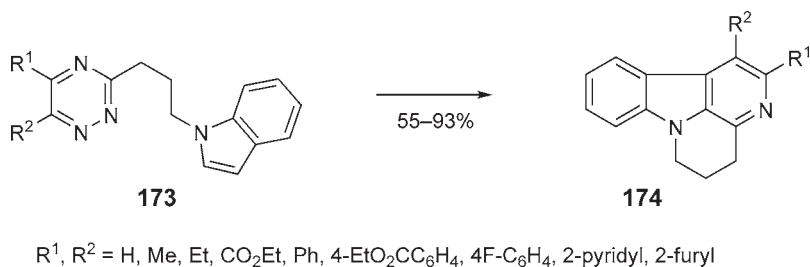
$n = 1-3$

Scheme 106



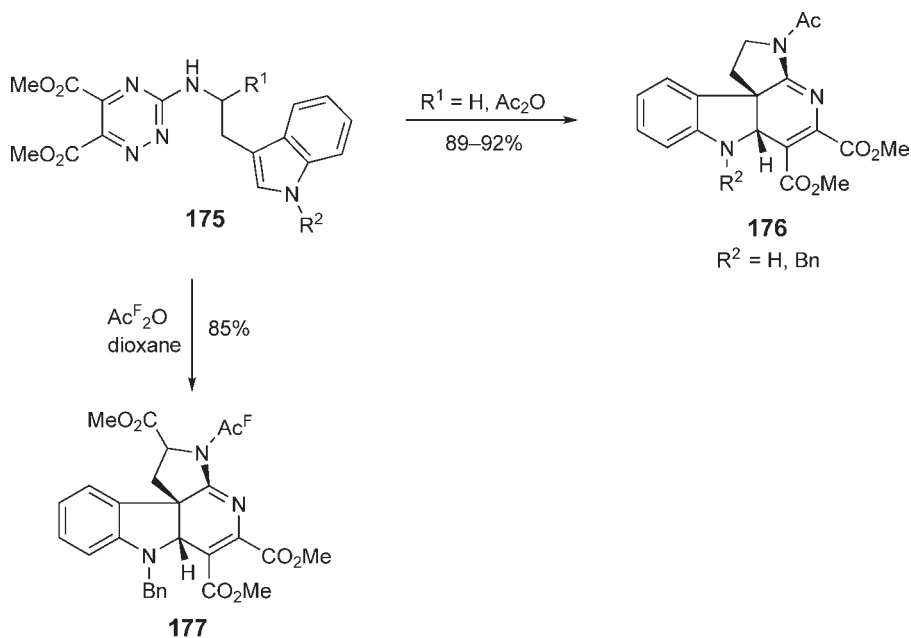
Scheme 107

Heating of 3-[3-(1-indolyl)propyl]-1,2,4-triazines **173** in tri(isopropyl)benzene, DMF, or use of microwave activation in the inverse electron demand Diels–Alder reaction results in the formation of fused derivatives **174** (Scheme 108) <2003TL4495, 2004JOC7171>.



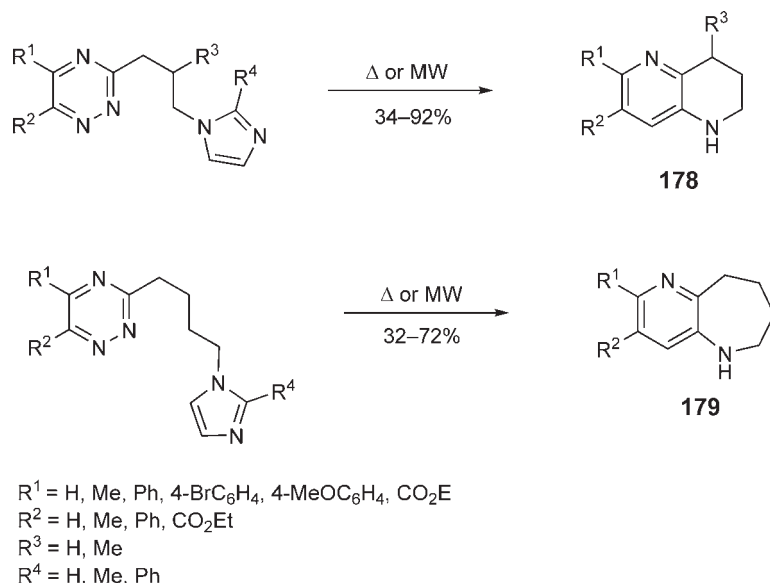
Scheme 108

Intramolecular cycloaddition of N^{10} -3-(1,2,4-triazinyl)tryptamines **175** takes place on heating in acetic anhydride to give fused indoles **176** and **177** (Scheme 109) <2000T1165>.



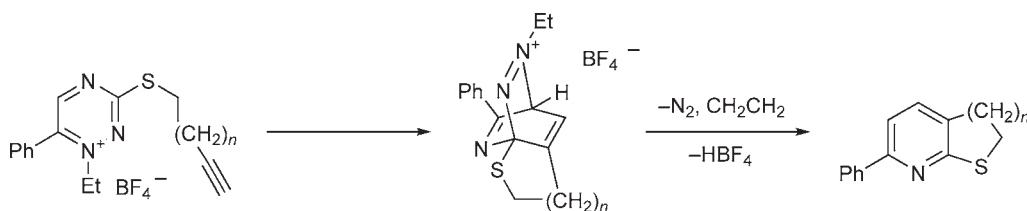
Scheme 109

The intramolecular inverse electron demand Diels–Alder reaction between imidazoles and 1,2,4-triazines linked by trimethylene or tetramethylene tethers from the imidazole N-1 position to the triazine C-3 proceeds smoothly on heating in triisopropylbenzene to give 1,2,3,4-tetrahydro-1,5-naphthyridines **178** or 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepines **179** in good yields (Scheme 110). The reaction can also be promoted by microwave irradiation <2004JOC7171>.



Scheme 110

Further, *N*-alkyl-1,2,4-triazinium salts proved to be appropriate compounds for intramolecular inverse electron demand Diels–Alder cycloaddition reactions. Indeed, 1-ethyl-5-phenyl-1,2,4-triazinium tetrafluoroborates bearing acetylenic 3-butynylthio or 4-pentynylthio substituents at C-3 undergo intramolecular [4+2] cycloaddition reactions under very mild conditions, thus being transformed into thieno[2,3-*b*]- or thiopyrano[2,3-*b*]pyridines (Scheme 111) <2001MC19>.



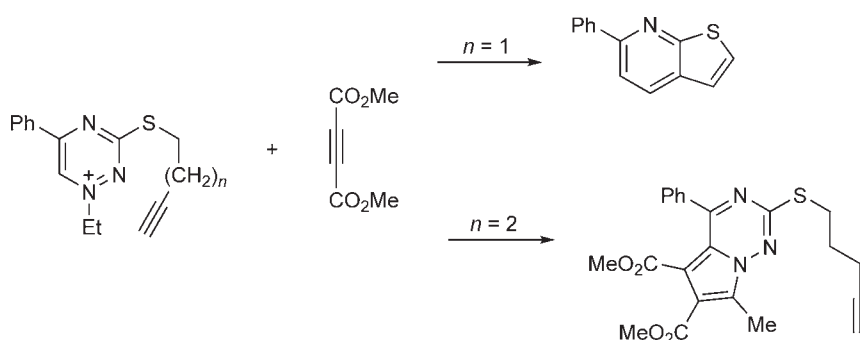
Scheme 111

Two concurrent reactions, in which either the acetylenic fragment at C-3 of the 1,2,4-triazine ring participates in an intramolecular [4+2] Diels–Alder ring-transformation reaction (*n* = 1), or diethyl acetylenedicarboxylate undergoes an intermolecular 1,3-dipolar cycloaddition reaction, leading to pyrrolo[2,1-*f*][1,2,4]-triazines, have been described (Scheme 112) <2001MC19>.

9.02.6 Reactivity of Nonconjugated Rings

In this section, reactivity of 1,2,4-triazinones, 1,2,4-triazin-3,5-diones, and 1,2,4-triazine thiones is considered.

1,2,4-Triazin-3,5-diones and their *N*-alkyl derivatives are regarded as aza analogs of uracil to be used for the synthesis of cyclic and acyclic nucleosides (Figures 8 and 9) <1995NN895, 1995NN1341, 1995NN1425, 1995NN1693, 2003NN1805, 2005NN161>.



Scheme 112

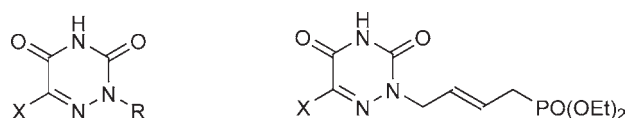


Figure 8

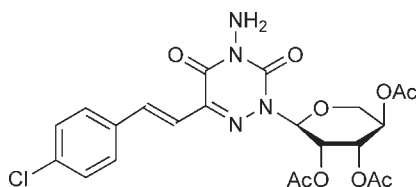
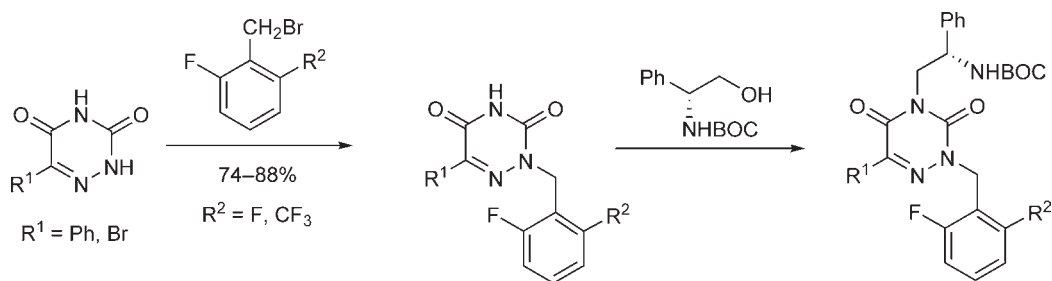


Figure 9

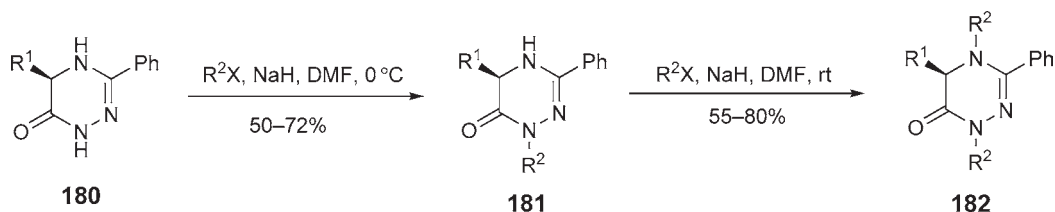
For instance, some new 2- α -L-arabinopyranosyl-1,2,4-triazines have been obtained for testing as potential anti-tumor chemotherapeutics (Figure 9) <2003NN1805>.

Indeed, N-alkylation of 1,2,4-triazin-3,5-diones has been considered as a synthetic approach to *N*-alkyl derivatives of azauracils, as antagonists of hormone receptors (Scheme 113) <2005BML4363>.



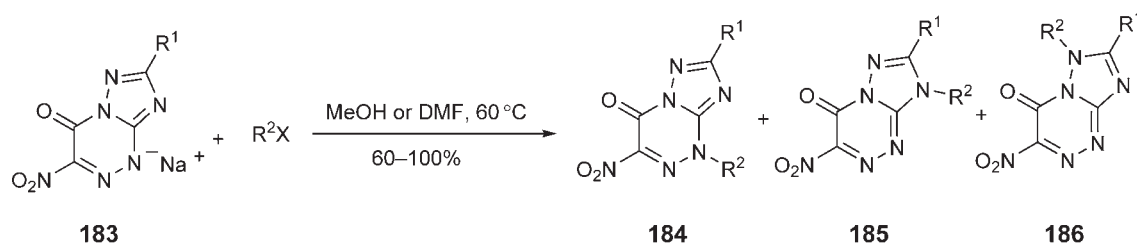
Scheme 113

N-Alkylation of 4,5-dihydro-1,2,4-triazin-6-ones **180**, including optically active compounds, takes place regioselectively to form predominantly 1-alkyl derivatives **181**. Additional treatment of 1,2,4-triazin-6-ones **181** with alkylhalogenides affords 1,4-dialkyl-4,5-dihydro-1,2,4-triazin-6-ones **182** (Scheme 114) <2000TL671>.



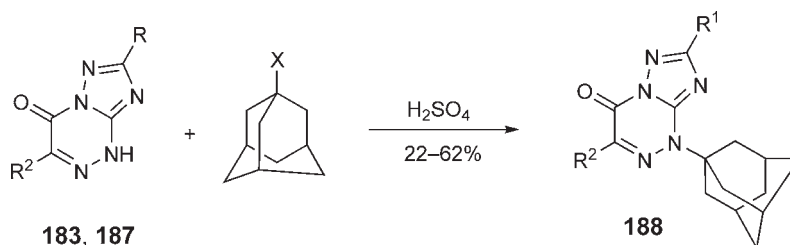
Scheme 114

N-Alkylation of sodium salts of 3-nitro-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-4-ones with alkylhalogenides or dimethyl sulfate affords a mixture of three isomeric products **184–186**. The main component of this mixture proved to be 1-alkyl derivatives **184** (Scheme 115) <1997MI103, 2006RCB2071>.



Scheme 115

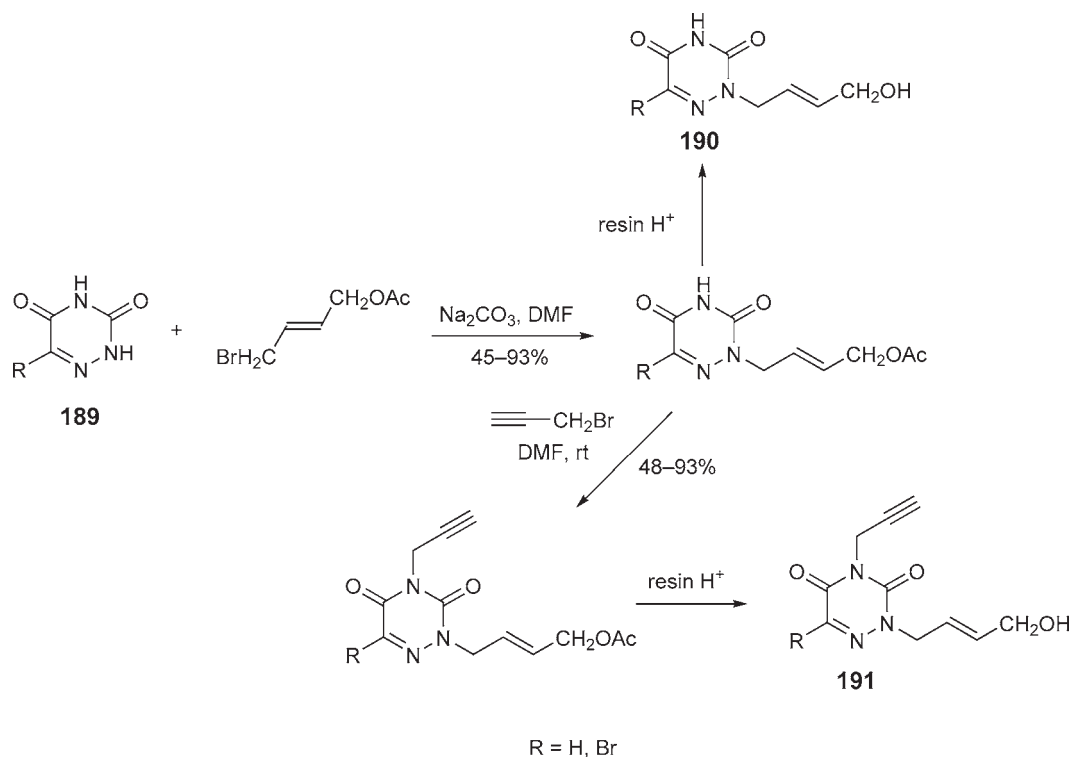
Interaction of 3-nitro- and 3-ethoxycarbonyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazin-4-ones **187** with adamantanyl cation, generated from the corresponding alcohol or adamantylnitrate in sulfuric acid, results in the formation of compounds **188** (Scheme 116) <2002RJO294, 2002RJO272>.



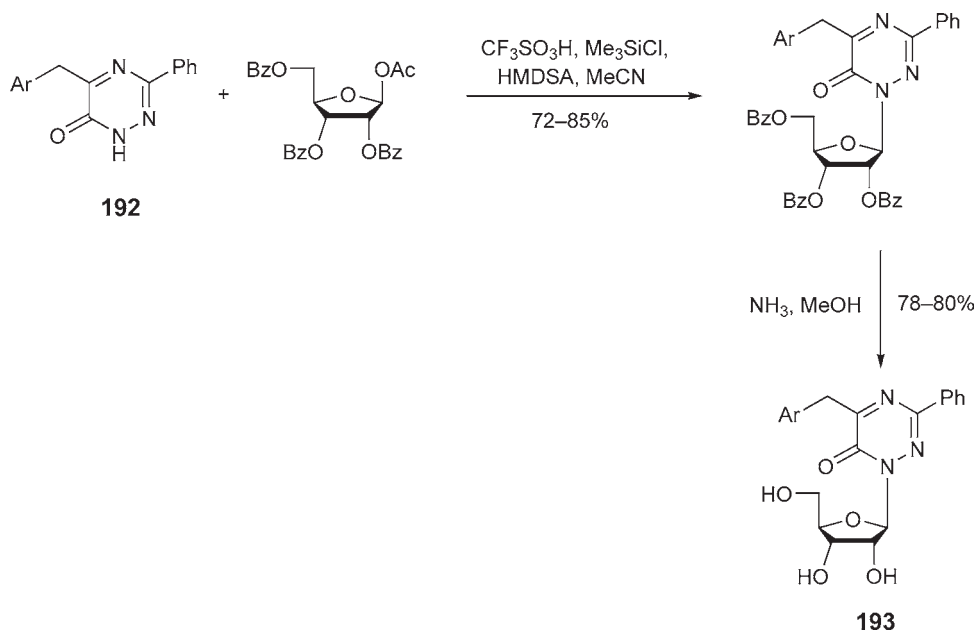
Scheme 116

N-Alkylation of azauracils **189** with O-acylated bromobutenol affords acyclonucleosides **190** and **191** (Scheme 117), while N-glycosylation of 1,2,4-triazinones **192** results in the formation of nucleosides **193** (Scheme 118) <2005NN161>.

In a similar manner, a number of abnormal nucleosides based on 5-azacytidine **194**, 6-azacytidine **195**, 6-azauracil (compounds **196–198**) and azoloannulated 1,2,4-triazinones (compounds **199** and **200**) have been obtained (Figure 10) <1996TL901, 2000BML2145, 2000JA10259, 2003JOC9012, 2005NN15>.



Scheme 117



Scheme 118

Further, 1,2,4-triazinones, 1,2,4-triazine thiones, and their numerous derivatives are of interest for the synthesis of biologically active compounds. For instance, 4-amino-6-arylmethyl-3-mercapto-1,2,4-triazin-5(4H)-ones were condensed with suitably substituted 5-aryl-2-furfurals or 5-aryl-2-furoic acids to obtain biologically active derivatives **201** and **202** which exhibit antibacterial activities compared to furacin (Figure 11) <2003IJH85>.

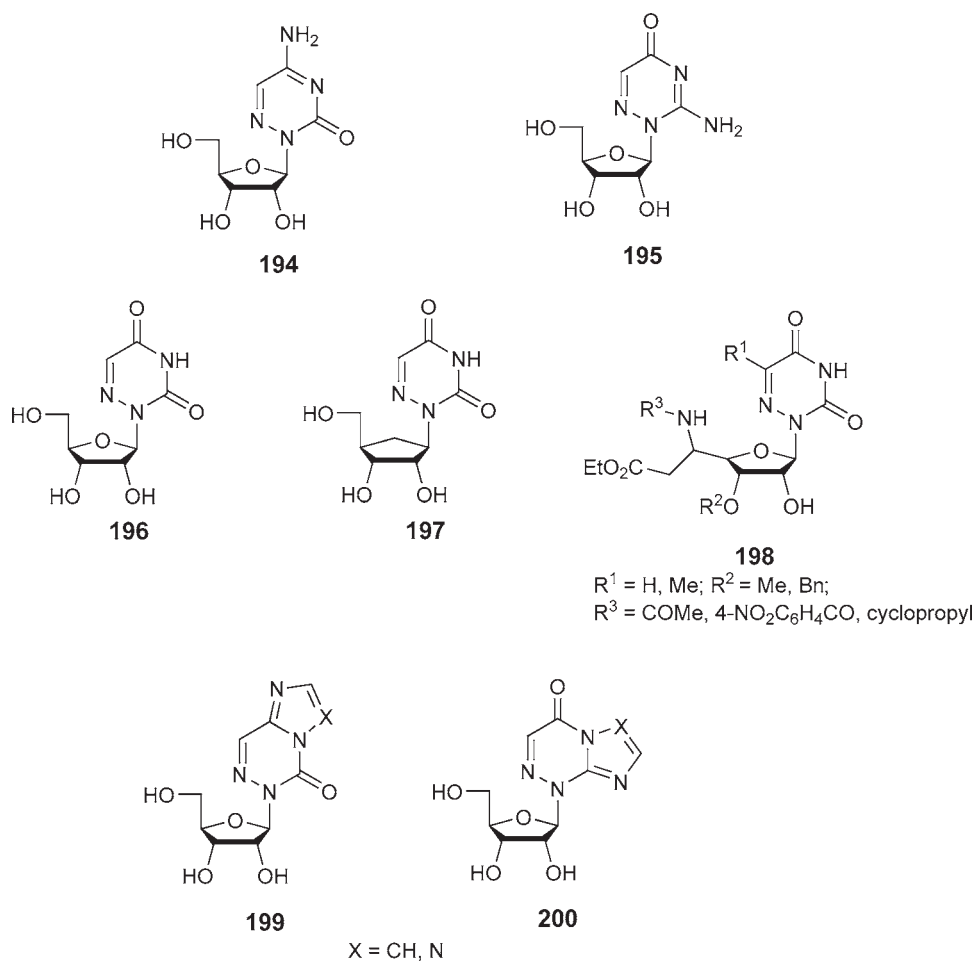


Figure 10

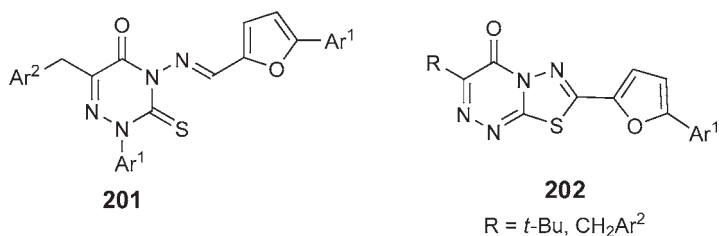


Figure 11

Chiral 3-acetyl-4,5-dihydro-1,2,4-triazinones (R = methyl, isopropyl, benzyl) were reacted, utilizing the template effect, with 1,3-diaminopropane in the presence of nickel acetate to give chiral tetraaza-type nickel complexes **203** (Figure 12) <2002MI31>.

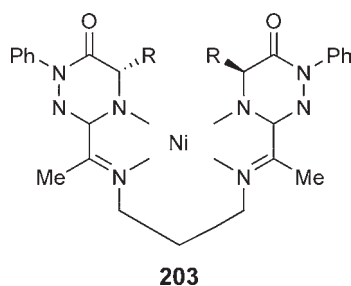
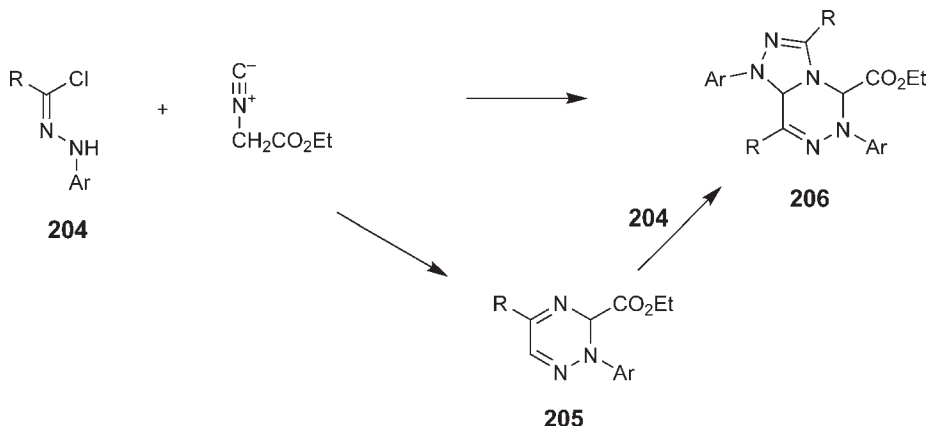


Figure 12

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

9.02.7.1 [3+3] Atom Combinations

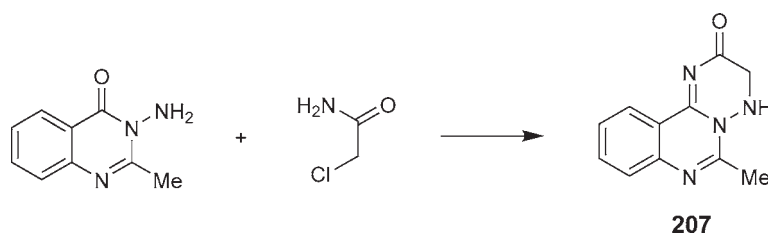
The synthesis of the triazine ring from [3+3] fragments is not as widely used as the [4+2] approach; nevertheless, several successful examples have been reported during the last decade. One of these is the reaction of nitrilimines, generated from chloroamidrazones **204**, with ethyl isocyanoacetate, which results in the formation of either 2-aryl-3-ethoxycarbonyl-1,2,3-dihydro-1,2,4-triazines **205** or 1,2,4-triazolo[4,5-*d*]-1,2,4-triazines **206** (Scheme 119) <2002M1165>.



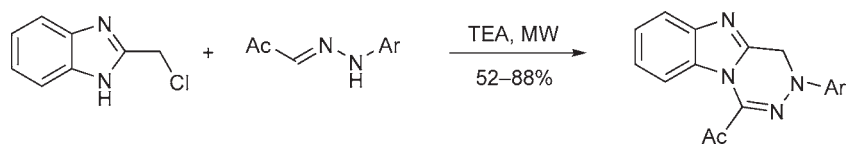
Scheme 119

The [3+3] atom combination has also been realized, as shown by the synthesis of quinazolino-[3,4-*b*]-1,2,4-triazine **207** (Scheme 120) <1997JCM157> and 1-aryl-3-acetyl-1,4,5,6-tetrahydrobenzimidazo[1,2-*d*]-1,2,4-triazine (Scheme 121) <2005TL1725>.

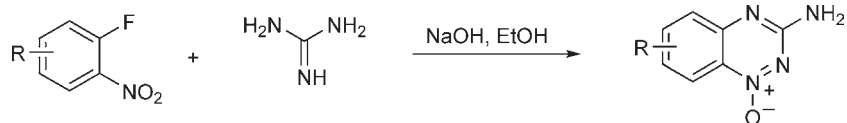
A number of methods, based on [3+3] fragments, exploit the reactions of nitroaromatic compounds, donating the C–C–N fragment into the formed 1,2,4-triazine ring, with guanidine, which provides the N–C–N triad of atoms. This approach is illustrated by cyclizations of 2-fluoronitrobenzenes or 4-chloro-3-nitroquinoline into the corresponding 1,2,4-triazine *N*-oxides by the action of guanidines (Schemes 122 and 123) <1997S855, 2004SOS(17)357>.



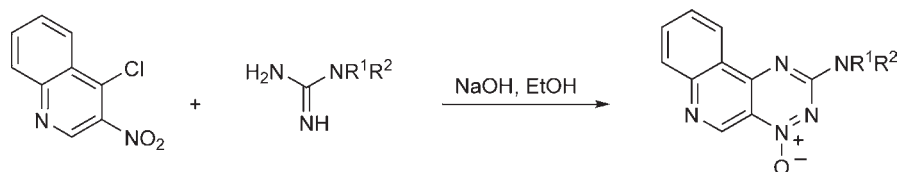
Scheme 120



Scheme 121

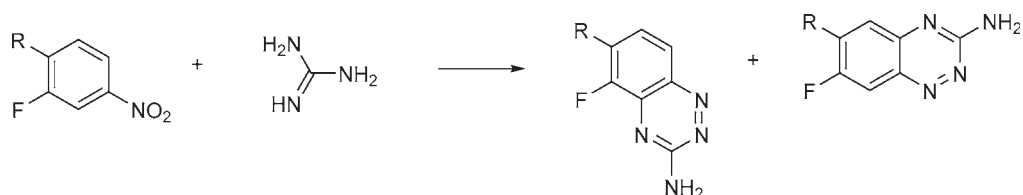


Scheme 122



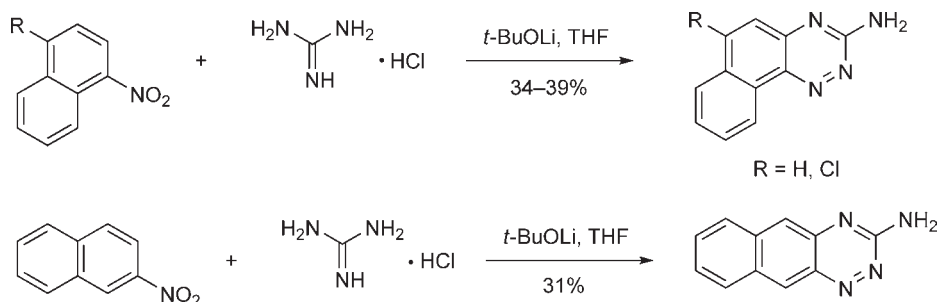
Scheme 123

A recently reported synthesis of 3-amino-1,2,4-benzotriazines is also based on the [3+3] combination of fragments (**Scheme 124**) <2006RCB1243>. The feature of this approach is that in 3-fluoro-substituted nitrobenzenes, nucleophilic displacement of hydrogen at C-2 or C-6 by the action of guanidine takes place, followed by intramolecular cyclization into the isomeric 3-amino-1,2,4-benzotriazines (**Scheme 124**) <2006RCB1243>.

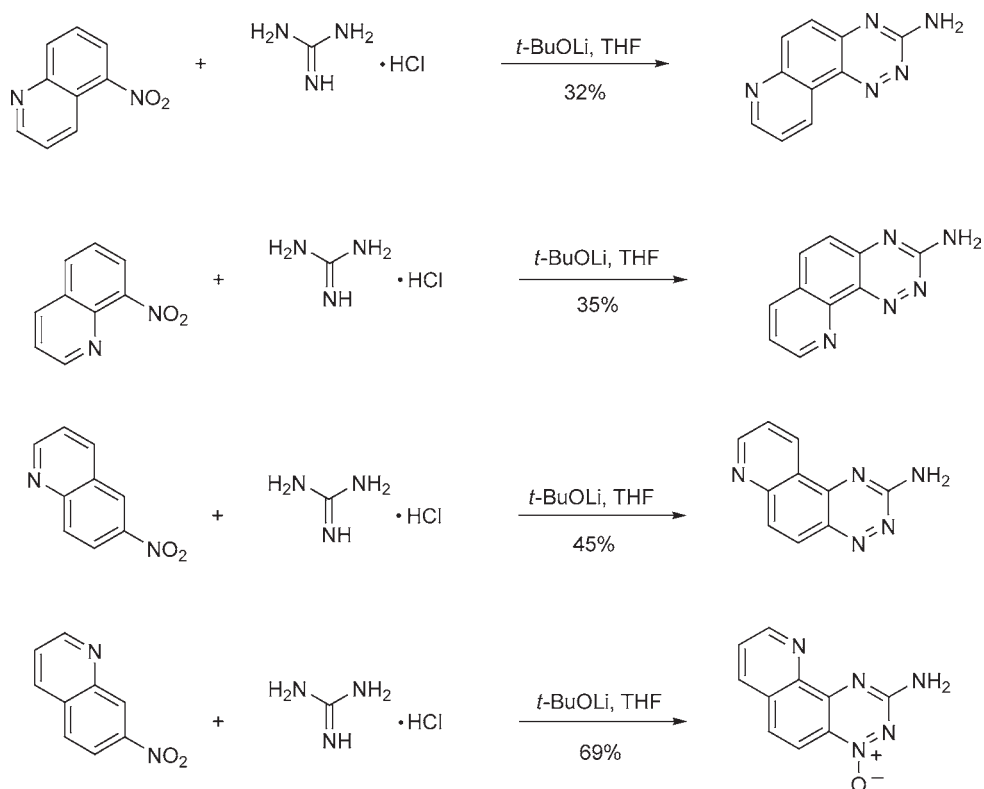


Scheme 124

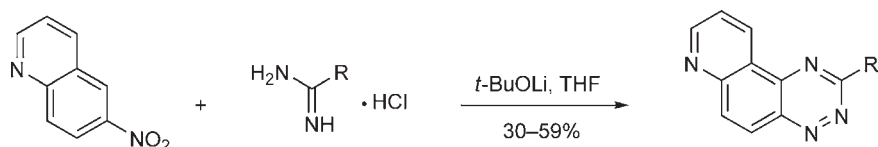
By using the same S_N^H methodology, a series of condensed 1,2,4-triazines have been obtained from the corresponding nitro derivatives of naphthalenes or quinolines (**Schemes 125–127**) <1997S855, 1999JOC3361, 2004SOS(17)357>.



Scheme 125

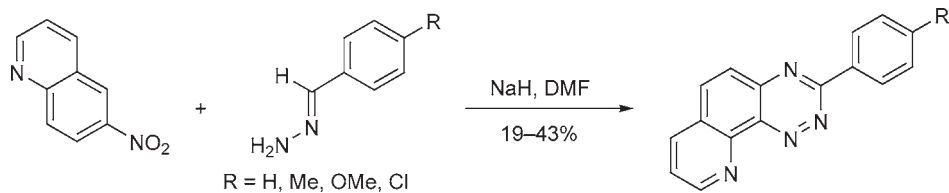


Scheme 126



Scheme 127

Another avenue to condensed 3-aryl-1,2,4-triazino[6,5-f]quinolines is again the $\text{S}_\text{N}^\text{H}$ process accompanied by cyclocondensation of 6-nitroquinoline with the hydrazones of aromatic aldehydes (Scheme 128) <2000OL413, 2002J(P1)696>.



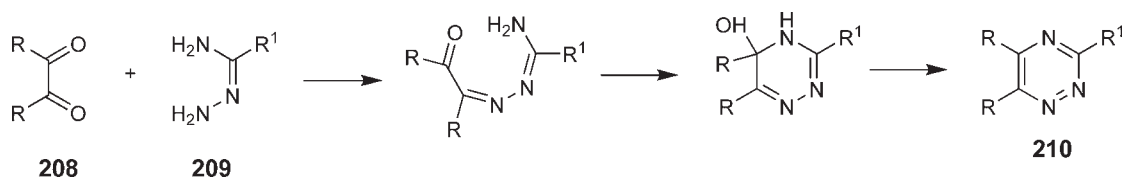
Scheme 128

9.02.7.2 [4+2] Atom Combinations

The formation of the 1,2,4-triazine ring from [4+2] atom fragments appears to be the most frequently used approach, which can be realized through six possible combinations (A–F), as illustrated in Scheme 129.

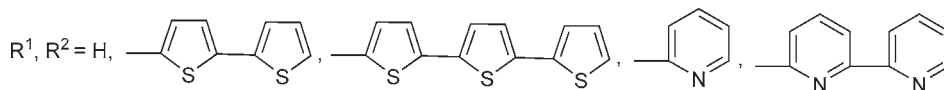
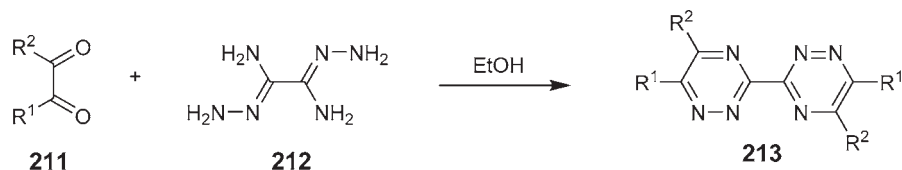


Since the pioneering works of H. Neunhoeffer [<1969TL3147>](#), the reactions of 1,2-dicarbonyl compounds [208](#) with amidrazones [209](#) have been studied thoroughly and have proved to be some of the best synthetic routes to a variety of 1,2,4-triazines [210](#) (**Scheme 130**) [<1997RJO1033, 1998TL6687, 1998TL6691, 1998TL8817, 1998TL8821, 1998TL8825, 1999T5047, 1999T5067, 2001J\(P1\)668, 2003T8489, 2003TL693, 2005TL6111>](#).



Scheme 130

The general character of the reactions is illustrated by their wide application. Indeed, condensation of diamidrazone **212** with α -diketones **211** bearing one or several pyridine or thiophene rings affords the corresponding bis-triazines **213** (Scheme 131) <1998TL8821, 1999T5067>.



Scheme 131

A similar condensation of α -dicarbonyl compounds with a 2,4,6-trisubstituted pyridine bearing three amidrazonyl fragments gave the star-like heterocyclic ensembles **214–218** (Figure 13) <1998TL8817>.

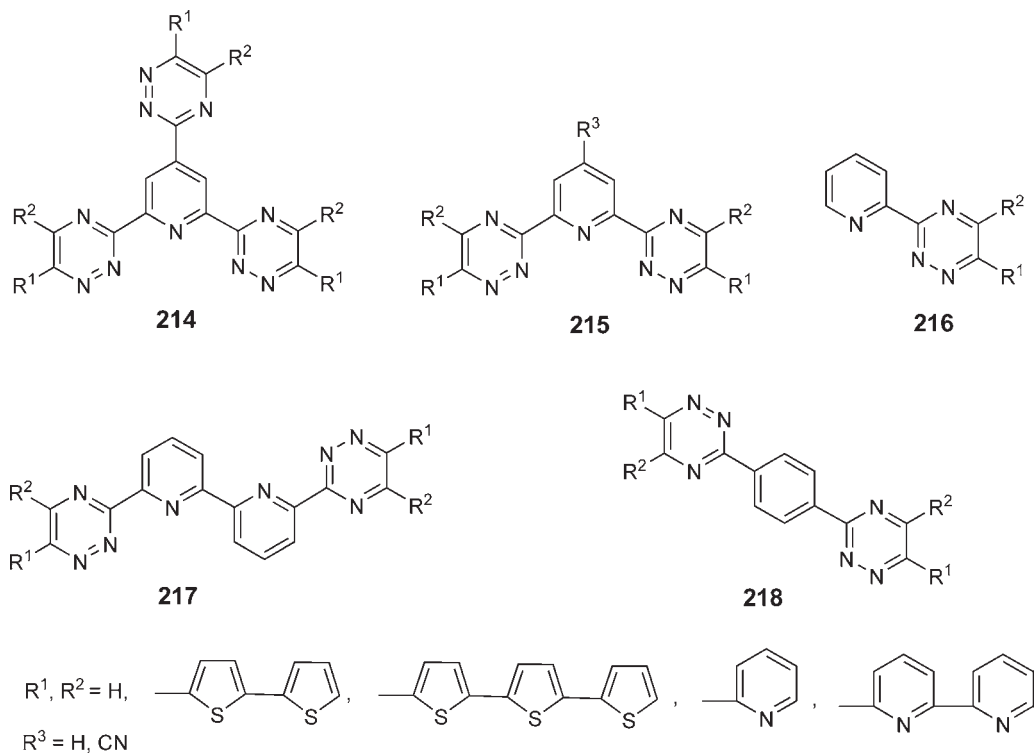


Figure 13

Further, a number of 2,6-bis-(1,2,4-triazinyl)pyridines **215** and related heterocyclic systems **214, 216, 217–221**, based on various combinations of pyridine and 1,2,4-triazine rings, have been obtained from 2-pyridinyl-substituted amidrazones <1998TL6691, 1998TL8825, 1999T5067>, pyridinyl-2,6- <1999T5047>, and 2,2'-dipyridinyl-6,6'-fragments (Figures 13 and 14) <1999T5047, 1998TL6687>.

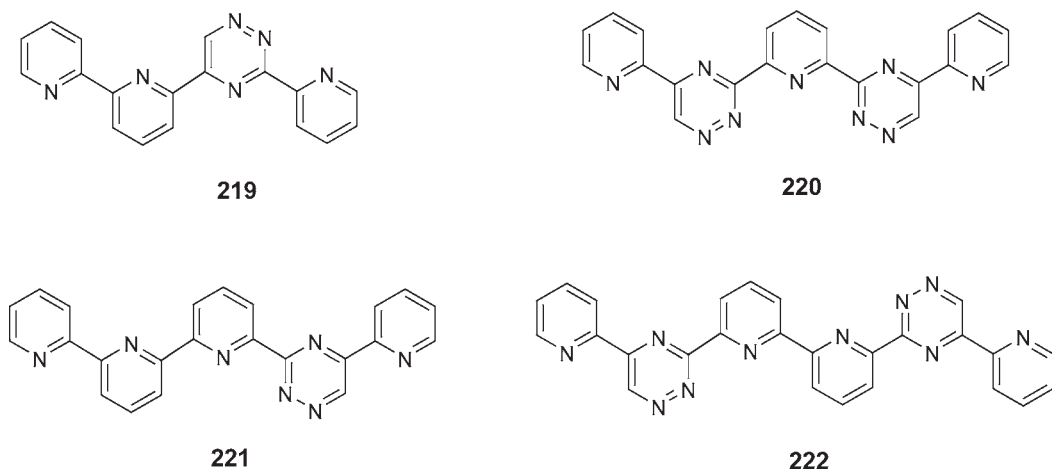
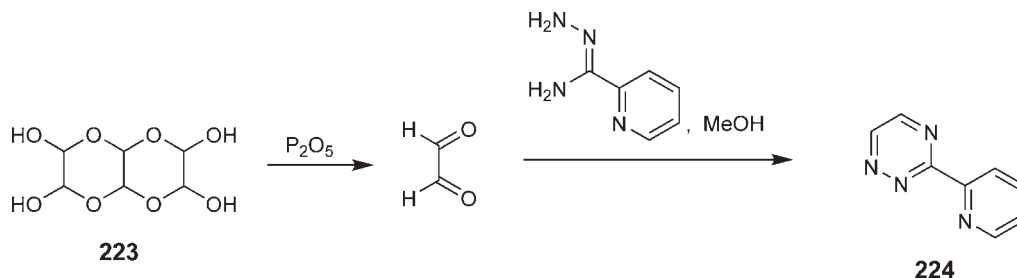


Figure 14

In the synthesis of 3-(2-pyridinyl)-1,2,4-triazine **224**, the trimer of glyoxal **223** proved to be the most appropriate form of the α -dicarbonyl compound <1999EJO313> (Scheme 132).

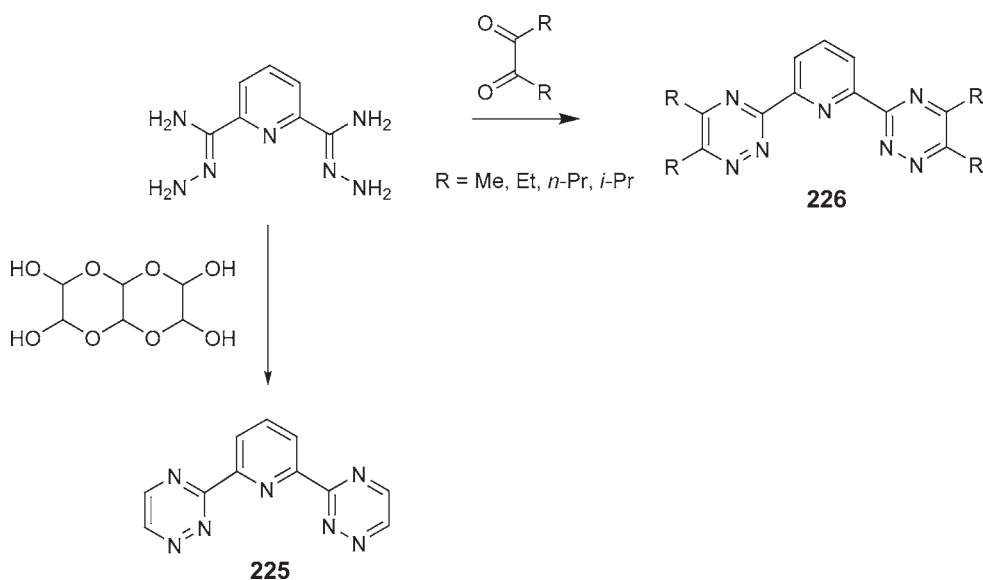


Scheme 132

Indeed, the trimer of glyoxal has been used successfully to obtain 2,6-bis(1,2,4-triazin-3-yl)pyridine **225**, bearing no substituents in the triazine rings <2002ICC596>. The reaction of glyoxal with pyridinyl-2,6 bis-amidrazone has been found to proceed very smoothly on stirring of the reagents in dry methanol at room temperature for 3 h under an argon atmosphere. The series of 2,6-(5,6-dialkyl-1,2,4-triazin-3-yl)pyridines **226** obtained by the use of this procedure are of interest as ligands which are able to give strong complexes with uranium, samarium <2001ICC12>, cerium <2002JCD3265>, thulium <2001ICC12>, ytterbium <2001ICC12>, praeosdymium <2002ICC596>, neodymium <2002ICC596>, and other rare metals. A number of triazines of this series have already found industrial application as effective agents useful for selective extraction of metals on treatment of wastes produced in nuclear power stations <1999MI23, 2000JNST1108, 2001HCC12> (Scheme 133; Figure 15).

Upon reaction with thiosemicarbazide, 4,5-dihydroxyimidazolin-2-ones provide the C-C fragment for the 1,2,4-triazine ring of the imidazo[4,5-*e*]-1,2,4-triazine ring system (Scheme 134) <2006RCB836, 2006RCB865>.

Upon condensation with α -diketones **227**, semicarbazide, thiosemicarbazide, selenocarbazine **228**, or aminoguanidines **229** give rise to the corresponding 1,2,4-triazine 3-ones, 3-thiones, 3-selenone-1,2,4-triazines **230** <2002M79, 2001CHE85, 2002JCO419, 2001J(P1)668, 2002M79, 2002T1525> and 3-amino-1,2,4-triazines **231** <2000CAR515, 2002M79, 2002JCO419, 2003OL2271> (Schemes 135 and 136). Also, 2-aryl-5,5-dimethyltriazolidines, which can be regarded as cyclic forms of semicarbazides, react in an analogous manner <2005BML4363>.



Scheme 133

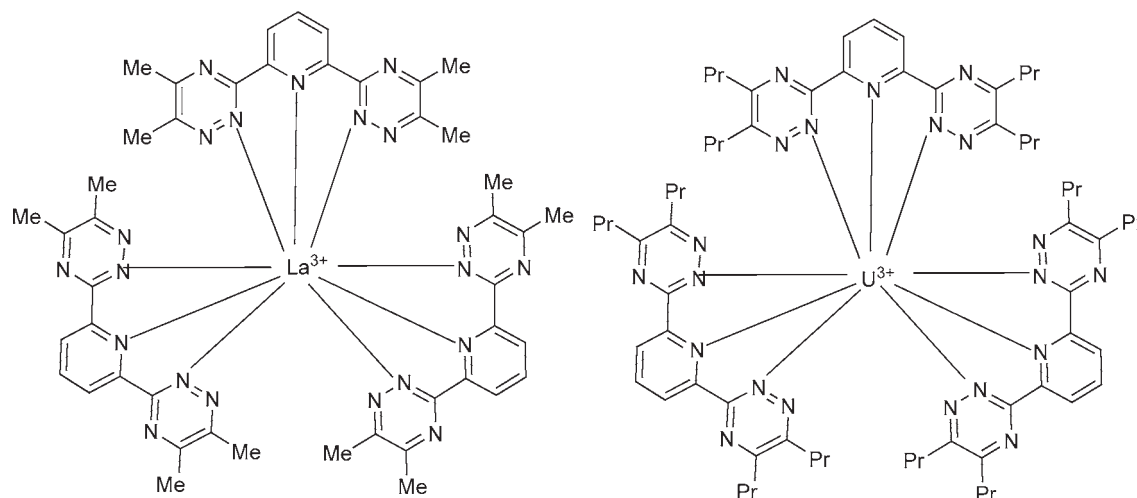
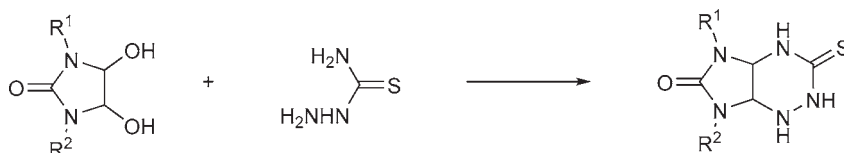
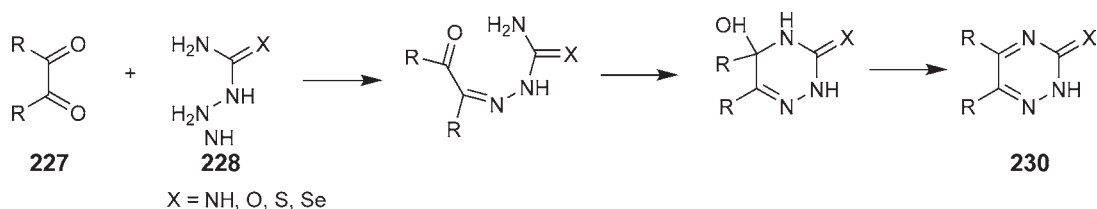


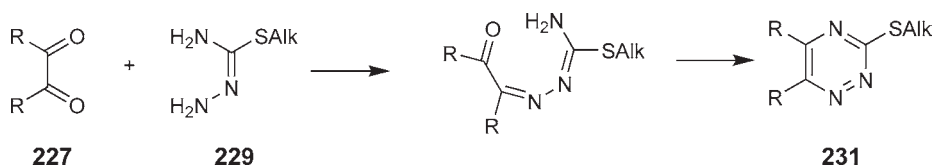
Figure 15



Scheme 134



Scheme 135

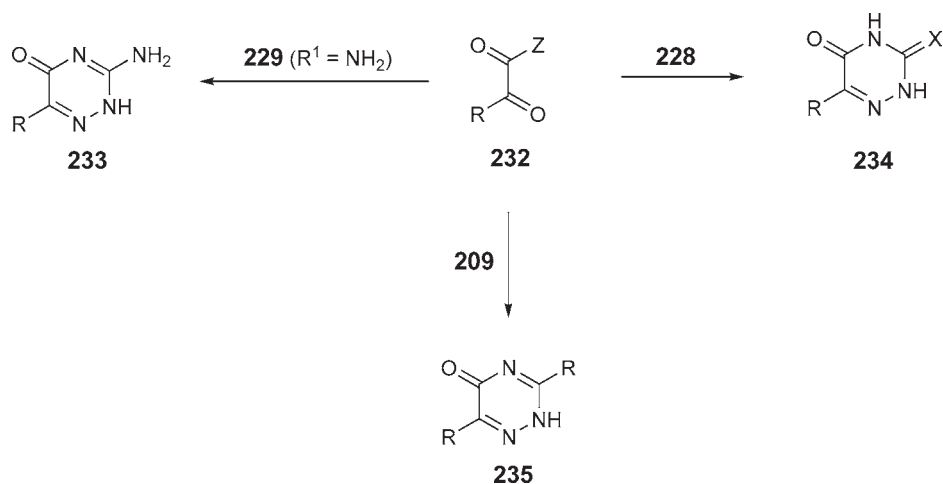


Scheme 136

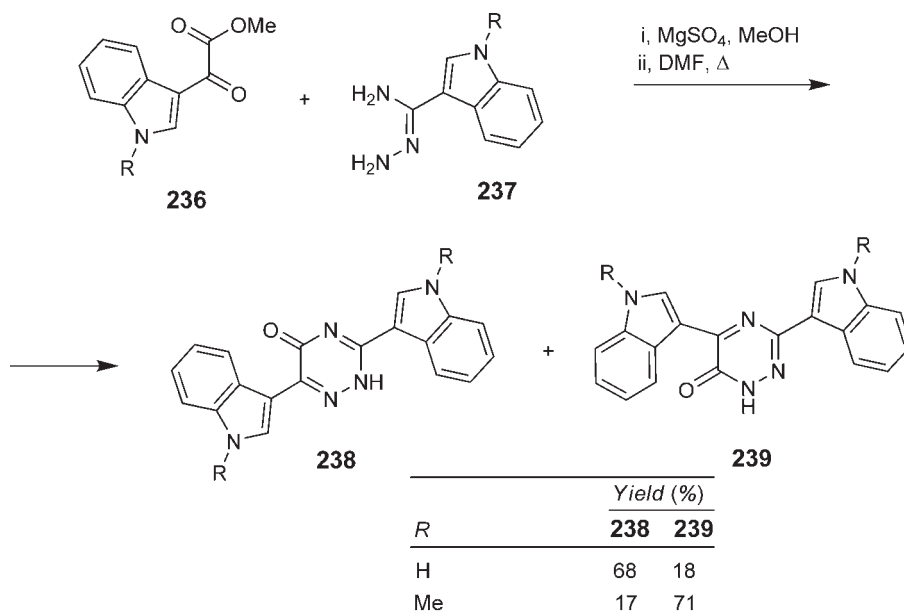
In a similar fashion, the reaction of **227** with alkylthiosemicarbazides results in the formation of 3-alkylthio-1,2,4-triazines **231** (Scheme 136) <2000J(P1)299, 2001J(P1)668>.

α -Oxo derivatives of carboxylic acids and their esters (**232**: $Z = \text{OH}, \text{OR}$) appear to be appropriate building blocks for the synthesis of 1,2,4-triazin-5-ones **233–235** (Scheme 137) <2001KGS1116, 2003TL5657, 2004JHC633, 2005BML4363, 2004JME5482, 2005TL1997, 2005TL4049>.

This process can be illustrated by the synthesis of bis-indolyl-substituted triazines **238** and **239** from indolylamido-drazones **237** and α -indolyl- α -oxoesters **236** <2005TL1997> (Scheme 138).

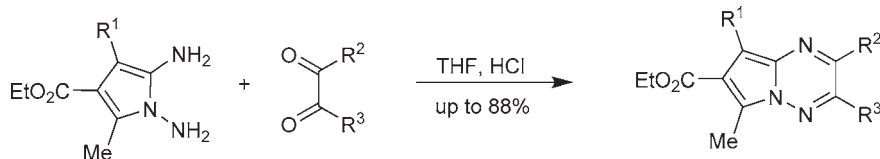


Scheme 137

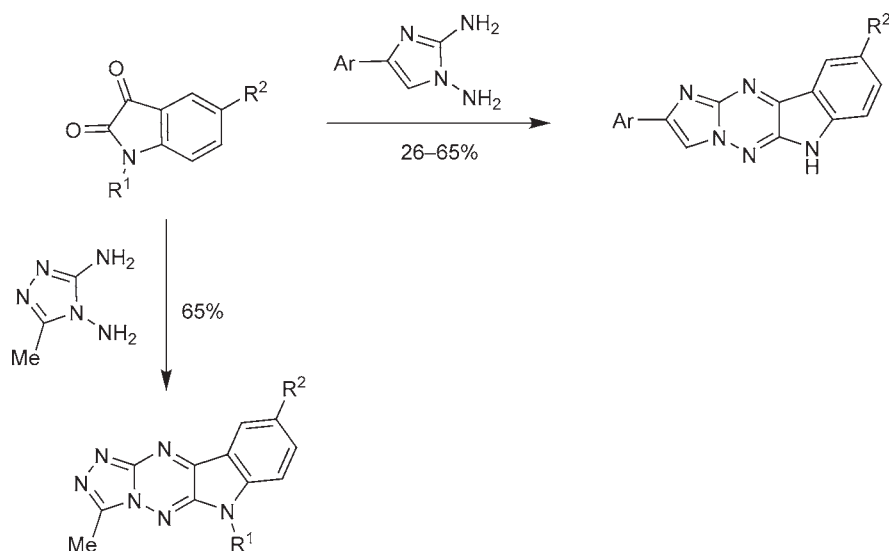


Scheme 138

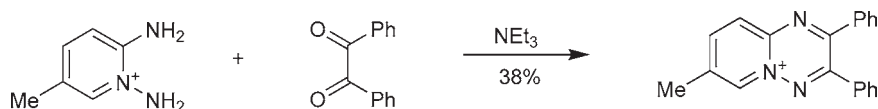
Various modifications of this approach are demonstrated by the synthesis of condensed 1,2,4-triazines from 1,2-dioxo compounds and *ortho*-amino derivatives of *N*-aminoazoles or *N*-aminoazines (Schemes 139–141) <1997J(P1)1829, 2000M487, 2001CPH77, 2002JCO419>.



Scheme 139

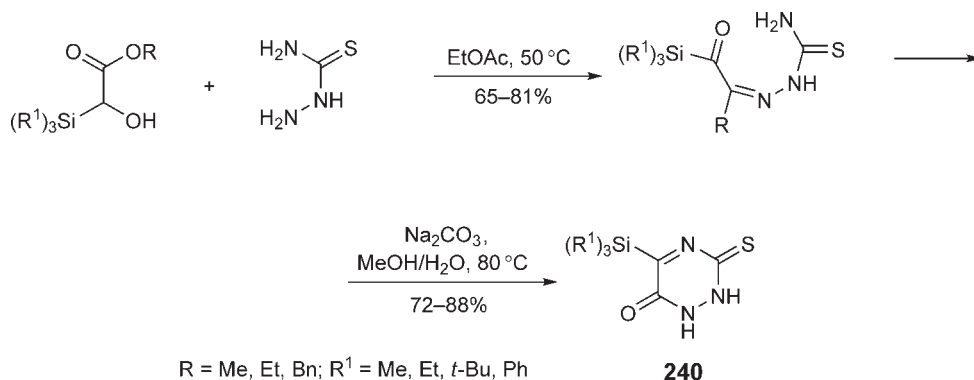


Scheme 140



Scheme 141

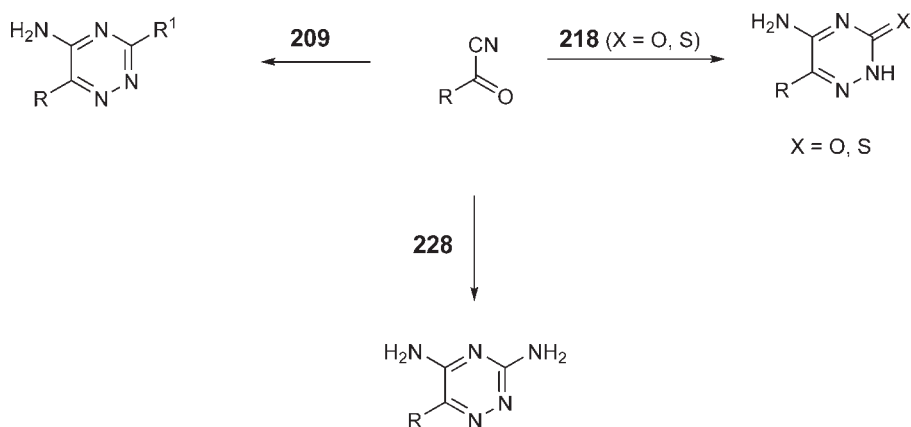
In addition, the synthesis of 5-silyl derivatives of 1,2,4-triazin-6-ones **240** has been performed on the basis of this approach (Scheme 142) <2005TL4049>.



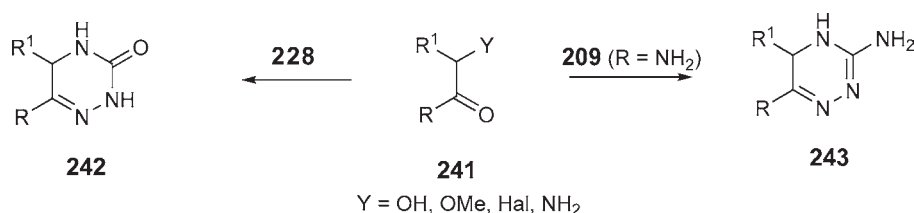
Scheme 142

The reactions of acylcyanides with amidrazones **209**, semicarbazides, thiosemicarbazides **218**, and aminoguanidines **228** result in the formation of 5-amino-1,2,4-triazines <2004SOS(17)357>, 5-amino-1,2,4-triazin-3-ones, the corresponding 3-thiones, and 3,5-diamino-1,2,4-triazines <2003TL5657, 2004SOS(17)357> (Scheme 143).

The reactions of α -hydroxy-, α -methoxy-, α -halo-, and α -amino-substituted α,β -unsaturated ketones **241** ($Z=OH, OMe, Hal, NH_2$) with semicarbazide **218** ($X=O$) or aminoguanidine **228** result in the formation of 2,3,4,5-tetrahydro-1,2,4-triazin-3-ones **242** or 3-amino-2,3,4,5-tetrahydro-1,2,4-triazines **243** (Scheme 144).

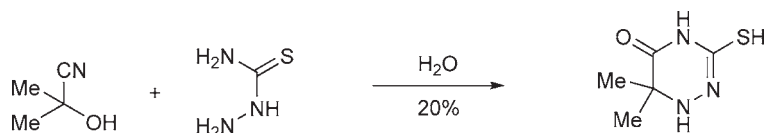


Scheme 143



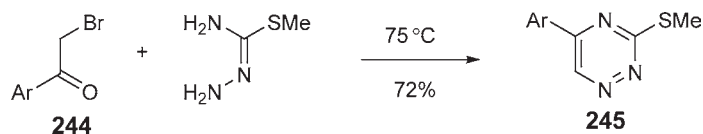
Scheme 144

Additionally, acetone cyanohydrin is an appropriate C–C reagent for the [4+2] condensation with thiosemicarbazide, resulting in 3-mercapto-6,6-dimethyl-1,2,4-triazin-5-one (**Scheme 145** <2002CHE992>).



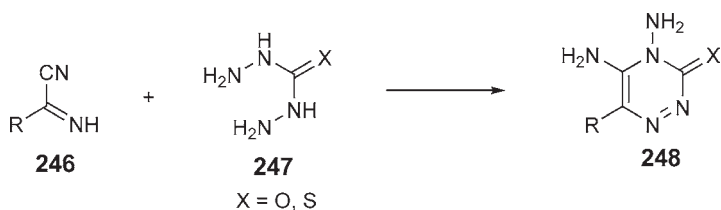
Scheme 145

In the reaction of phenacyl bromides **244** with *S*-methylthiosemicarbazide, nucleophilic amino-debromination is accompanied by condensation of the oxo and hydrazono groups, followed by aromatization into triazines **245** (**Scheme 146** <2004SOS(17)357>).



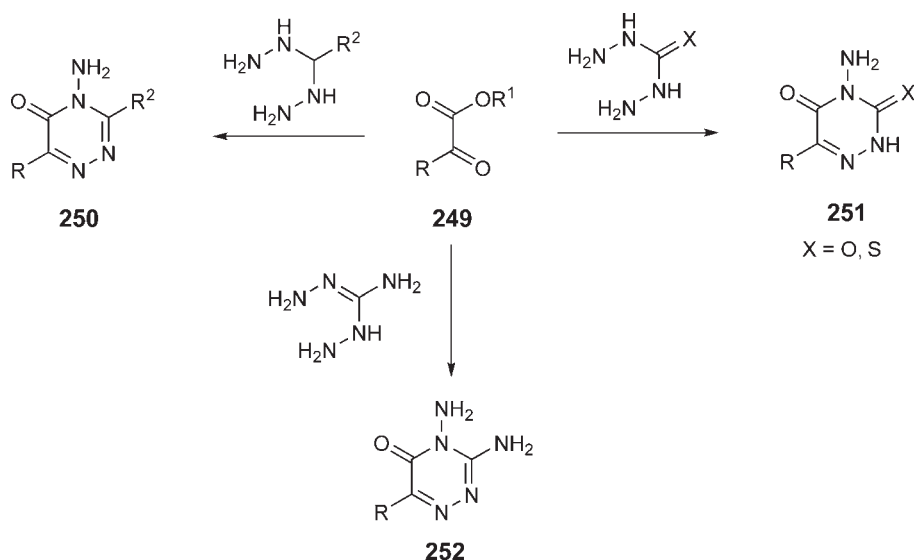
Scheme 146

The [4+2] synthesis of triazines (combination A) can also be based on the use of α -iminonitriles **246**, as the C–C unit, and carbonohydrazide or thiocarbonohydrazide **247** ($\text{X} = \text{O}, \text{S}$), as the N–N–C–N component. This is an attractive avenue to 4,5-diamino-1,2,4-triazin-3-ones **248** <1996CHEC-II(6)507> (**Scheme 147**).



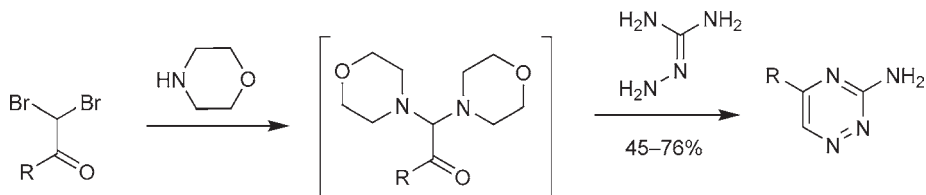
Scheme 147

The approach can be modified slightly by the use of α -keto-substituted acids or their esters **249** instead of α -iminonitriles to obtain triazines **250–252** (Scheme 148).



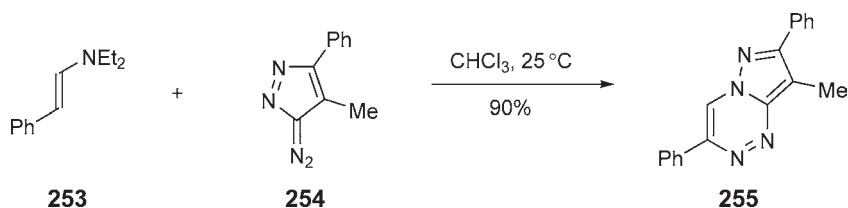
Scheme 148

Ketoaminals, obtained by the nucleophilic displacement of two bromo atoms in α,α -dibromoketones by action of an excess of morpholine, were shown to react regioselectively with aminoguanidine to form 5-substituted-3-amino-1,2,4-triazines (over 95% of the major regioisomer is formed) (Scheme 149) <2003OL2271>.



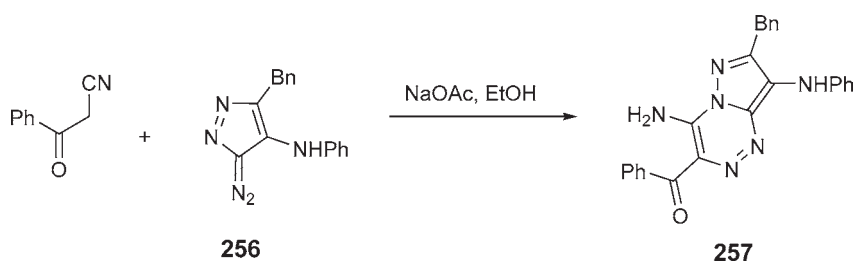
Scheme 149

The cycloaddition reaction between electron-rich enamine **253**, acting as the C–C unit, and 3-diazopyrazole **254**, donating the N–N–C–C fragment, to afford the 1,2,4-triazine ring containing compound **255**, is an example of successful realization of the synthetic approach A (Scheme 150). It is of general character, as illustrated by similar [4+2] cyclizations performed with other diazo-1,2-azoles and enamines or alkynamines, as the C–C components <1997S556, 1998EJM237, 2004SOS(17)357, 2004BML5013>.



Scheme 150

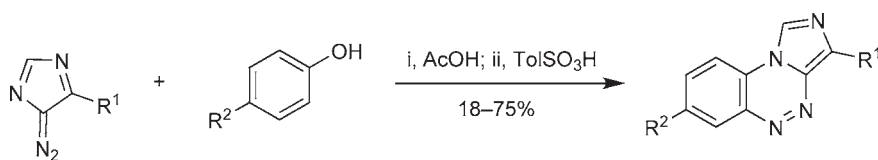
Additionally, a number of azolo-1,2,4-triazines have been prepared by reacting diazo-1,2-azoles with malononitrile <1997JCM392, 1998JCM632, 1999HAC385, 1997JCM392, 2001IJB284>, cyanomethyl ketones <1999HAC385, 1998CHE702>, cyanomethyl esters <1997JCM198, 1997JCM392, 1998JCM632, 1998KGS805, 1998CHE702>, cyanomethyl carboxamides <1998JCM632, 1998CHE702>, cyanomethyl benzimidazoles <1997JCM392, 1999RJO1355>, and cyanomethyl thiazoles <2000JCM206>. For instance, 3-diazopyrazole **256** reacts with 3-oxo-3-phenylpropionitrile to form the corresponding pyrazolotriazine **257** in 76% yield (Scheme 151) <1998HAC571>.



Scheme 151

The reaction of diazoazoles with nitro-substituted acetonitriles, as well as ethyl nitroacetate, takes place in a similar manner <1996RJO770, 1997MI103, 2001SC2351>.

Further, condensed 1,2,4-benzotriazines have been obtained by the reaction of diazoazoles with phenols or naphthols <1997JCM198, 2000CHE465>, as illustrated by the synthesis of benz[e]imidazo[5,1-*c*][1,2,4]-triazines <2000CHE465> (Scheme 152).



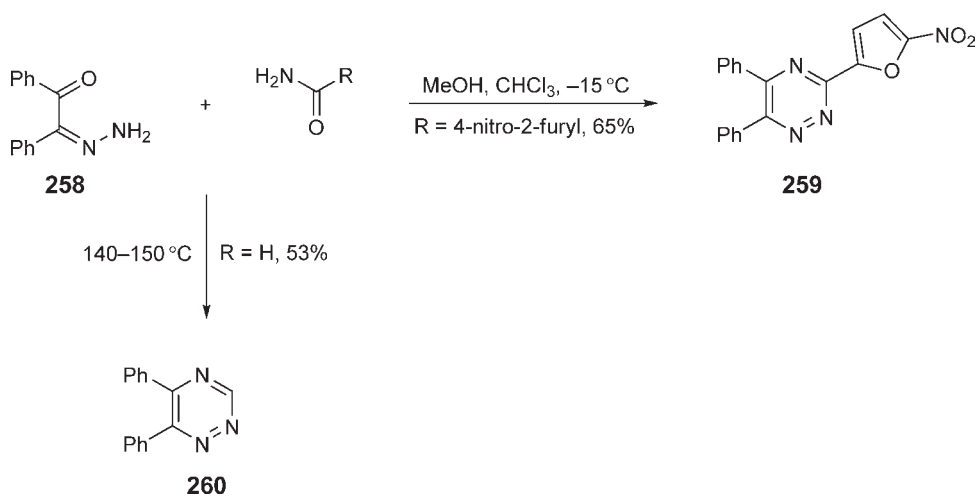
Scheme 152

9.02.7.2.2 Combination B (N(1)N(2)C(5)N(6) + C(3)N(4))

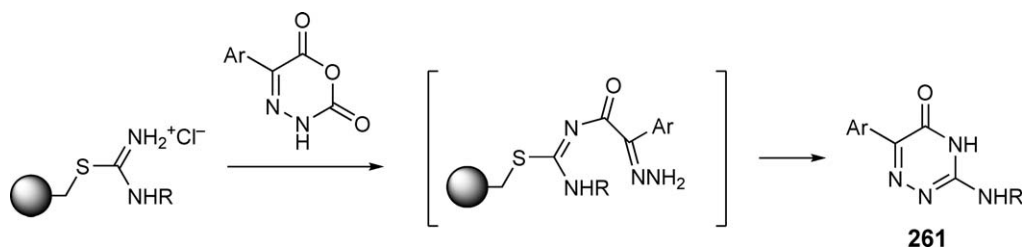
1,2,4-Triazines **259** and **260** can be obtained through combination of N–N–C–C and C–N fragments, for instance, by reacting 2-hydrazono ketones **258** with amides <1984CHEC-I(2)385, 1996CHEC-II(6)507, 2003JOC4345, 2004SOS(17)357> (Scheme 153).

Additionally, isothiuronium chloride attached to a polymer matrix donates the C–N fragment for the 1,2,4-triazine ring in a solid-phase reaction with 2,3-diaza-3-pentenedionic anhydride to give 3-amino-1,2,4-triazinones **261** in 50–74% yields (Scheme 154) <2001TL4433>.

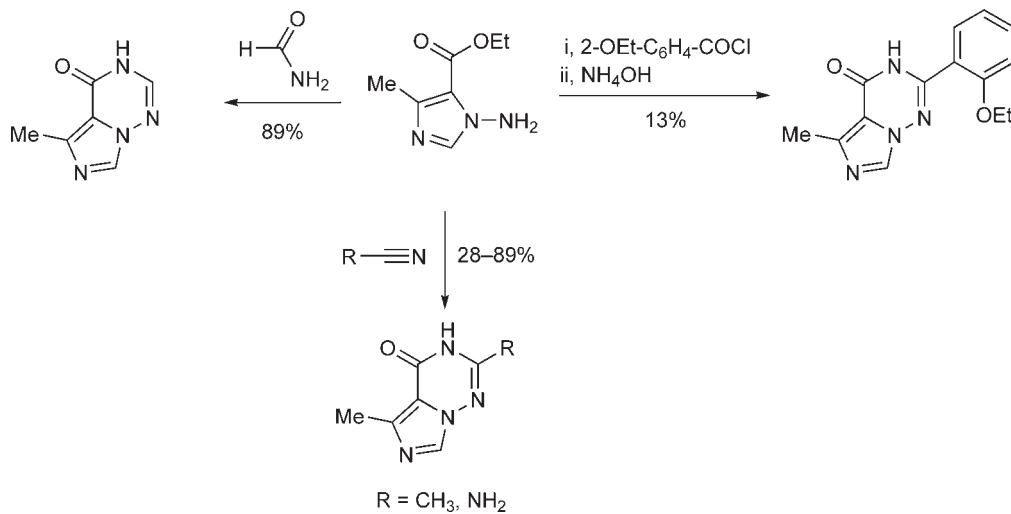
A number of isosteres of purines in the series of imidazo[5,1-*f*]-1,2,4-triazines have been obtained through the [5+1] synthetic approach, starting from ethyl 1-aminoimidazole 5-carboxylate by the action of various reagents which can donate a C–N fragment (Scheme 155) <2005JOC7331>.



Scheme 153

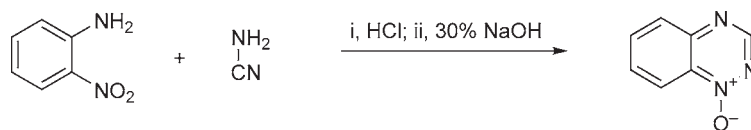


Scheme 154



Scheme 155

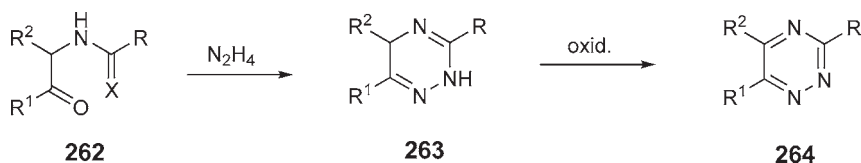
Cyclization of *ortho*-nitroaniline with cyanamide demonstrates a simple synthetic approach to benzo[*e*]-1,2,4-triazine 1-oxides (Scheme 156) <2002TL9569>.



Scheme 156

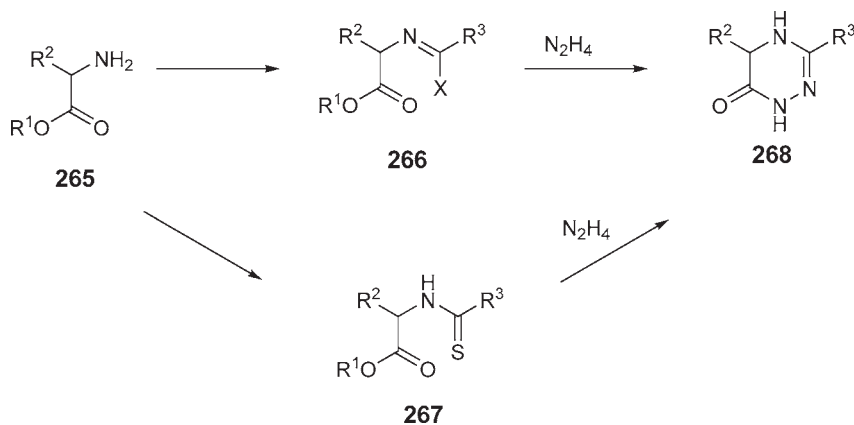
9.02.7.2.3 Combination C (C(3)N(4)C(5)C(6) + N(1)N(2))

The approach C, which is based on combination of C–N–C–C and N–N fragments, appears to be a rather common avenue to 1,2,4-triazines, as illustrated, for instance, by the reaction of α -acylamino- or α -thioacylamino-substituted ketones **262** ($\text{X}=\text{O}, \text{S}$) with hydrazine to form dihydro-1,2,4-triazines **263**, followed by their oxidation into aromatic derivatives **264** (Scheme 157) <2004MI49>.



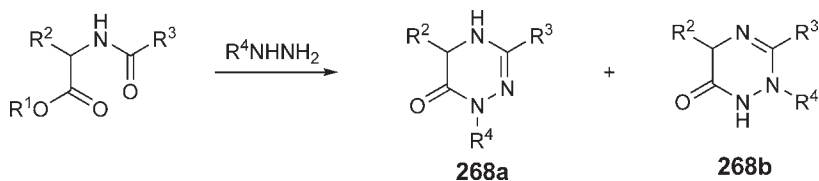
Scheme 157

In order to obtain 4,5-dihydro-1,2,4-triazin-6-ones **268**, α -amino-substituted alkyl carboxylates **265** were transformed into the corresponding imidates **266** ($\text{X}=\text{OR}$), amidines **266** ($\text{X}=\text{NR}_2$), chloroformamidines **266** ($\text{X}=\text{Cl}$), or thioacyl aminoacids **267**, followed by condensation with hydrazine or substituted hydrazines (Scheme 158) <1999AJC379, 2000JFC83, 2001TL6455, 2002RJO602, 2002TL8165, 2003TL459, 2004BML2323>.



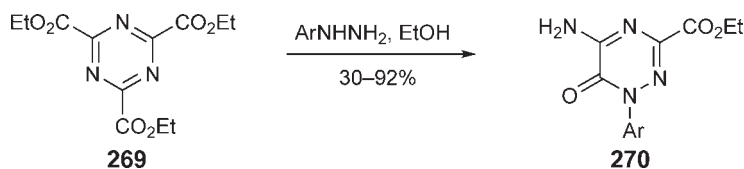
Scheme 158

Interaction of α -acylamino-substituted alkyl carboxylates with substituted hydrazines leads to regioisomeric products **268a** and **268b** in a ratio that is dependent on the nature of the substituents (Scheme 159) <1999AJC379, 2000JFC83, 2001TL6455>.



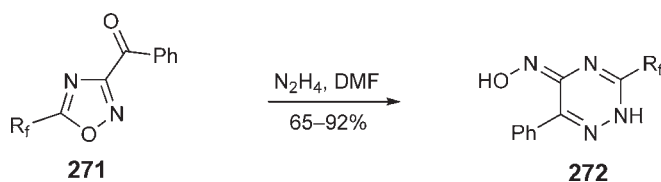
Scheme 159

It is worth noting that the C–N–C–C fragment can be derived from heterocyclic compounds. For instance, interaction of triethyl 1,3,5-triazine-2,4,6-tricarboxylate **269** with arylhydrazines affords esters of 5-amino-6-oxo-1,6-dihydro-1,2,4-triazin-3-carboxylic acid **270** in good yields (Scheme 160) <2004TL2791>.

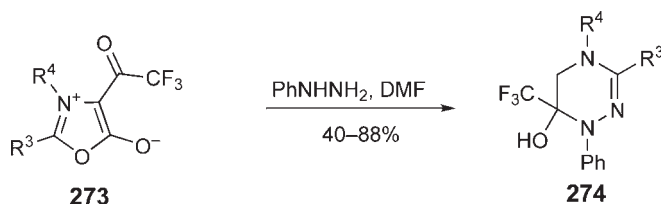


Scheme 160

The reaction of 3-benzoyl-1,2,4-oxadiazoles **271** with hydrazine affords 1,2,4-triazines **272** <2005JOC3288> (Scheme 161), while, on treatment of mesoionic trifluoroacetyl-1,3-oxazolyl-3-olate **273** with phenylhydrazine, 1,4,5,6-tetrahydro-6-trifluoromethyl-1,2,4-triazine **274** is formed (Scheme 162) <1998TL663>.

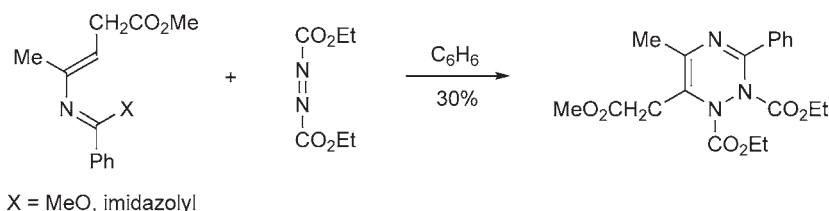


Scheme 161



Scheme 162

The cycloaddition reaction between diethyl azodicarboxylate and 1,3-azadienes affords the corresponding 1,2-dihydro-1,2,4-triazines (Scheme 163) <1999JOC49>.



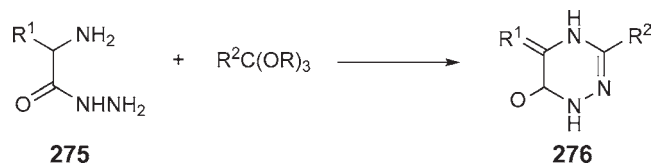
Scheme 163

9.02.7.3 [5+1] Atom Combinations

This atom combination is usually applied to incorporate either C-3 or N-4 atoms into the forming 1,2,4-triazine ring, as followed from the data presented in CHEC(1984) <1984CHEC-I(2)385> and CHEC-II(1996) <1996CHEC-II(6)507>. Some recent examples of [5+1] syntheses are discussed in the next sections.

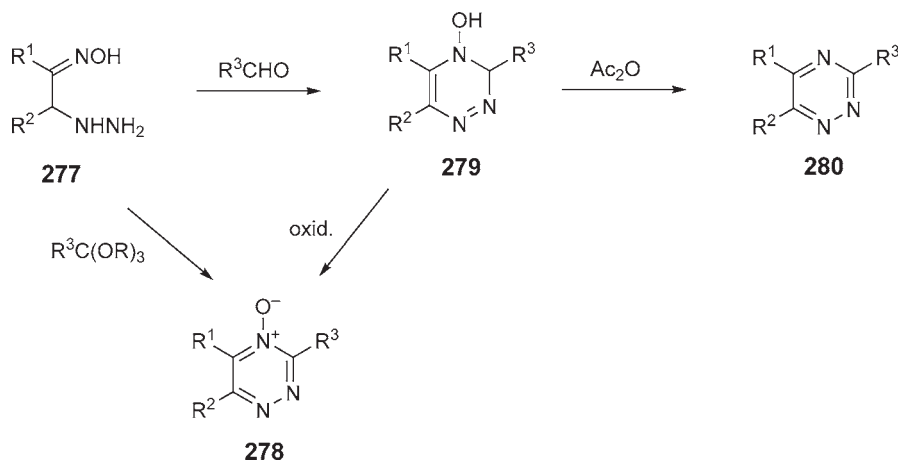
9.02.7.3.1 C-3 as the one-atom fragment

The reaction of α -aminoacyl hydrazides **275** with orthoesters appears to be a simple method to obtain 1,4,5,6-tetrahydro-1,2,4-triazine-6-ones **276** <1996CHEC-II(6)507, 1996M557> (Scheme 164).



Scheme 164

Further, cyclization of α -hydrazinoximes **277** with orthocarboxylates or aldehydes is a useful synthetic avenue to 1,2,4-triazine 4-oxides (Scheme 165) <1996CHEC-II(6)507, 1997MC238, 1998RJO393, 2002AHC(82)261, 2002MC30, 2003JOC2882, 2002TL4923, 2004RCB1295, 2004SOS(17)357, 2005TL1791>. For instance, interaction of oximes **277** with aldehydes affords 4-hydroxy-3,4-dihydro-1,2,4-triazines, which are formally related to the σ^H -adducts **279**, derived from nucleophilic addition reactions on the 1,2,4-triazine ring. Oxidative aromatization of the dihydro derivatives results in the formation of 1,2,4-triazine 4-oxides **280**, while treatment of **279** with acetic anhydride leads to compounds **280** <1997MC238, 1998RJO393, 2002AHC(82)261, 2002MC30, 2003JOC2882>.



Scheme 165

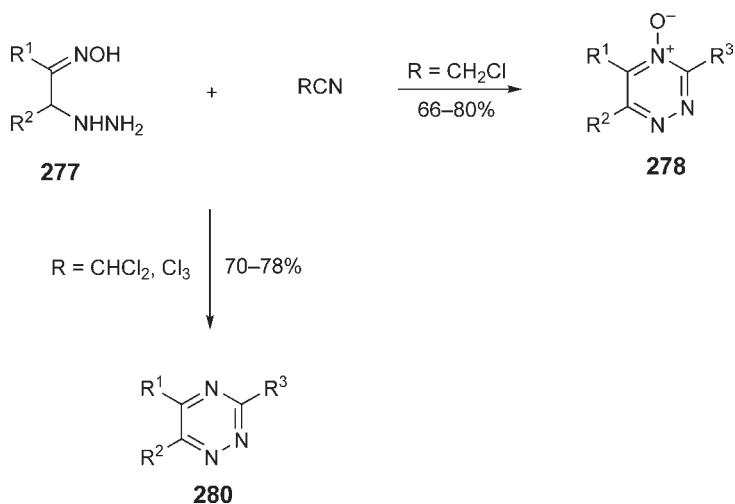
α -Hydrazinoximes **277** react with chloroacetonitrile to form 1,2,4-triazine 4-oxides **278**, while the reaction of **277** with dichloro- and trichloro-substituted acetonitriles affords 1,2,4-triazines **280** (Scheme 166) <2004RCB1295>.

Another example of successful use of the [5+1] approach is the reaction of 2-arylhydrazonocynoacetamides with triethyl orthoformate, which affords either 2,3,4,5-tetrahydro-1,2,4-triazin-5-ones or 2,5-dihydro-1,2,4-triazin-5-ones (Scheme 167) <1998CHE1444, 2000CHE1066, 2000JCM1367>.

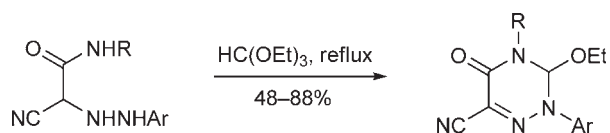
Heterocyclic hydrazides **281** react with orthoesters to form dihydropyrrolo[1,2-*d*]- and thiazolo[3,4-*d*]-1,2,4-triazines **282** with incorporation of the N–N–C–C–N fragment into the 1,2,4-triazine ring (Scheme 168) <1998BMC349>.

The N–N–C–C–N fragment may be a part of a heterocyclic system. Indeed, the reaction of 2,4-diamino-6-hydrazino-5-nitrosopyrimidine with 1,1-diethoxy-2-chloroethane affords the condensed system of pyrimido[5,4-*e*]-1,2,4-triazines (Scheme 169) <2003BML2895>.

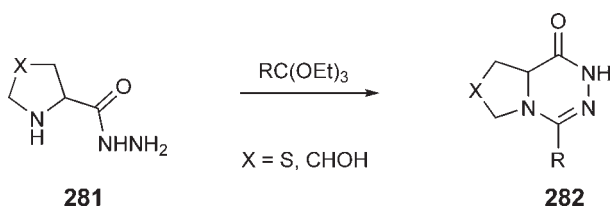
Orthoesters can be used for the synthesis of condensed 1,2,4-triazines, provided the appropriate N–N–C–C–N fragment with terminal amino groups is donated by another reactant. For instance, 1-amino-5-arylaminomethyl-1,2,3-triazoles **283** were shown to react with triethyl orthoformate to give the intermediate dihydro compounds **284**, which can be oxidized with cerium(IV) ammonium nitrate into the corresponding triazolo[5,1-*f*][1,2,4]-triazine **285**. It is worth noting that aromatization of **284** is accompanied by elimination of the *N*-aryl group (Scheme 170) <1996JHC599>.



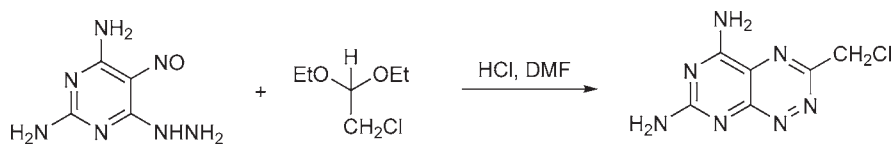
Scheme 166



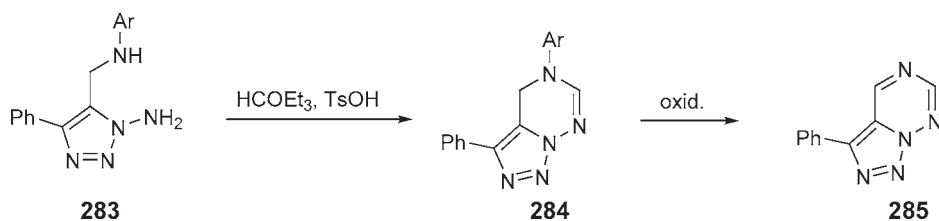
Scheme 167



Scheme 168

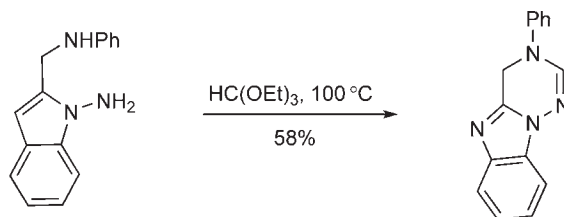


Scheme 169



Scheme 170

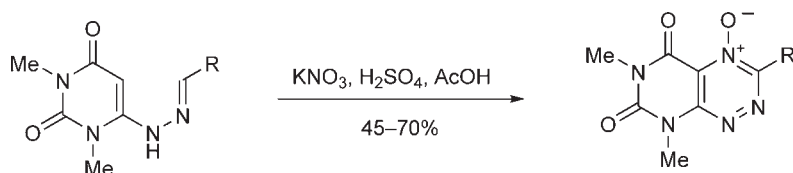
A similar cyclization has been found to occur when 1-amino-2-phenylamino-methylbenzimidazole reacts with triethyl orthoformate to yield a benzimidazo[2,1-*f*][1,2,4]triazine (**Scheme 171**) <2003CHE819>.



Scheme 171

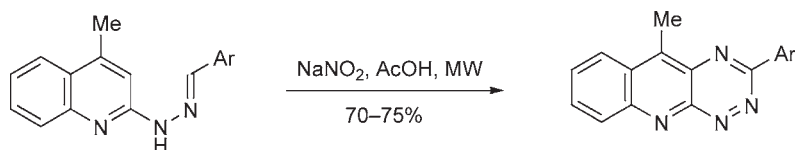
9.02.7.3.2 N-4 as the one-atom fragment

Condensed 1,2,4-triazines can also be obtained by incorporating the N-4 nitrogen atom into the forming 1,2,4-triazine, as exemplified by the reaction of uracil hydrazones with nitronium or nitrosonium cations (**Scheme 172**) <1999M819, 2004SOS(17)357>.



Scheme 172

Use of the microwave technique facilitates condensation of 2-hydrazinoquinolines with aromatic aldehydes, as well as a subsequent nitrosation reaction which takes place, thus leading to 3-aryl-5-methylquinolino[3,2-*e*][1,2,4]triazines in 70–75% yields (**Scheme 173**) <1998IJB1063>.



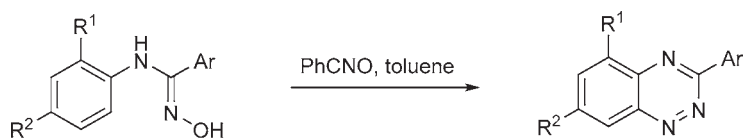
Scheme 173

The reaction of arylbenzamidoximes with nitrile oxides is also an approach to 1,2,4-triazines, although yields are rather low (**Scheme 174**) <1997T1089>.

9.02.7.4 [6+0] Atom Combinations

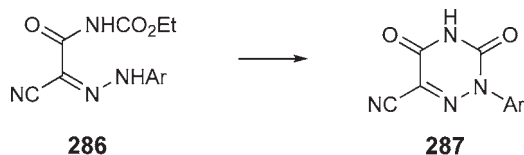
There are several types of intramolecular cyclizations in which the 1,2,4-triazine skeleton is obtained due to the formation of a new C–N bond. For instance, the cyclization of hydrazones of cyanoacetyl carbamates **286** takes place under basic conditions, thus leading to azauracils **287** (**Scheme 175**) <2001JHC1465, 2002JHC357, 2005ARK30, 2005JME2167>.

Upon reflux in dioxane, oxohydrazones are transformed into alkyl 5-hydroxy-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-carboxylates in good yields <2001JOC2820>.



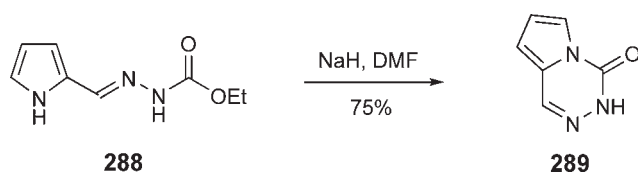
R^1	R^2	Ar	Yield (%)
H	H	Ph	3
H	H	4-Tol	4
Me	H	Ph	18
OMe	H	Ph	31
Me	Me	Ph	20
Me	Me	4-Tol	20
Cl	OMe	Phl	20

Scheme 174



Scheme 175

Hydrazones of pyrrole-2-carboxaldehyde **288**, containing the fragment N-C-C-N-N-C, are appropriate substrates for the [6+0] synthesis of 1,2,4-triazines **289** through base-induced intramolecular C₃-N₄ bond formation (Scheme 176) <1997T13703>.

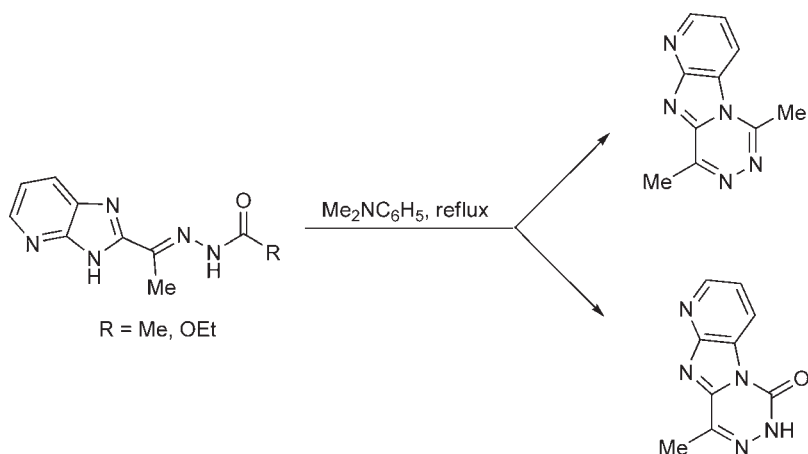


Scheme 176

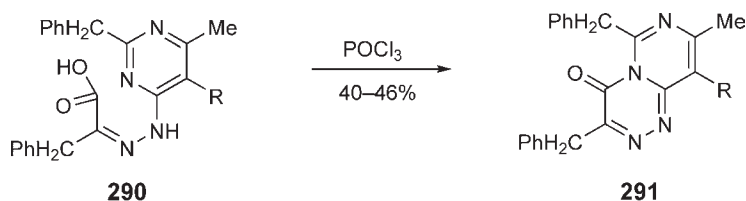
The same pattern of C₃-N₄ bond formation is observed in the intramolecular [6+0] cyclization of hydrazones of imidazo[4,5-*b*]pyridine-2-carboxaldehyde (Scheme 177) <2002CHE828>.

Another pattern for the synthesis of 1,2,4-triazines from [6+0] fragments is the intramolecular C₆-N₁ bond formation which takes place in the intramolecular cyclization of hydrazones **290** derived from the reaction of 2-benzyl-4-hydrazino-substituted pyrimidines and phenylpyruvic acid. The cyclization proceeds smoothly by the action of phosphorus oxychloride and results in pyrimido[6,1-*c*][1,2,4]triazines **291** (Scheme 178) <2000CHE185>.

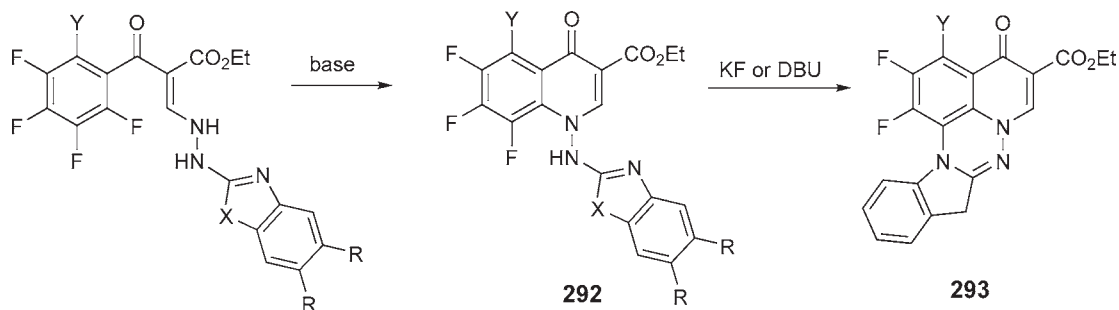
An intramolecular amino-defluorination reaction at C-8 in the N-amidino-substituted quinolones **292**, activated by acetic anhydride, affords tricyclic compounds **293** with the [5,6,1-*i,j*]-annulation of the triazine ring relative to the quinoline system through the N₄-C₅ bond formation (Scheme 179) <1997MC109, 2001JFC25, 2002RCB663, 2006HAC579>.



Scheme 177



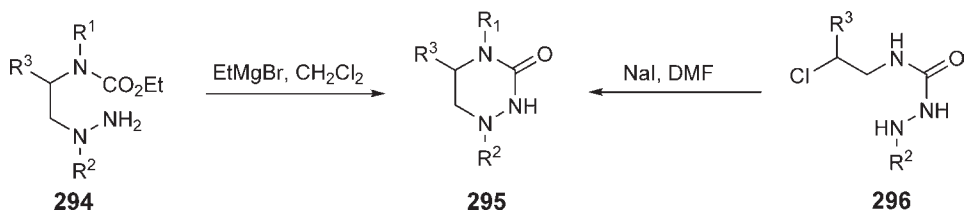
Scheme 178



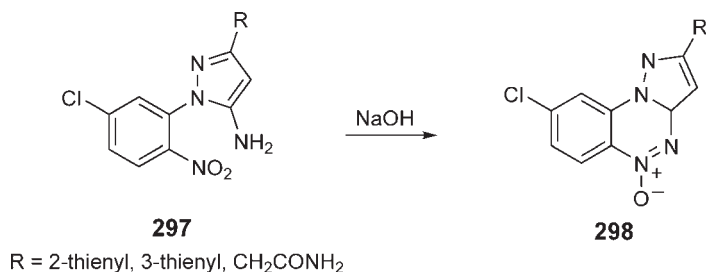
Scheme 179

It is interesting to note that hexahydro derivatives of 1,2,4-triazin-3-one **295** can be obtained by two methods: (1) from hydrazinoethylcarbamates **294**, through the $\text{N}_2\text{--C}_3$ bond formation, or (2) starting from *N*-(2-chloroethyl)-aminocarbonyl-substituted hydrazines **296** through the intramolecular formation of the $\text{C}_6\text{--N}_1$ bond (Scheme 180) <1996JME3938>.

A few papers report on use of the $\text{N}_1\text{--N}_2$ bond formation for closure of the 1,2,4-triazine ring. For instance, pyrazolo[5,1-*c*]-1,2,4-triazine 5-oxides have been obtained through the intramolecular cyclization of 1-(2'-nitroaryl)-5-aminopyrazoles under alkaline conditions (Scheme 181) <1996EJM259, 1997S556, 1999JME2218, 2004SOS(17)357>.

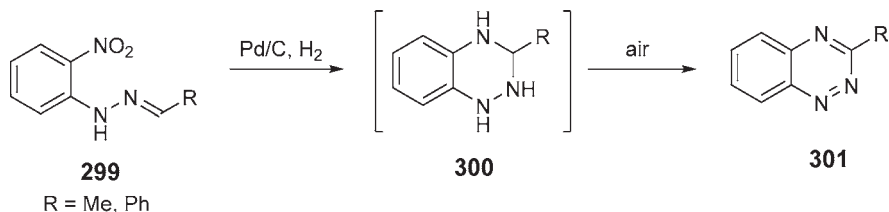


Scheme 180



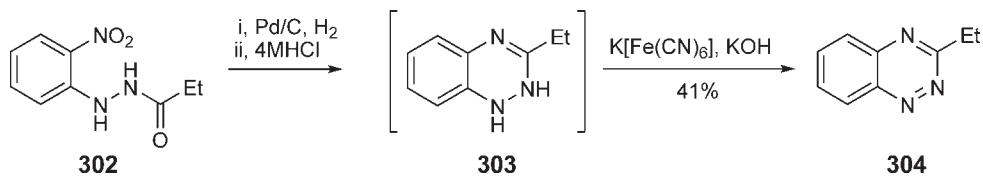
Scheme 181

Hydrogenation of 2-nitrophenylhydrazones **299** on palladium on carbon results in the formation of the tetrahydro-1,2,4-benzotriazines **300**, which are oxidized by air oxygen to give the corresponding aromatic compounds **301** (Scheme 182) <1999JHC589, 2004SOS(17)357>.



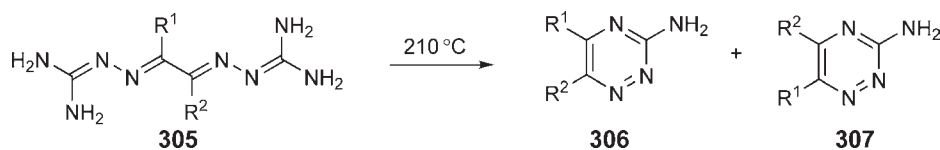
Scheme 182

In a similar manner, reduction of the nitro group in the N_2 -(*ortho*-nitrophenyl)-substituted hydrazide **302** of propionic acid provides, by intramolecular cyclization of the intermediate amino compound, the 1,2-dihydro-1,2,4-benzotriazine **303** followed by oxidation of the latter with potassium hexacyanoferrate to give 3-ethyl-1,2,4-benzotriazine **304** (Scheme 183) <1997J(P1)3107, 2004SOS(17)357>.



Scheme 183

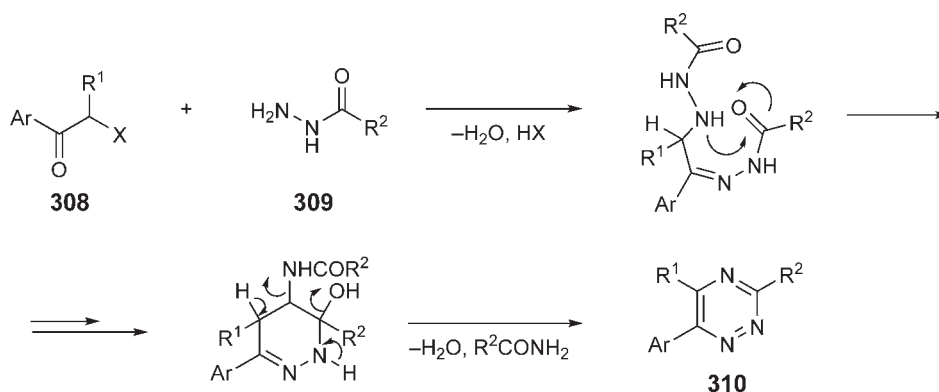
Heating of bis-hydrazones of glyoxal and aminoguanidine, viz. **305**, leads to isomeric 3-amino-1,2,4-triazines **306** and **307** (Scheme 184) <2004MI49-2>.



Scheme 184

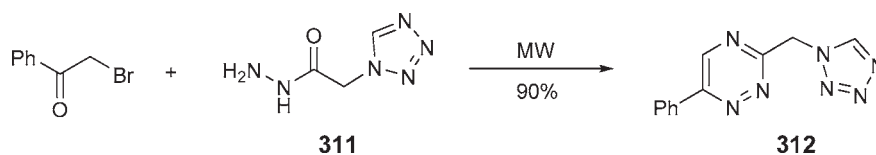
9.02.7.5 [3+2+1] Atom Combinations

A convenient method for the synthesis of 1,2,4-triazines **310** is the reaction of phenacyl halides **308** with 2 equiv of acylhydrazides **309**, which takes place in the presence of acetic acid (Scheme 185). It is noteworthy that, in this reaction, one molecule of acylhydrazide donates the C–N–N fragment while another one provides only one nitrogen atom <1996CHEC-II(6)507, 2004SOS(17)357, 2003SC11, 2004JOC7171>.



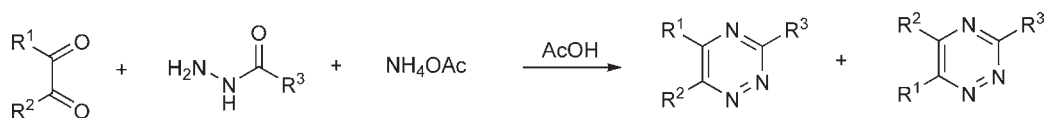
Scheme 185

In a similar manner, a microwave-assisted reaction between phenacyl bromide and acylhydrazide **311** affords a high yield of the corresponding 1,2,4-triazine **312** in a few minutes, as shown in Scheme 186 <2003SC11>.



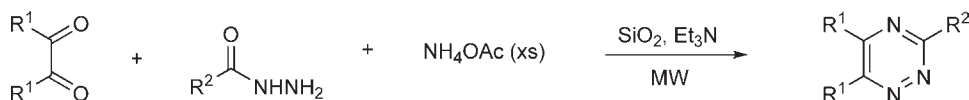
Scheme 186

Another version of the three-component [3+2+1] approach to 1,2,4-triazines is the use of the condensation of 1,2-dicarbonyl compounds with acylhydrazides and ammonia or ammonium acetate, as shown in Scheme 187 <1996CHEC-II(6)507, 2001CHE85, 2001SC1639, 2002SC1899, 2003SC11, 2003TL1123, 2003TL4495, 2004SOS(17)357>.



Scheme 187

Again, use of the microwave technique enables one to change reaction times from hours to minutes and to improve yields of 1,2,4-triazines (Scheme 188; Table 16) <2003TL1123, 2004SOS(17)357>.



Scheme 188

Table 16 Microwave-assisted condensations of 1,2-dicarbonyl compounds with acylhydrazides and ammonium acetate

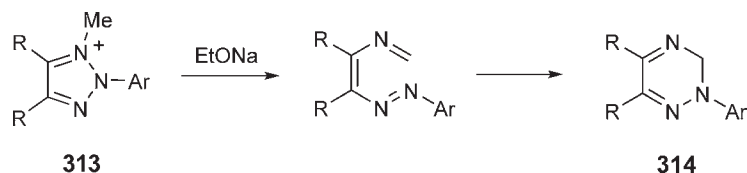
R ¹	R ²	Yield (%)	Reference
Ph	2-Pyridyl	90	2003TL1123
Ph	2-Pyrimidyl	83	2003TL1123
Ph	5-Thiazolyl	92	2003TL1123
Ph	5-(1-Methylpyrazolyl)	80	2003TL1123
Ph	2-Imidazolyl	85	2003TL1123
Ph	5-(1,2,3-Triazolyl)	89	2003TL1123
Ph	2-(1,2,3,4-Tetrahydro)-furyl	79	2003TL1123
Ph	2-(1,3-Oxazolyl)	84	2003TL1123
2-Pyridyl	2-(1,3-Oxazolyl)	92	2003TL1123
2-Furyl	2-(1,3-Oxazolyl)	90	2003TL1123
3-(2,5-Dimethylthienyl)	Ph	60	2001CHE85
3-(2,5-Dimethylthienyl)	4-NO ₂ -C ₆ H ₄	56	2001CHE85
3-(2,5-Dimethylthienyl)	2-Furyl	51	2001CHE85
3-(2,5-Dimethylthienyl)	2-Furyl	51	2001CHE85
Ph	(Indolyl-1)propyl	83	2003TL4495
Ph	(Indolyl-1)propyl	83	2003TL4495

9.02.8 Ring Syntheses by Transformations of Another Ring

Ring-transformation reactions are widespread in heterocyclic chemistry <1984CHEC-I(2)385, 1996CHEC-II(6)507>. The ability of 1,2,4-triazines to be transformed into other ring systems has been considered in Sections 9.02.5.7.5 and 9.02.5.8. In addition, there are ring-transformation reactions in which the 1,2,4-triazine ring is prepared from five-, six-, or seven-membered rings. Examples are discussed in the following sections.

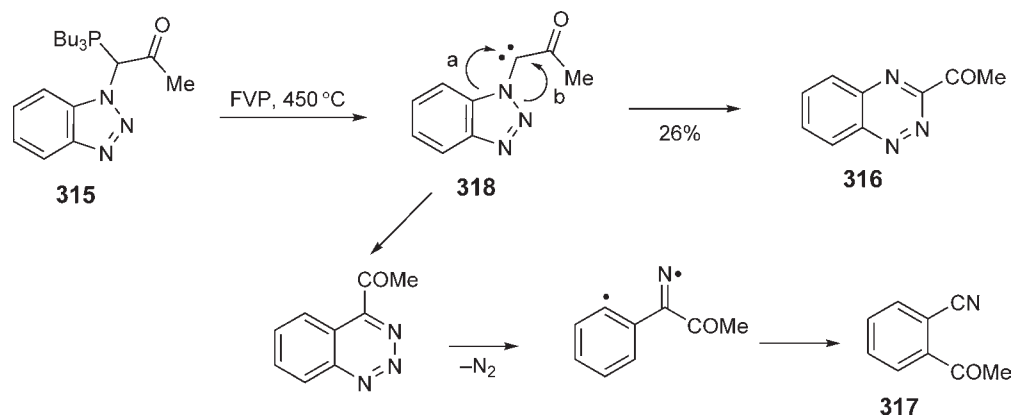
9.02.8.1 From Five-Membered Rings

N-Alkyl-substituted 1,2,3-triazole derivatives are appropriate starting materials for enlargement of the 1,2,3-triazole ring into the 1,2,4-triazine, provided that an active intermediate (carbene, *N*-ylide, or carbanion) can be generated from the *N*-alkyl group for incorporation of a one-carbon fragment into the 1,2,4-triazine ring. For instance, treatment of 1-alkyltriazolium salts **313** with sodium ethoxide initiates the ring-transformation reaction, resulting in the formation of 2,3-dihydro-1,2,4-triazines **314** in good yields (up to 92%) through the intermediacy of 1,2,5-triazahexatrienes (Scheme 189) <1996CHEC-II(6)507, 1997J(P1)1047, 1997J(P1)2919>.



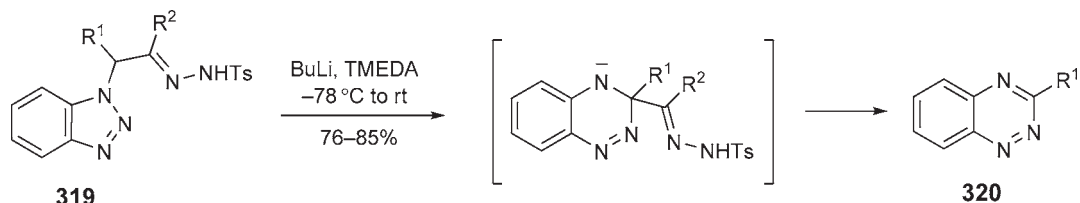
Scheme 189

Flash vacuum pyrolysis of α -benzotriazolyl- β -oxotributylphosphorus **315** at 450 °C generates the corresponding acetyl benzotriazolyl carbene **318**, which is transformed into either 3-acetyl-1,2,4-benzotriazine **316** or 4-acetyl-1,2,3-benzotriazine followed by decomposition of the latter and rearrangement of an intermediate into *ortho*-cyanoacetophenone **317**. The formation of **317** involves a novel 1,3-acetyl-migration process (Scheme 190) <1996CHEC-II(6)507, 1997J(P1)3107, 2004SOS(17)357>.



Scheme 190

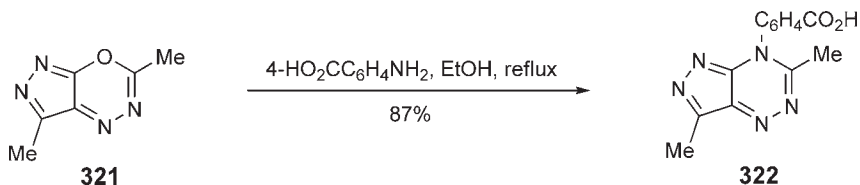
In addition, lithiation of α -(benzotriazolyl)-1-substituted tosylhydrazones **319** with butyllithium initiates the ring-opening and ring-closure reactions, leading to 1,2,4-benzotriazines **320** (Scheme 191) <1997SC3963, 2004SOS(17)357>.



Scheme 191

9.02.8.2 From Six-Membered Rings

The 1,3,4-oxadiazine ring in the pyrazolo[4,3-*e*][1,3,4]oxadiazine **321** is transformed into the 1,2,4-triazine, as in **322**, when compound **321** is treated with a primary amine (Scheme 192) <2002IJB664, 2004SOS(17)357>.



Scheme 192

9.02.8.3 From Seven-Membered Rings

CHEC-II(1996) provided an example of the ring-transformation reaction in which 6,7-dihydro-1-methyl-1*H*-1,2,5-triazepines were transformed into 1,2,4-triazines by the action of hydroxide ion <1996CHEC-II(6)507>. To our knowledge, no data concerning contraction of seven-membered rings into 1,2,4-triazines have been reported during the last decade.

9.02.9 Important Compounds and Applications

The list of biologically active compounds of the 1,2,4-triazine family involves 3,5-diamino-6-aryl-1,2,4-triazines <1995AXC440, 1995AXC685, 1996AXC2627, 1999JCX163, 2000AXC362>, analogs of anticonvulsant lamotrigine **323** <1999JCX701, 2001JST53>, and 3-amino-1,2,4-benzo-triazin-1,4-dioxide **324**, known as anticancer drug tirapazamine (**Figure 16**) <1998HOU(E9c)582, 2001JOC107, 2004SOS(17)357>.

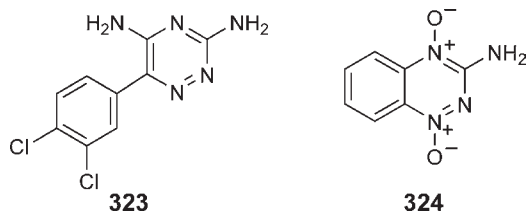


Figure 16

The 1,2,4-triazine ring is a part of the family of biologically active pyrimido[5,4-*e*][1,2,4]triazines of natural origin, such as anticancer antibiotic reumycin **325** and its N-methylated analogs fervenulin **326** and toxoflavin **327** (**Figure 17**) <1998HOU(E9c)582, 2004JHC637, 2004SOS(17)357>.

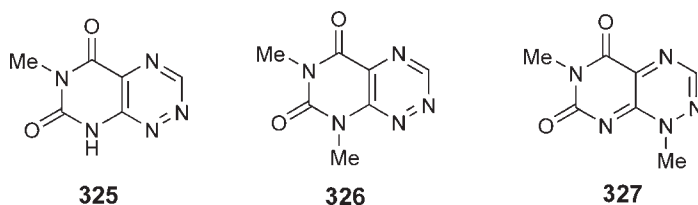


Figure 17

Many synthetic 1,2,4-triazines are also of practical importance. Compound **328** proved to be one of the best chelating ligands for iron(II), while tetracyclic derivative **329** is a dyestuff (**Figure 18**) <1998HOU(E9c)582, 2004SOS(17)357>.

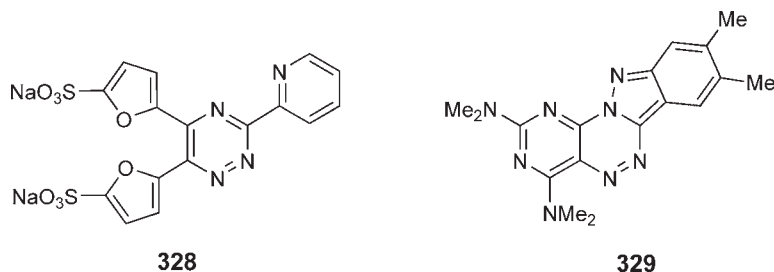


Figure 18

Some 1,2,4-triazines, such as 1-(5,6-diphenyl-1,2,4-triazinyl-3)thiosemicarbazide **330** and 6-(1-cyclohexenyl)-5(4*H*)-oxo-1,2,4-triazin-3(2*H*)-thione **331**, are important as plant-protection agents (**Figure 19**) <2001PHA195, 2004SOS(17)357>.

Considerable attention has been paid to 6-azauracil **332**, 6-azathymine **333**, and 6-azacytidine **334**, as aza analogs of pyrimidine bases and nucleosides, 2-thio-6-azathymine <1995JCD3035>, 5-substituted-6-aza-2'-deoxyuridines <1998NN187>, 6-aza-2'-deoxy-2'-arabinofluorouridine <2004AXC884>, as well as derivatives of 6-aza-2'-deoxyisocytidine (**Figure 20**) <2003AXCo194, 2005NN111>.

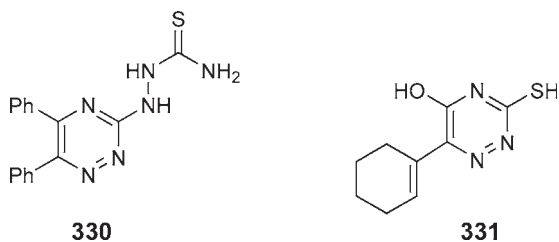


Figure 19

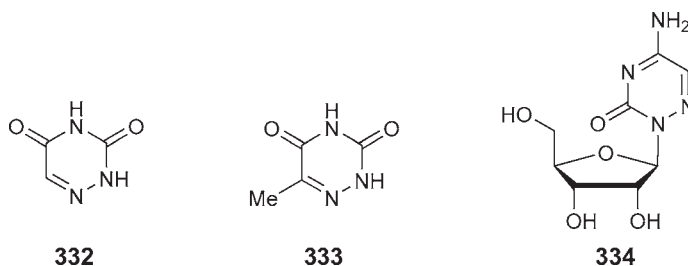


Figure 20

Further, the research and development of anticancer drug **335**, anti-human immunodeficiency virus (anti-HIV) agent **336** (Figure 21) <2004SOS(17)357>, and antibacterial sulfonamides <2005EJM377> have been reported.

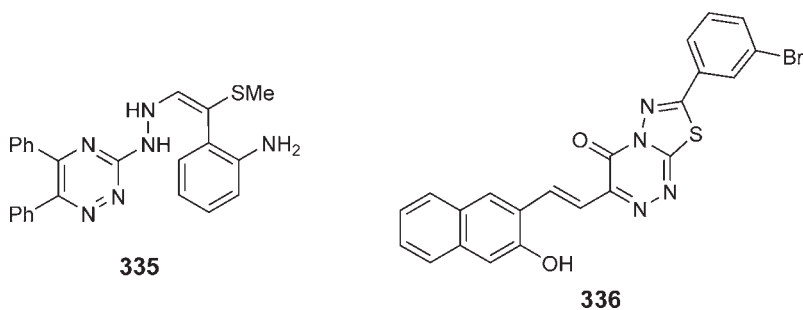


Figure 21

A number of 1,2,4-triazinones **337** bearing arylfuryl fragments, including their condensed analogs **338**, exhibit antibacterial activities comparable to furacin (Figure 22) <2002IJB2690, 2003IJH85>.

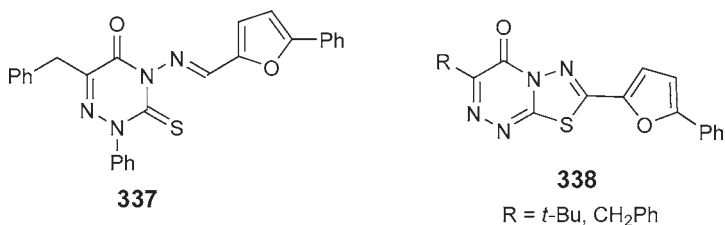


Figure 22

A series of 4-amino-6-arylfuranylmethyl-3-mercapto-1,2,4-triazin-5(4*H*)-ones **339** (R = 4-chloro, 4-nitro, 4-bromo, 2-nitro, 3-nitro, 2-chloro), obtained by refluxing pyruvic acids **340** in ethanol with thiocarbohydrazide, show a good level of antibacterial activity (Figure 23) <2003IJB2649>.

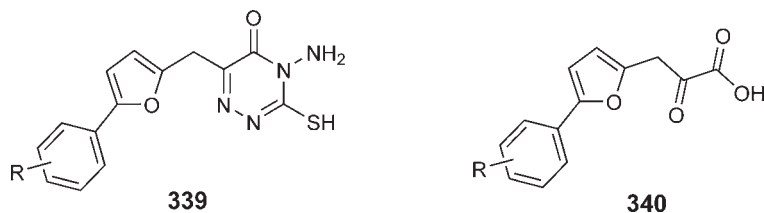


Figure 23

Pyridinyl-substituted 1,2,4-triazines are of great importance as polydentate ligands. In particular, 5,6-diphenyl-3-(2-pyridinyl)-1,2,4-triazine (dppt) is a commercially available ligand which is widely used in coordination and analytical chemistry (Figure 24) <1998TAL531, 2000ANA289, 2000JEC117, 2005CR1087, 2005JCR1631>.

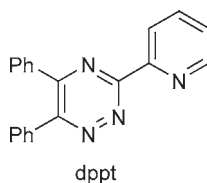


Figure 24

Dppt forms complexes with iron(II) <2000ANA289>, zinc(II) (Zn(dppt)Cl₂·0.5H₂O (A) <cCA> and Zn(dppt)₂Cl₂·2H₂O (B)) <2005CR1087>, lead(II) and cadmium(II) <2000JEC117>, as well as rhenium [ReCl(CO)₃(dppt)] <1996POL203> and other ions. Also, derivatives of 3-(pyridinyl-2)-1,2,4-triazines are effective ligands for copper ions, forming symmetric binuclear complexes (Figure 25) <2005RJO>.

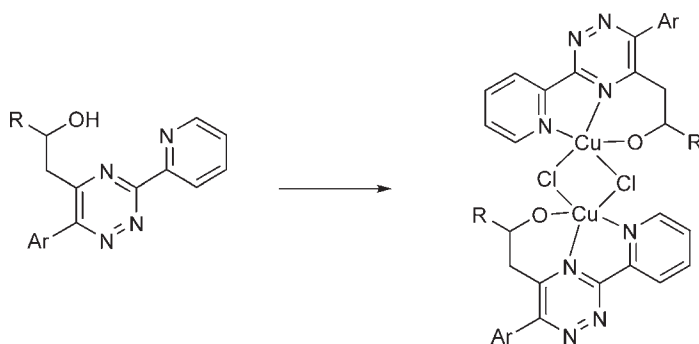


Figure 25

2,6-Bis(5,6-dialkyl-1,2,4-triazin-3-yl)pyridines belong to a new family of extracting agents, recently developed in the framework of nuclear fuel reprocessing. These compounds exhibit exceptional properties for the separation of actinides(III) from lanthanides(III) in nitric acid solutions (Figure 26) <2004IC6745>. The selectivity factor for Am/Eu for extraction from 1.9 M aqueous nitric acid solutions into an organic phase is over 100–120 <1999MI1155, 1999MI1155, B-1999MI2286, 2001JCX397, 2001ICC462>.

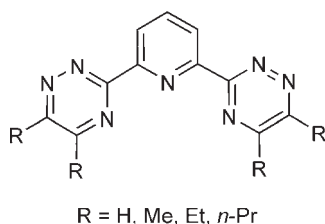


Figure 26

Dipyridinyl-1,2,4-triazines are able to form complexes with a variety of ions, including ruthenium and palladium (Figure 27) <2006POL888>. The ability of ruthenium complexes of dppt to intercalate with DNA has been used for the development of stereoselective sensors <2003ICC773, 2005ICA3430>.

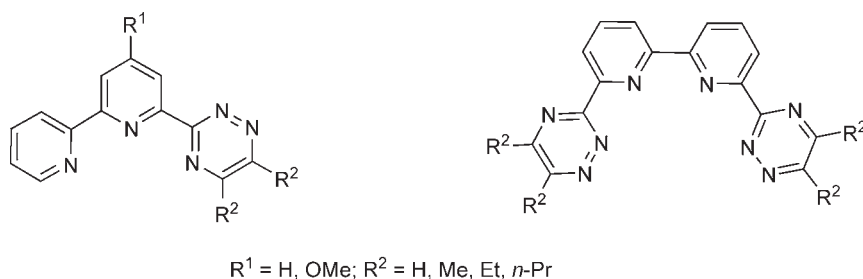
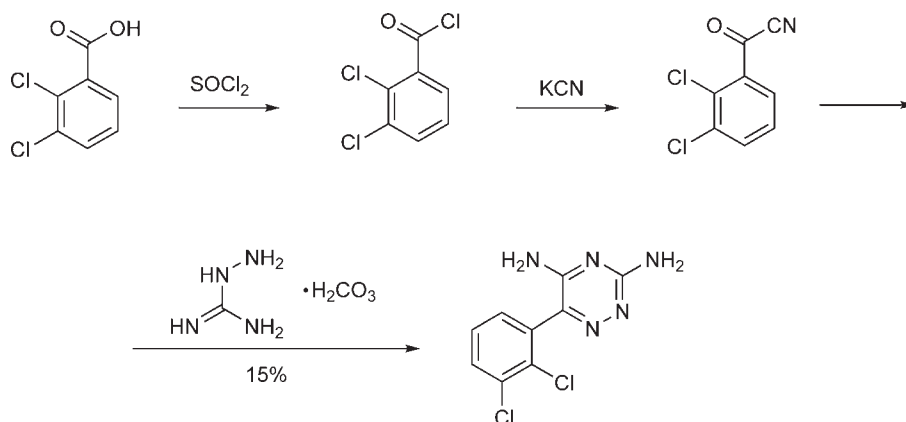


Figure 27

9.02.10 Syntheses of Particular Classes of Compounds and Critical Comparison of Various Routes Available

The data presented in Sections 9.02.6–9.02.8 show that a variety of synthetic routes to 1,2,4-triazines and their functional derivatives are available in the literature. Various synthetic methodologies can be applied to obtain particular classes of compounds, for instance, 3,5-diamino-6-aryl-1,2,4-triazines, as illustrated by the synthesis of lamotrigine (Schemes 193–195).

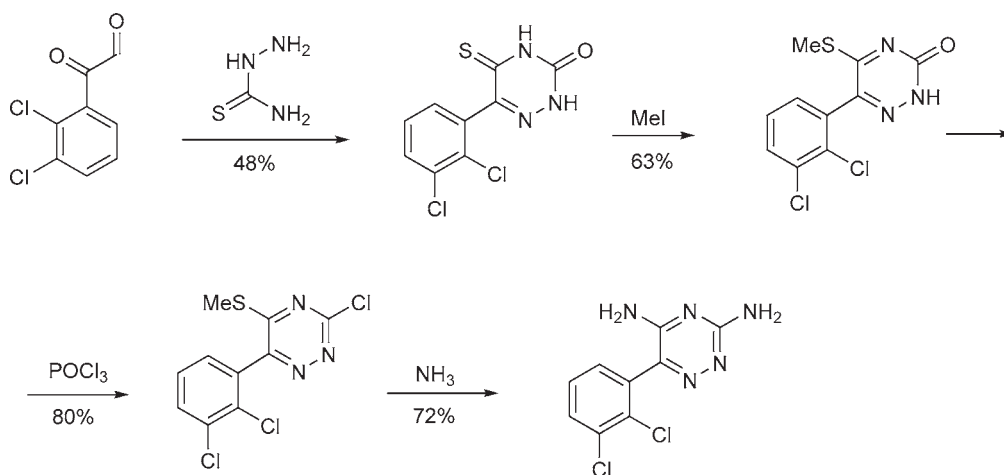


Scheme 193

The principal approach to build the 1,2,4-triazine ring is condensation of 1,2-dioxo derivatives or their synthetic equivalents (for instance, α -keto esters or α -keto substituted nitriles) with 1,2,4-triazine compounds, such as thiosemicarbazides or amidrazones. Indeed, the first synthetic route to lamotrigine is based on a direct condensation of 2,3-dichlorobenzoyl cyanide with aminoguanidine (Scheme 193) <B-1999MI2286>. Disadvantages of the method are

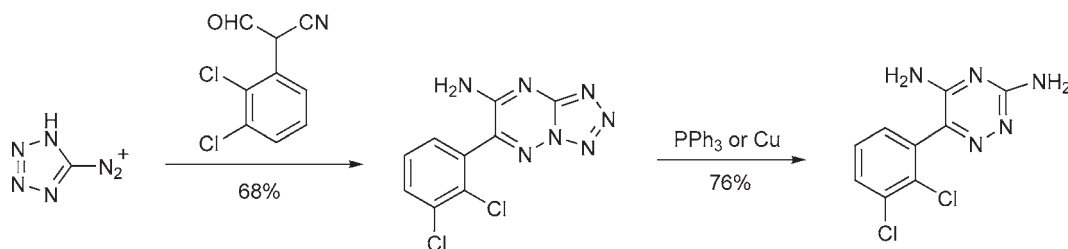
the following: (1) it is difficult to avoid the formation of by-products in the reaction of 2,3-dichlorobenzoyl chloride with potassium or copper cyanide; (2) a low yield is obtained for the condensation of 2,3-dichlorobenzoyl cyanide with aminoguanidine; (3) an overall yield of lamotrigine from 2,3-dichlorobenzoic acid does not exceed 12–13% [<B-1999MI2286>](#).

Another synthetic pathway to lamotrigine involves the synthesis of 3,5-disubstituted-1,2,4-triazines followed by amination by means of nucleophilic displacement of one or two leaving groups at positions 3 and 5, for instance, a chloro atom and the methylthio group, as shown in [Scheme 194](#). Unfortunately, the amination procedure is not very smooth, and requires rather severe reaction conditions [<1995MI3>](#).



Scheme 194

A new synthetic approach to lamotrigine has recently been suggested [<2005RCB726>](#). It is based on the coupling of tetrazolyldiazonium salts with α -formyl- α -(2,3-dichlorophenyl)acetonitrile followed by treatment of the corresponding tetrazolo[4,5-*b*][1,2,4]triazine with triphenyl phosphine ([Scheme 195](#)) [<2005RCB726>](#).



Scheme 195

The last example concerning the synthesis of lamotrigine shows that, in spite of the availability of a variety of synthetic procedures in the chemistry of 1,2,4-triazines, there is still room for development of new and more efficient methods.

9.02.11 Further Developments

Recent publications on the chemistry of 1,2,4-triazines [<2006CHE403, 2006MI139, 2007BML2126, 2007EJM394, 2007BML2474, 2007BML2828, 2007BML3987, 2007MC249, 2007MI45>](#), condensed 1,2,4-triazines [<2006BMC758, 2006EJM539, 2006EJM1373, 2006JME2049, 2006SC3647, 2007BMC2837, 2007CPB541, 2007JOC4358, 2007JHC617, 2007JHC639, 2007JHC701, 2007JME1069, 2007JME2459, 2007JME4606, 2007SC261, 2007TL5035, 2007TL5069, 2007T1568, 2007T5490, 2007T6004>](#), and their biological activity [<2006BMC758, 2006EJM539, 2006EJM1373, 2006JME2049, 2007BMC2837, 2007BML2126, 2007BML2474, 2007BML2828, 2007BML3987, 2007JME1069, 2007JME2459, 2007JME4606, 2007MI494, 2007PCJ75>](#) demonstrate a continuing interest in this promising class of heterocyclic compounds.

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Biographical Sketch



Prof. Valery Charushin was born in Sverdlovsk Region, Russia, in 1951. He began his academic career after graduation from the Urals State Technical University (USTU). He joined the Organic Chemistry Department of USTU as a postgraduate student in 1973 and maintained his thesis 'Reactions of azinium cations with aromatic nucleophiles' under the guidance of Prof. Oleg N. Chupakhin in 1976.

During the next 10 years, he did research in the field of heterocyclic chemistry at the Department of Organic Chemistry of the Urals State Technical University (Ekaterinburg, Russia). In 1981–82 and 1988, he worked in the Organic Chemistry Laboratory of the Agricultural University of Wageningen (The Netherlands) under the guidance of Prof. Henk van der Plas, studying ring transformations of pyrimidines, 1,2,4-triazines, and other aza-aromatics by action of nucleophiles. In 1987, he maintained his doctoral dissertation 'Reactions of azines with bifunctional nucleophiles' and was promoted to Full Professor of Organic Chemistry.

Prof. V. Charushin is author of over 380 publications in the fields of heterocyclic and medicinal chemistry, including the book *Nucleophilic Aromatic Substitution of Hydrogen*, (Academic Press, New York, 1994), several chapters in *Advances in Heterocyclic Chemistry* and *Progress in NMR Spectroscopy*, over 20 review articles, and a lot of papers in international journals. He is a member of the editorial boards for *Mendeleev Communications*, *Russian Chemical Reviews*, *Russian Chemical Bulletin*, and *Russian Journal of Organic Chemistry*.

Prof. Charushin was promoted to the Russian Academy of Sciences (RAS), first as Corresponding Member of RAS (1997) and then as Full Member of RAS (2003). He currently holds the positions of Deputy Chairman of the Ural Branch of the Russian Academy of Sciences, and Director of I. Postovsky Institute of Organic Synthesis.



Prof. Oleg Chupakhin was born in Chelyabinsk Region, Russia, in 1934 and obtained his degree in chemistry from the Urals State Technical University (USTU), Ekaterinburg, Russia, in 1957. He started as a junior researcher, and then as postgraduate student at the same university. In 1964, he maintained his candidate dissertation (similar to Ph.D.) 'Reactions and Derivatives of Quinaldine.'

During the next 12 years, he worked as assistant professor and a lecturer at the Organic Chemistry Department of USTU. His research interests include heterocyclic and medicinal chemistry. In 1977, he maintained doctoral dissertation 'Nucleophilic Substitution of Hydrogen in Azines,' and was promoted to Full Professor of Organic Chemistry and Head of Organic Chemistry department of USTU.

Prof. Oleg Chupakhin is author of more than 500 research papers in the fields of organic and medicinal chemistry, including two books *Nucleophilic Aromatic Substitution of Hydrogen* (Academic Press, New York, 1994), and *Nitroazines* (Nauka, Novosibirsk, 1991), several chapters in *Advances in Heterocyclic Chemistry* and *Progress in NMR Spectroscopy*, and over 25 review articles in international and Russian journals. He is a member of editorial boards for the *Russian Journal of Organic Chemistry*, *Chemistry of Fuels*, and other chemical journals issued in Russia.

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He got a useful research experience at the Organic Chemistry Laboratory of Technische Hochschule, Darmstadt, Germany, working under the guidance of Prof. Hans Neunhoeffer (1994–95). Currently, he is Full Professor of Organic Chemistry Department in the Urals States Technical University.

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Prof. Rusinov was awarded with the USSR Council of Ministers Prize (1990), I.Y. Postovsky Prize (2004), and N. D. Zelinsky Prize (2005). He was also promoted to the rank of the Honoured Chemist of the Russian Federation (2000).

9.03

1,3,5-Triazines

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9.03.1 Introduction

The chemical compound 1,3,5-triazine, also called *s*-triazine, is an organic chemical compound whose chemical structure has a six-membered heterocyclic aromatic ring consisting of three carbon atoms and three nitrogen atoms. The atoms in triazine rings are analogous to those in benzene rings, which makes triazines aromatic compounds like benzene. 1,3,5-Triazine is a common reagent, and readily forms derivatives, which are used as pharmaceutical products and herbicides. Common trivial names used include cyanuric acid (CYA; 2,4,6-trihydroxy-1,3,5-triazine **1**), cyanurates (2,4,6-trialkoxo-1,3,5-triazines **2**), cyanuryl chloride (2,4,6-trichloro-1,3,5-triazine **3**), isocyanurates (1,3,5-trialkyl-1,3,5-triazine-2,4,6-triones **4**) (Figure 1). Heterocycles are numbered, by convention, to begin at a heteroatom, hence, 1,3,5-triazine **5** <1996CHEC-II(6)575>.

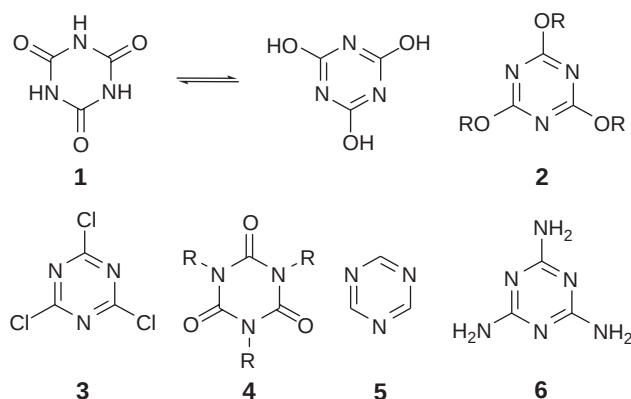


Figure 1

The most common derivative of 1,3,5-triazine is 2,4,6-triamino-1,3,5-triazine **6**, commonly known as melamine or cyanuramide. CYA is a stable, colorless solid at room temperature. Synonyms include 1,3,5-triazinetriol, *s*-triazinetriol, 1,3,5-triazine-2,4,6-(1H,3H,5H)-trione, *s*-triazinetrione, tricarbimide, isocyanuric acid, and pseudocyanuric acid. CYA is used as a stabilizer in recreational water treatment to minimize the decomposition of hypochlorous acid by light in outdoor swimming pools and hot tubs. Chlorinated derivatives of CYA, such as trichloro-*s*-triazinetrione and sodium dichloro-*s*-triazinetrione, are used as algacides or microbiocides in swimming pool water and large-scale water systems in industry, etc. The chemistry of 1,3,5-triazine, CYA, and cyanuric halides has been reviewed by Tilstam and Weinmann <2002OPD384> and Giacomelli *et al.* <2004COR1497>.

Melamine is a strong organic base, which is used primarily to produce melamine resin, which when combined with formaldehyde produces a very durable thermoset plastic. This plastic is often used in kitchen utensils or plates (often sold under the brand name Melmac), and is the main constituent of Formica® and Arborite®. Melamine tile wall panels are known as whiteboards. Melamine is also used to make decorative wall panels and is often used as a laminate. Melamine is produced from urea, mainly by either of two methods: catalyzed gas-phase production or high-pressure liquid-phase production.

With up to six active hydrogen sites, melamine reacts with formaldehyde and methanol to form a large family of resins. A resin ratio of 2 mol formaldehyde to 1 of melamine is used extensively to impregnate countertop surface paper laminates, making them flame and boil resistant. A resin ratio of 6 mol of formaldehyde to 1 of melamine followed by excess methanol forms a methylolated cross-linking resin used to impart heat and solvent resistance to numerous latex-based coatings.

Melamine, dicyandiamide (or cyanoguanidine), and cyanamide are related. The first is considered the trimer and the second the dimer of the third. All contain 66% N and provide fire-retardant properties to resin formulas by releasing nitrogen when burned or charred.

Melamine foam has an interlinking bubble format, which produces a structure more like a block of microscopic fiberglass than normal foam. It is used for soundproofing, as a fire-retardant material (but not as insulation, because it allows air to pass through its structure), and also as a cleaning product, the brand name version of which is Magic Eraser, though other companies chop up and sell the same foam under their own, or generic, names. Because of its interlocking microporous nature, and the extreme hardness of the resulting fibers, it can seem to clean 'uncleanable' things from any relatively smooth, hard surface, such as a crayon from a painted wall, or road grease from a hubcap.

9.03.2 Theoretical Methods

Quantum chemistry is an invaluable tool in determining the details of reaction mechanisms as well as in characterizing other properties of molecules <1987ADP249>. The next four sections describe the application of this methodology to the triazine area.

9.03.2.1 *Ab Initio*

The major spectroscopic techniques for determining molecular structure in fluid phases have their limitations, and so it is rare that any one method alone can give a complete structural determination for any but the simplest of compounds. It is therefore common practice to combine data from these techniques to arrive at a final solution. The best results were obtained combining experimental and *ab initio* data to give more complete, reliable structure determinations <1996JPC15368>.

The r_α , r_0 , and r_s structures of 1,3,5-triazine in the gas phase have been determined by analysis of electron diffraction data and high-resolution Fourier transform infrared (FTIR) spectra, including those for the isotopomers $^{12}\text{C}_3^{15}\text{N}_3\text{H}_3$, $^{13}\text{C}_3^{14}\text{N}_3\text{H}_3$, $^{13}\text{C}_3^{15}\text{N}_3\text{H}_3$, and $^{12}\text{C}_3^{14}\text{N}_3\text{D}_3$, in solution in liquid crystal solvents by nuclear magnetic resonance (NMR) spectroscopy, and by *ab initio* calculations. Combining gas- and solution-phase data in a single analysis yields a very precise structure, with final parameter values (r_α°) $r(\text{C}-\text{N})$ 133.68(1) pm, $r(\text{C}-\text{H})$ 108.9(2) pm, and $\angle(\text{CNC})$ 113.82(9)°. The final structure obtained was compared also with the crystal structure <1997JPC10029>.

Electronic structures of cationic states (2^+ and 3^+) of 1,3,5-triazine (TA) and its derivative, hexahydro-1,3,5-triazine (HTA), have been explored using the *ab initio* molecular orbital (MO) method including the electron correlation by the Møller-Plesset (MP) perturbation treatment. It has been found that σ -radical spins give rise to low- and high-spin states in both TA and HTA. The present calculation at the MP3 level predicts that the spin multiplicity of the ground state of dicationic TA is a high-spin state triplet while that of tricationic TA is a doublet. On the other hand, low- and high-spin states are almost degenerate in both the dicationic and the tricationic states of HTA. This result will hopefully lead to the discovery of a high-spin state occurring from σ -radical spins in molecules containing heteroatoms as the spin accommodators <1998PCA8021>.

Gas-phase hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) is a relatively stable molecule which releases a large amount of energy upon decomposition. Although gas-phase unimolecular decomposition experiments suggest at least two major pathways; there is no mechanistic understanding of the reactions involving RDX or other energetic molecules. For the unimolecular decomposition of RDX, Goddard III and co-workers have found three pathways: (1) 'concerted decomposition' of the ring to form three CH_2NNO_2 molecules; (2) 'homolytic cleavage' of an NN bond to form NO_2 plus the ring-opened structure of the RDX radical (RDR) <2000PCA2261>, which subsequently

decomposes to form various products; and (3) successive ‘HONO elimination’ to form three HONO molecules plus stable 1,3,5-triazine (TAZ), with subsequent decomposition of HONO to HO and NO and, at higher energies, of TAZ into three HCN molecules. Experimental studies suggest that the concerted pathway is dominant while theoretical calculations have suggested that the homolytic pathway might require significantly less energy <2000PCA2261>.

Cation– π -interactions are noncovalent binding forces with great importance in many systems. *Ab initio* calculations were performed on complexes between cations and *s*-triazine, which has a small and positive quadrupole moment. Minimum-energy π -complexes were found between *s*-triazine and cations (Figure 2). A likely explanation of this duality is the stabilization obtained from the ion-induced polarization <2003OL2227>.

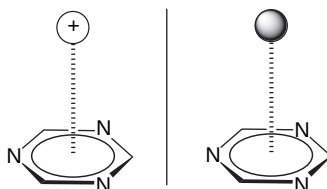


Figure 2

Chu *et al.* have reported that the calculated singlet gap and triplet gap of 2,4,6-tris(diarylamino)-1,3,5-triazine derivatives (TRZ1–TRZ4) are in full agreement with experimental results (Figure 3). The calculated triplet band-gap energy of TRZ1 has been found to be larger than that of TRZ2. On the other hand, the TRZ1 molecules have the lowest dipole moment, which infer the highest carrier mobility. Therefore, TRZ1 has the potential to be a superb triplet host material and electron-transport material <2005CPL137>.

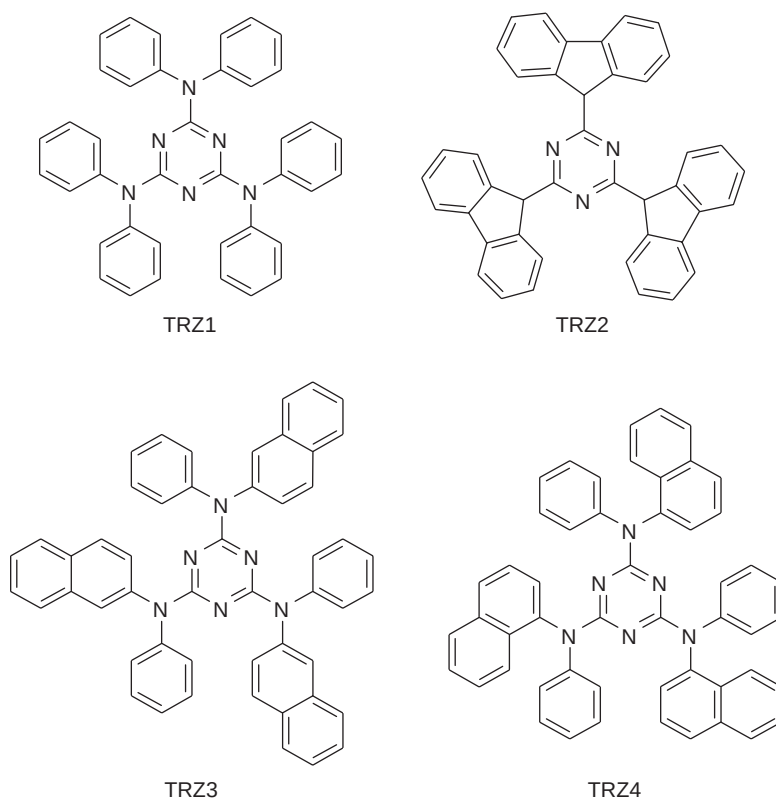


Figure 3

The results derived from theoretical calculations have revealed that isocyanuric acids are suitable for use as binding blocks for the molecular recognition of anions. They are synthetically more versatile than other electron-deficient aromatic rings, such as perfluorobenzene and nitrobenzenes. The substitution of oxygen atoms by sulfur atoms does not affect the binding ability of the ring due to a Q_{zz}/a compensating effect (Figure 4). The nature of the interaction derives from electrostatic and anion-induced polarization effects. The latter term increases as the number of sulfur atoms increases <2005CEJ6560>.

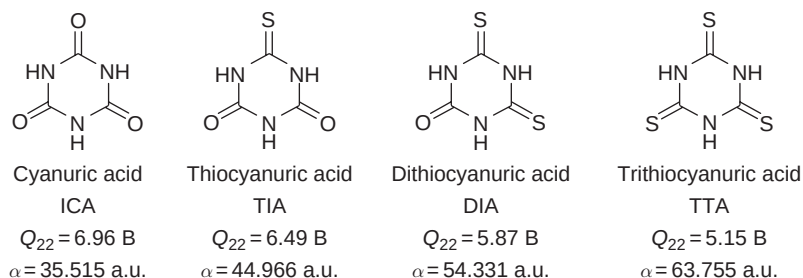


Figure 4

9.03.2.2 CASSCF Study

In 1997, Yamabe and co-workers presented the results of an *ab initio* MO study (at the ROHF, GVB, and CASSCF levels) of *m*-phenylenediamine and 2,4-diamino-1,3,5-triazine dication diradicals, which are model molecules for two possible high-spin polymers, poly(*m*-aniline) and poly(imino-1,3,5-triazinediyl) cation radicals. On the basis of qualitative MO considerations, it was seen that the electronic structures of **7** and **8** differed considerably (Figure 5). The singlet–triplet splittings (ΔE_{S-T}) of **7** and **8** were calculated to be 0.7 and 12.5 kcal mol^{−1}, respectively, at the CASPT2 level. Moreover, *m*-1,3,5-triazinediyl was shown to be a strong ferromagnetic coupler for aza-substituted systems <1997JOC38>.

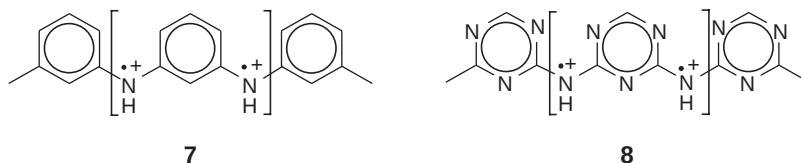


Figure 5

Ultraviolet (UV) light can degrade polymeric materials via a variety of chemical mechanisms <2002C216>. To prevent destructive degradation of such materials, the absorbed energy must be removed before the material can degrade via some reactive product channel. Recently, Robb and co-workers have presented a detailed CASSCF study of the mechanism of excited-state intramolecular proton transfer (ESIPT) in the *o*-hydroxyphenyl triazine class of photostabilizers (Figure 6). The valence-bond analysis of the ground state and the two $\pi-\pi^*$ excited states permit a simple chemical interpretation of the mechanistic information. Their results showed that the barrier to enol–keto tautomerism on the ground-state adiabatic surface is high. Following photoexcitation to the charge-transfer (CT) state, the ESIPT is predicted to take place without a barrier. Radiationless decay to the ground state is associated with an extended seam of conical intersection, with a sloped topology lying parallel to the ESIPT path, which can be accessed at any point along the reaction path. These results indicate that the triazine class of photostabilizers has the photochemical and photophysical qualities associated with exceptional photostability <2005PCA7527>.

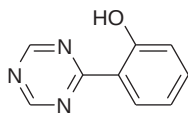


Figure 6

9.03.2.3 Density Functional Theory

Within the last decade, density functional theory (DFT) has offered a computationally less expensive yet reasonably accurate alternative to *ab initio* methods for including correlation corrections in calculating molecular properties such as geometries, frequencies, and energies <1991CRV651>. Stable points and transition states on the potential energy surface (PES) for *s*-triazine ($C_3N_3H_3$) have been calculated by using nonlocal density functional theory (NDFT) methods. Two decomposition mechanisms for *s*-triazine were investigated. The first is a concerted triple dissociation of the *s*-triazine ring to form the HCN products. The second is a stepwise decomposition mechanism involving the formation of an intermediate dimeric species. The NDFT results were compared with previously reported *ab initio* calculations. Geometries predicted by all methods were in excellent agreement with experimental values for *sym*-triazine and HCN. Further, all methods predicted that the concerted triple-dissociation mechanism is the low-energy decomposition pathway for *sym*-triazine (Figure 7) <1996JPC15368>.

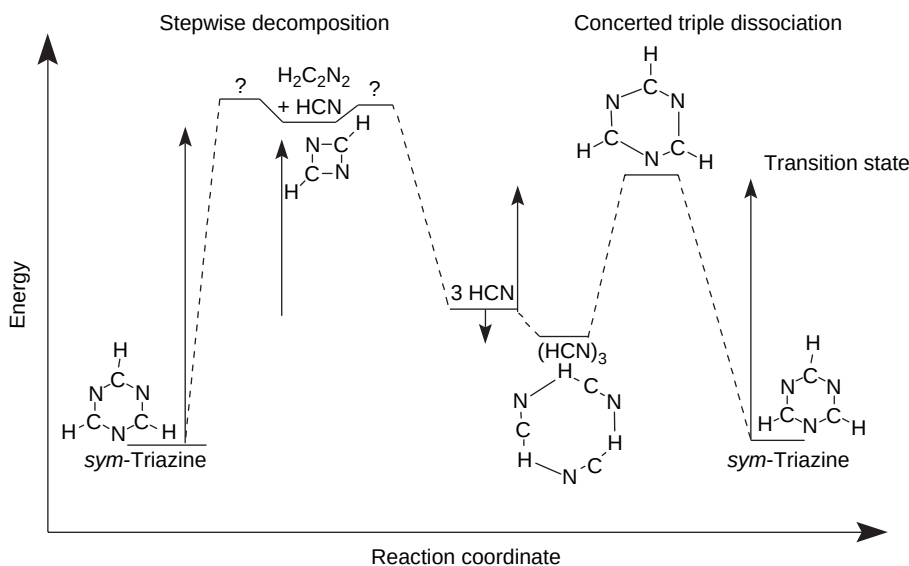


Figure 7 Decomposition pathway for *sym*-triazine.

The ring-current model of π -electrons in planar conjugated molecules has a long history and has become part of the language of chemistry. The model can now be checked and supplemented by *ab initio* current density maps. A distributed-origin coupled Hartree–Fock (HF) method was used to compute and map the π and total current densities induced by a magnetic field in the planar, monocyclic molecules benzene, borazine, boroxine, *s*-triazine, the cyclopentadienyl anion, and the tropylium cation. The maps show that *s*-triazine, the cyclopentadienyl anion, and the tropylium cation have delocalized π -ring currents similar to that in benzene, whereas the π -currents are localized on the nitrogens in borazine and on the oxygens in boroxine.

Computed magnetic susceptibilities show trends that follow those observed for the ring currents and provide measures of the ‘aromaticity’ of molecules. Thus, current density maps of the symmetric trifluorides of benzene ($C_6H_3F_3$) and triazine ($C_3N_3F_3$), and of perfluorobenzene (C_6F_6), show independent localized circulations of π -charge on the fluorines with a weak compression of the region of circulation in the ring <1997PCA1409>.

Ab initio computations of the conformers and bond-dissociation energies of hexahydro-1,3,5-trinitro-1,3,5-triazine **9** (RDX) with the Becke3–Lee–Yang–Parr (B3LYP) NDFT and the standard 6-31G* and 6-311G** Gaussian basis sets were described. Five conformational minima, closely spaced in energy, were located at the B3LYP/6-31G* level of theory. The rather short N–N bonds in the experimental crystal structure suggested that intermolecular interactions lead to enhanced donation of the amine lone pair into the nitro group in the solid state. The RDX nitrogen and carbon radicals were shown to play key roles in the thermal decomposition of **9** suggesting that initiation of decomposition by N–N cleavage and propagation of the decomposition by hydrogen atom transfers should be facile. The mechanism of the gas-phase unimolecular decomposition of RDX has been investigated using first-principles gradient-corrected DFT. Among all possible reaction pathways, Wu and Fried have considered only two specific reaction channels: N–NO₂ bond rupture and symmetric concerted ring fission, since they are best supported by experiments (Figure 8).

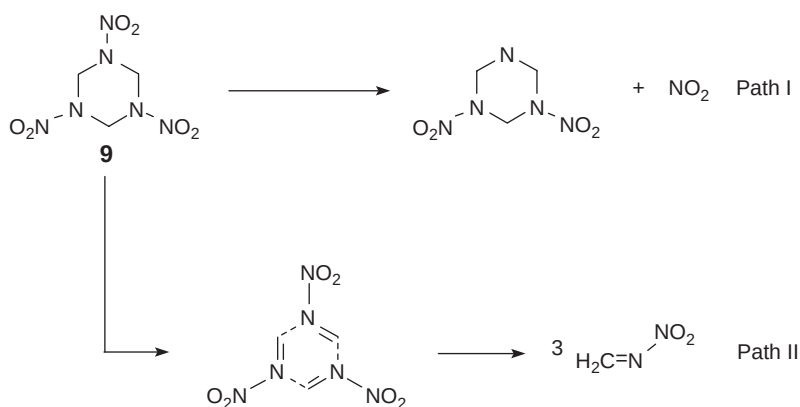


Figure 8

It was found that the activation barrier for concerted ring fission is roughly 18 kcal mol^{-1} greater than that for N– NO_2 bond rupture, a difference that is significantly larger than the maximum deviation found between different functionals. This suggested that thermal gas-phase decomposition at temperatures significantly under 18 kcal mol^{-1} (9000 K) most likely proceeds via N– NO_2 bond rupture [<1997PCA8675>](#).

9.03.2.4 Other Models

The Henry's law constants (H) for triazine-derived herbicides have been calculated using quantum-chemical solvation models, SM2, SM3, PCM–DFT, and CPCM–DFT, and their performances have been discussed. The results showed considerable differences in performance among the different levels of theory. The differences were discussed in terms of the different contributions, electrostatic and nonelectrostatic, to Gibbs free energy of solvation [<2003JCI1226>](#).

9.03.3 Experimental Structural Methods

9.03.3.1 Circular Dichroism

Optically active 1-(9-anthryl)ethylamine (ANTEA) has been synthesized recently and used as a CSA (chiral stationary phase) for the NMR determination of the enantiomeric composition of carboxylic acids [<1993TA274>](#). The problem of the determination of the absolute configuration of the enantiomers of ANTEA can be solved nicely by circular dichroism (CD) spectroscopy, after a suitable modification of its structure. The absolute configuration of (+)-1-(9-anthryl)ethylamine was determined in a nonempirical way by circular dichroism using *s*-triazine as a chromophore to give rise to an exciton coupling reflecting the stereochemistry of the amine [<1999JOC5754>](#). Analysis of the CD spectra has afforded the conformational characterization of the three 1,3,5-triazine derivatives **10–12** (Figure 9).

CD spectroscopy appeared highly suitable because compounds **10–12** possess two chromophores, naphthalene and *s*-triazine, having electrically allowed, well-characterized electronic transitions. In Figure 10 is reported the absorption and CD spectra (acetonitrile solution) of 2,4,6-tris[(*R*)-1(1-naphthyl)ethylamino]-1,3,5-triazine **12** [<2000EJO1767>](#).

On the basis of the analysis of the CD spectra by the nonempirical DeVoe approach, it was possible to establish that each 1-(1-naphthyl)ethylamino moiety assumes the same closed conformation with respect to the *s*-triazine aromatic ring (dihedral angle naphthalene–triazine, 90°), independently of the number or absolute configuration of the other 1-(1-naphthyl)ethylamino groups linked to the *s*-triazine moiety [<1998JOC8765>](#).

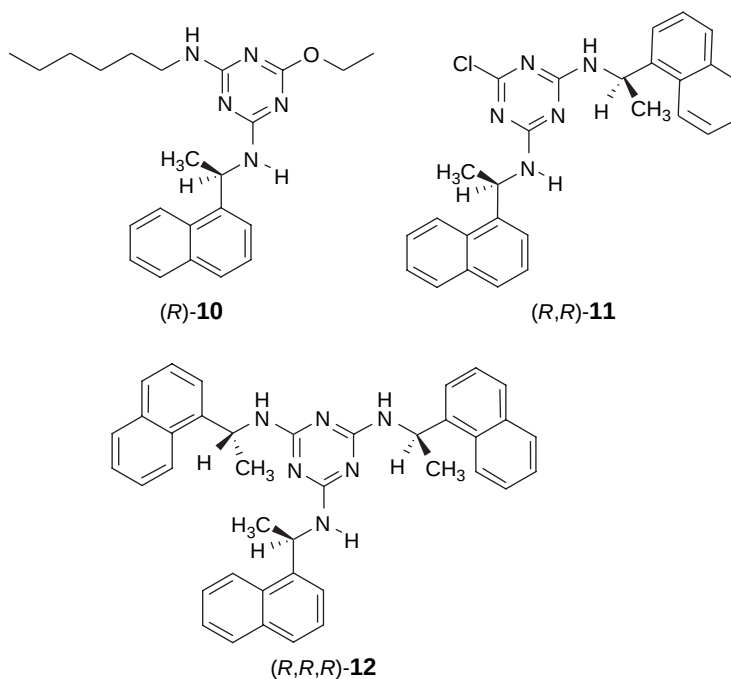
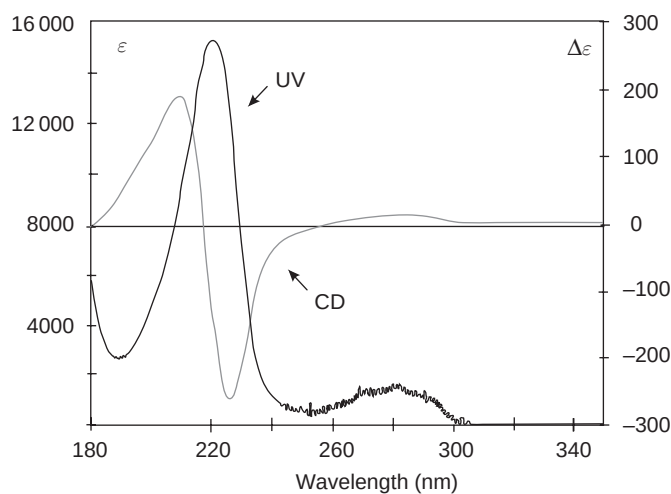


Figure 9

Figure 10 The absorption and CD spectra of **12**.

9.03.3.2 X-Ray Analysis

The molecular organization in thermotropic liquid-crystal line phases is associated predominantly with a rigid anisometric architecture of the constituent single molecules. The triazines **13** were the first examples of electron donors that form columnar phases, which give rise to the induction of smectic liquid crystalline structures through donor–acceptor interactions (Figure 11).

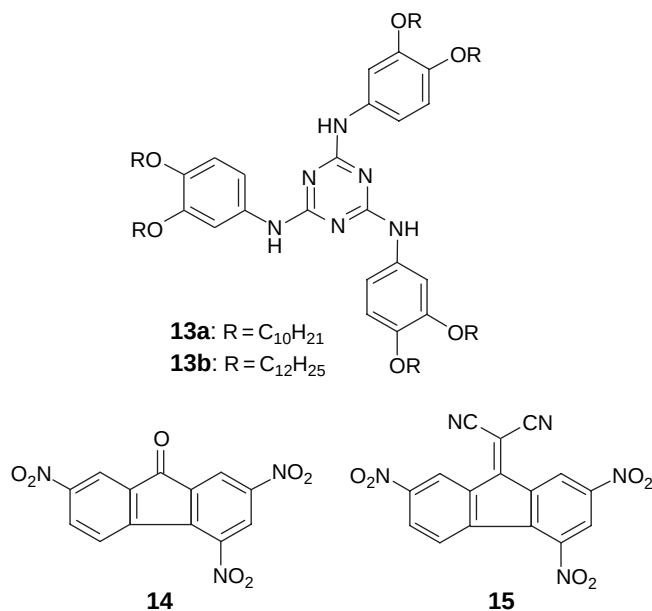
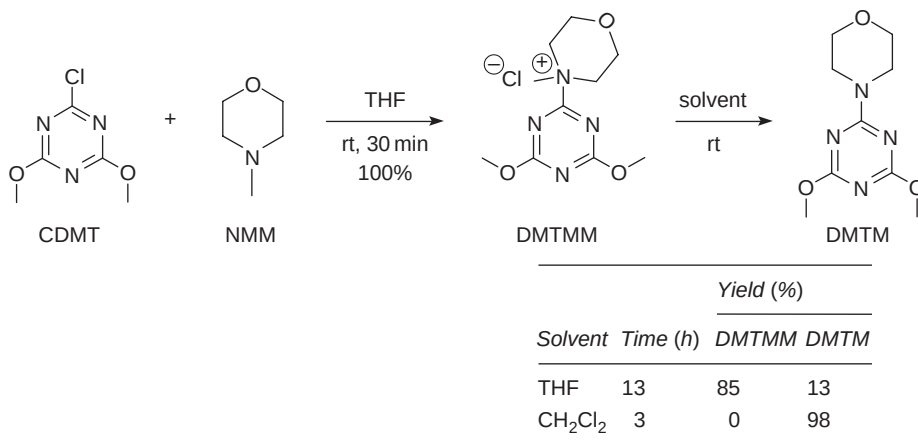


Figure 11

X-Ray investigations were performed to identify the types of mesophase structures displayed by the mixed systems **13/14** and **13/15** in more detail. The formation of the pure triarylmelamine structures as well as of the CT complexes arises from the distinct segregation of polar from nonpolar molecular regions along with certain specific anisometric conformations that become favored during the process of self-organization [\[2000AGE1851\]](#).

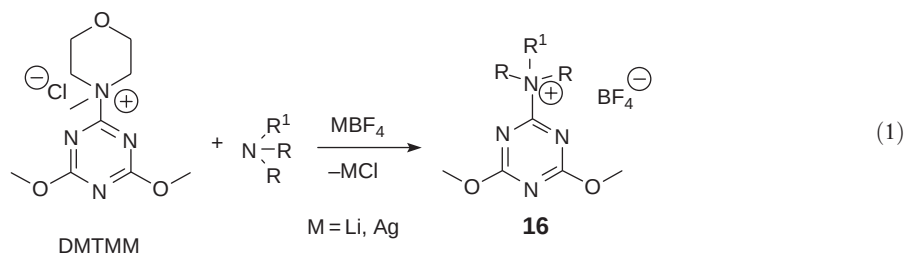
A preliminary investigation of the efficacy of the synthesis of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium (DMTMM) chloride [\[1998JOC4248\]](#) evidenced the formation of methyl chloride in a demethylation side reaction, which decreased the yield and caused contamination of the final products (**Scheme 1**) [\[1999TL5327\]](#). The demethylation product from DMTMM was isolated and identified unequivocally as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine (DMTM) by X-ray diffraction.



Scheme 1

The study showed a very strong conjugation of the morpholine nitrogen with the triazine ring, tested by the shortening of the C(2)-N(morpholine) bond to 1.350(2) Å, being equal to the two endocyclic C–N bond lengths of 1.353(2) and 1.347(2) Å, thus making a regular guanidine fragment. Due to the conjugation, the triazine ring was found to be coplanar with the C–N–C fragment of the morpholine ring <2005JA16912>.

Recently, a new generation of triazine-based coupling reagents (TBCRs), designed according to the concept of ‘superactive esters’, was obtained by treatment of DMTMM chloride with lithium or silver tetrafluoroborate (Equation 1) <2005JA16912>.



The structure of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate **16** was confirmed by X-ray diffraction.

Over the last two decades, two-dimensional (2-D) and 3-D structures of C_xN_y composition have been proposed. However, in the absence of single crystal structure data, the atomic connectivity and composition of these materials remain controversial. Three important graphitic C_3N_4 structures in which triazine is linked by nitrogen atoms have been proposed. Conceptually, such structures are derived from the hypothetical CN graphitic structure by creating either carbon vacancies (cf. **17** and **18**) or triazine vacancies (cf. **19**; Figure 12).

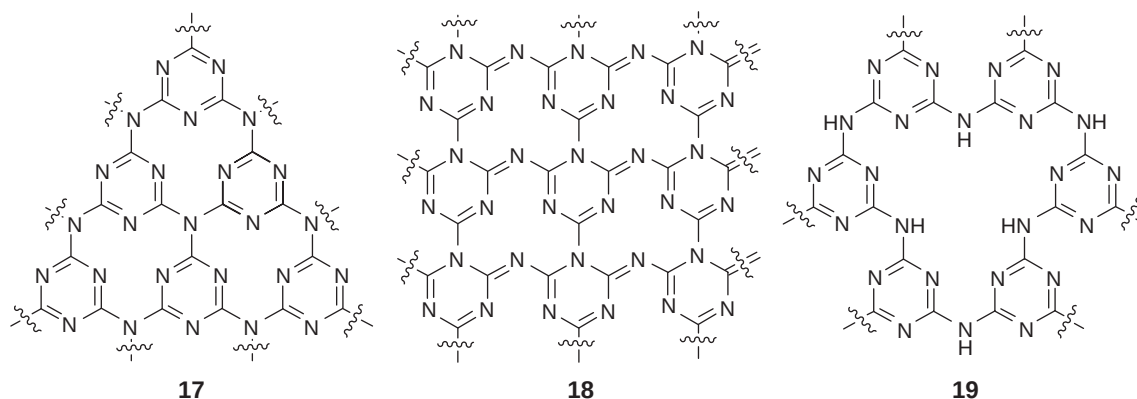


Figure 12

A report by Yaghi illustrates the utility of a simple molecule, $N(C_3N_3)_3Cl_6$, in answering the question of whether triazine-based C_3N_4 phases are layered or instead adopt 3-D structures. The structure showed that the central nitrogen atom, which lies on a threefold axis, and its three carbon neighbors are coplanar (Figure 13). The molecules are chiral with C3 (very close to D3) point group symmetry; however, they pack in columns with the opposite-handed molecules alternating and are separated by 3.722(4) Å (distance between trigonal nitrogen atoms in the stack) <2003CEJ4197>.

Although the chemistry of thallium compounds bears some resemblance to that of alkali metal analogs, thallium bis(trimethylsilyl)amide was only structurally characterized <1994JOM167>. Lappert and co-workers have reported on the reactions of the corresponding sodium and thallium amides $MN(SiMe_3)_2$ with 1,3,5-triazine, and the structures of the novel products, 1,3,5,7-tetraazaheptatrienylsodium **20** and -thallium **21** (Equation 2).

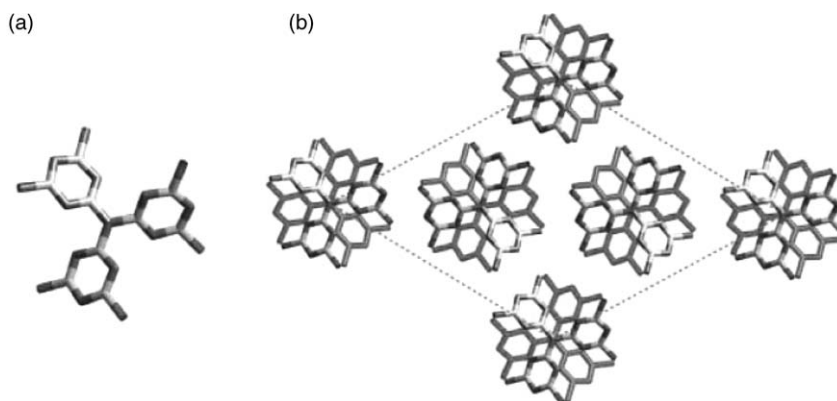
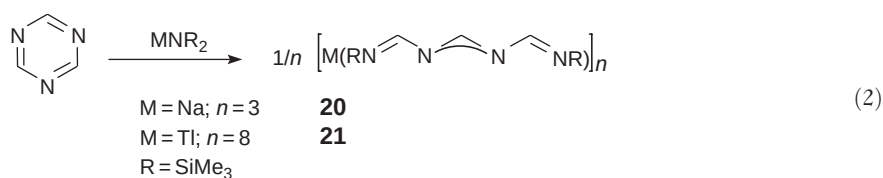


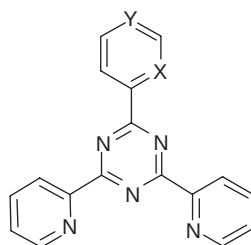
Figure 13



The X-ray molecular structure of the crystalline sodium complex **20** showed the presence of two crystallographically independent, trinuclear molecules and a disordered cyclohexane molecule in the unit cell <2000AGE222>.

A family of tridentate ligands **22a–e**, based on the 2-aryl-4,6-di(2-pyridyl)-*s*-triazine motif, was prepared by Loiseau and co-workers along with their hetero- and homoleptic Ru(II) complexes **23a–e** and **24a–e**, respectively (Figure 14).

Single crystal X-ray analysis of **23a** and **23e** demonstrated that the triazine core is nearly coplanar with the noncoordinating ring, with dihedral angles of 1.2° and 18.68°, respectively <2004CEJ3640>.



22a: X = C–H; Y = C–H
22b: X = C–Me; Y = C–H
22c: X = C–H; Y = C–Me
22d: X = N; Y = C–H
22e: X = C–H; Y = N

23a: X = [Ru(tpy)**22a**](PF₆)₂
23b: X = [Ru(tpy)**22b**](PF₆)₂
23c: X = [Ru(tpy)**22c**](PF₆)₂
23d: X = [Ru(tpy)**22d**](PF₆)₂
23e: X = [Ru(tpy)**22e**](PF₆)₂

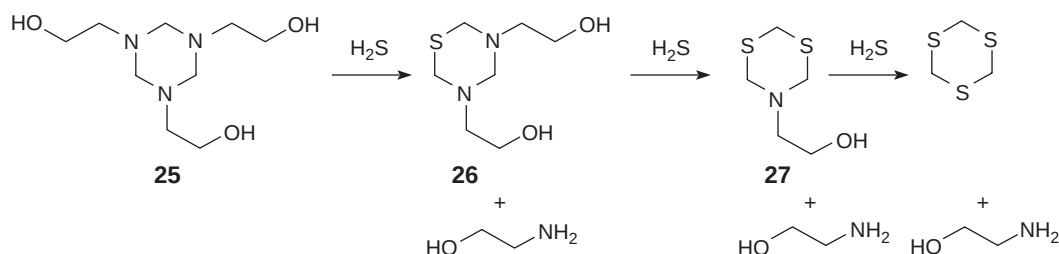
24a: X = [Ru(**22a**)₂](PF₆)₂
24b: X = [Ru(**22b**)₂](PF₆)₂
24c: X = [Ru(**22c**)₂](PF₆)₂
24e: X = [Ru(**22e**)₂](PF₆)₂

Figure 14

9.03.3.3 NMR Spectra

Hydrogen sulfide is present in natural gas and it is a highly undesirable constituent. Therefore, several methods for its removal have been developed. One such method is the injection of an aqueous solution of 1,3,5-tris(2-hydroxyethyl)-hexahydro-*s*-triazine **25** into the gas stream (Scheme 2). The main product of this reaction is generally assumed to be 5-(2-hydroxyethyl)hexahydro-1,3,5-dithiazine **27**, presumably formed as indicated in Scheme 2.

The kinetics of the hydrolysis of triazine were studied by ¹H NMR spectroscopy, comparing the area of one triazine signal (2.7 ppm) with the signal of acetonitrile (1.94 ppm), an internal standard not taking part in the reaction.



Scheme 2

At high pH, the hydrolysis was slow enough to be monitored directly in the NMR spectrometer. At lower pH, samples were quenched by addition of a buffered basic solution <2001IEC6051>.

Microsomes isolated from shoot tissues of etiolated wheat seedlings (*Triticum aestivum* L. var. Olaf) oxidized the sulfonylurea herbicide prosulfuron (CGA 152005). Identification of the major oxidation product as 1-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-3-[2-(3,3,3-trifluoropropyl)-5-hydroxyphenylsulfonyl]-urea **28** was confirmed by proton NMR spectroscopy (Figure 15). Proton NMR spectra of isolated minor oxidation products were not obtained because of insufficient sample size for analysis. However, these products were identified tentatively as 1-[4-(hydroxymethyl)-6-methoxy-1,3,5-triazin-2-yl]-3-[2-(3,3,3-trifluoropropyl)phenylsulfonyl] urea **29** and an intermediate oxidation product 1-[4-[(hydroxymethyl)oxy]-6-methyl-1,3,5-triazin-2-yl]-3-[2-(3,3,3-trifluoropropyl)phenylsulfonyl]urea **30**, that degraded to 1-(4-hydroxy-6-methyl-1,3,5-triazin-2-yl)-3-[2-(3,3,3-trifluoropropyl)phenylsulfonyl]urea **31** <1996JFA3658>.

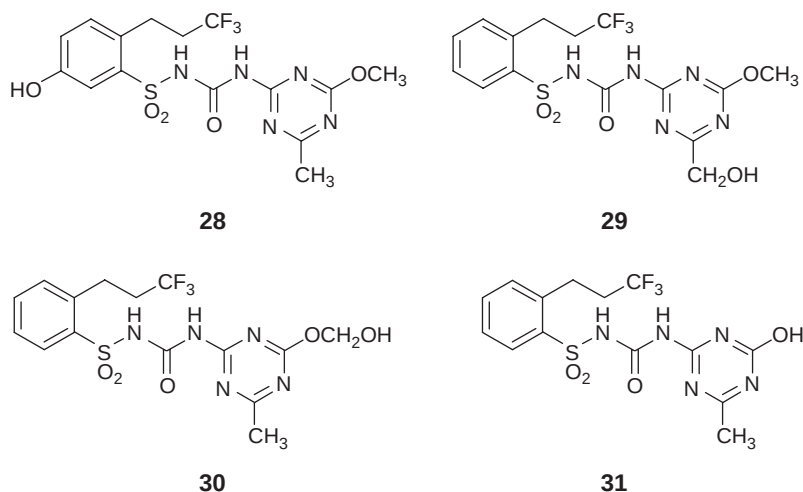
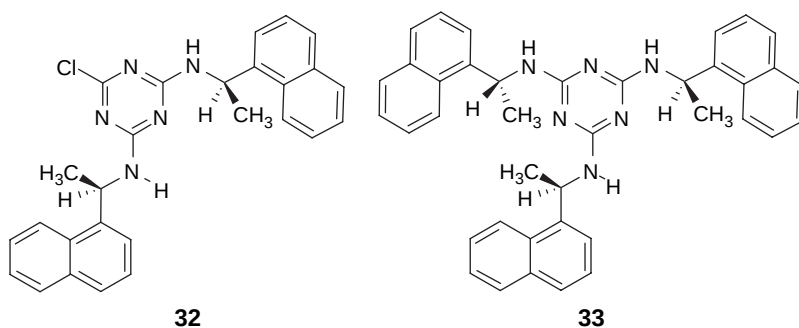


Figure 15

In the development of multiselective chiral auxiliaries, triazine derivatives open interesting new perspectives. Compounds **32** and **33** were shown to be attractive chiral solvating agents for NMR spectroscopy, which cover a wide range for analysis (Figure 16). Both compounds induced significant nonequivalences in the proton nuclei of enantiomers of 3,5-dinitrophenyl derivatives of amines, amino acids, alkyl esters, amino alcohols, and acids. In addition, compound **33** produced enantiodiscrimination in underivatized chiral compounds, showing a remarkable versatility toward hydroxy compounds <1998JOC9197>.

9.03.3.4 Mass Spectra

Phase-transfer-catalyzed alkylation provides an excellent analytical approach for many polar active hydrogen compounds. The perceived advantages of the method for the trace analysis of polar CYA are the relative simplicity, the low detection limits, and the absence of interferences. Furthermore, the reaction conditions, although harsh, leave the molecule intact during the analysis, providing convenient identification by gas chromatography/mass spectrometry (GC/MS). It was seen that the detection limits for CYA between MS-SIM and FTD differed by 2 orders of

**Figure 16**

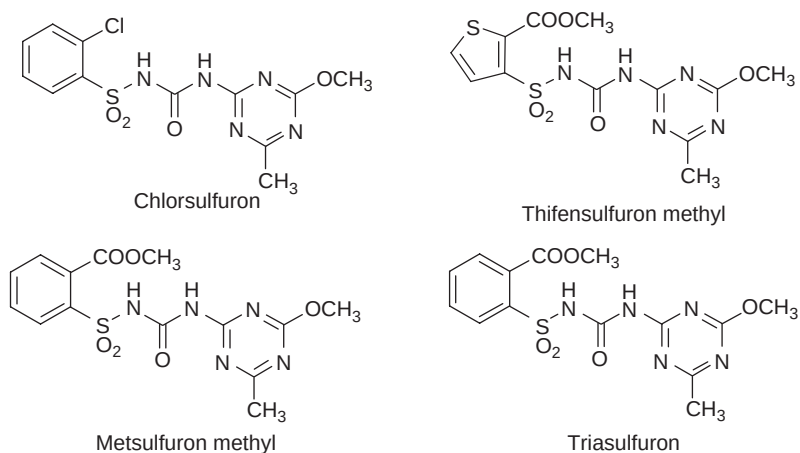
magnitude under the optimum established conditions, with the former being far better (SIM=selective ion monitoring; FTD=flame thermionic detector). The minimum, quantifiable concentration was found to be less than 1 and 90 $\mu\text{g l}^{-1}$ using GC-MS-(SIM) and GC-FTD, respectively <2003ANC4034>.

The sialic acid, or *N*-acetylneuraminic acid (NANA) moiety of an oligosaccharide, is liable to dissociation in- or post-source during mass measurement (MALDI-MS; MALDI=matrix-assisted laser desorption ionization). Accordingly, this moiety was stabilized by amidation using DMTMM chloride as a condensing agent. Amidation stabilized the glycosidic bond with NANA and suppressed its preferential cleavage by in-source decay, post-source decay, or collision-induced dissociation. In addition, the suppressed dissociation considerably improved the yield of the B/Y-type ions for structural analysis by tandem mass spectrometry (MS/MS) <2005ANC4962>.

Desorption electrospray ionization (DESI), an ambient MS technique, was used for trace detection of the explosive RDX, directly from a wide variety of surfaces (metal, plastic, paper, polymer) without sample preparation or pretreatment. Increased selectivity was obtained both by MS/MS and by performing additional experiments in which additives were included in the spray solvent. Pure water could be used as the spray solution for DESI, and it showed ionization efficiencies for RDX in the negative ion mode similar to those given by methanol/water <2005ANC6755>.

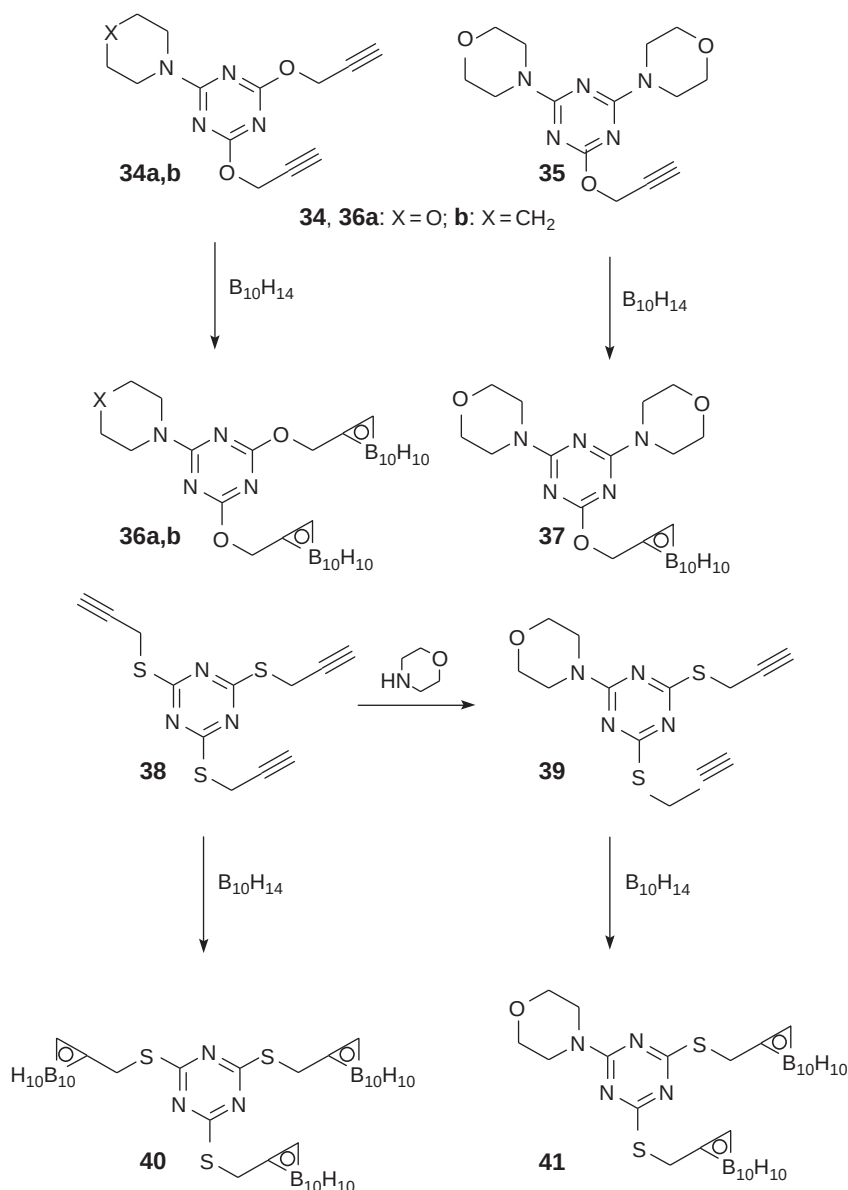
CYA has gained interest as a potential degradation product of triazine herbicides, such as simazine and atrazine. The use of a mass selective complexing agent reduces the possibility of spectroscopic interferences for a sample that has not been subjected to prior separation. Investigation of the various complexation agents provides insight into the nature of the electrosprayed association complexes. The results for CYA determination by complex electrospray mass spectrometry (cESI-MS) compare well with conventional high-performance liquid chromatography (HPLC), even for a difficult matrix, namely urine. This increases confidence in the accuracy of the CYA concentration reported by both techniques <2001JAM1085>.

A multiresidue method for the determination of chlorsulfuron, metsulfuron-methyl, thifensulfuronmethyl, and triasulfuron in soil by high-performance liquid chromatography/electrospray/mass spectrometry (LC/ES/MS) was reported by Marek *et al.* (Figure 17). The herbicides were quantified using SIM <1996JFA3878>.

**Figure 17**

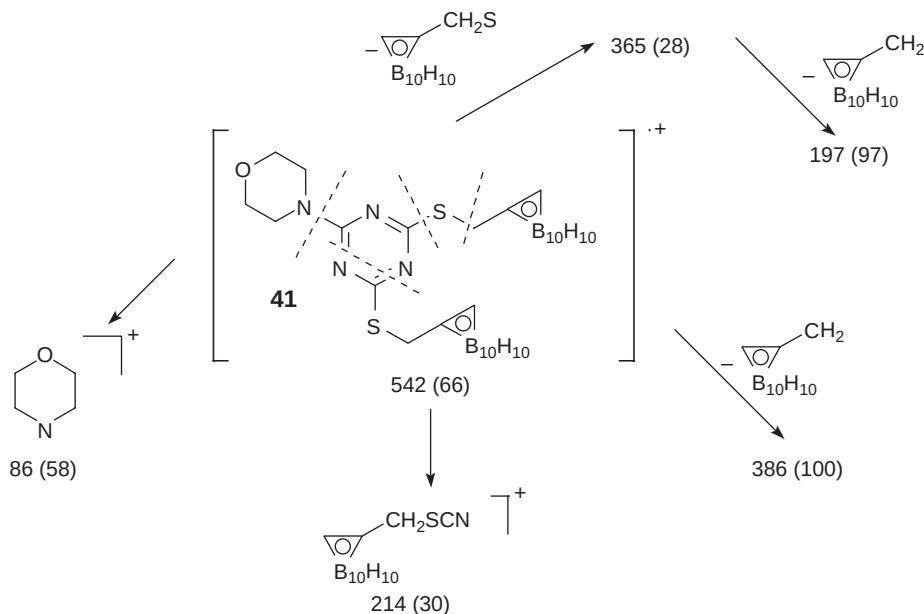
Over the past few years, cyanogen fluoride (FCN) has been the subject of many theoretical and experimental investigations, owing to its role in different fields. Gaseous (FCN)H⁺ ions were obtained by protonation of cyanuric fluoride by strong Brønsted acids such as H₃⁺ (D₃⁺) and C_nH₅⁺ (*n* = 1, 2), and their structures and reactivity were examined by Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry and computational methods at the G2 level of theory. The results show that FCNH⁺ is considerably more stable than the HFCN⁺ protomer, the gap amounting to 360 kJ mol⁻¹ at the G2 level. The gas-phase basicity (GB) of FCN was estimated by 'bracketing' experiments by measuring the efficiency of H⁺ transfer from FCNH⁺ to reference bases <2000PCA5545>.

The transport and accumulation of boron-containing compounds into tumor tissue, which is necessary for further improvement of BNCT (boron neutron cancer therapy), is a continuing challenge <1998CRV1515>. It seemed advantageous to use *s*-triazines as heterocyclic carriers of boron-containing fragments since these compounds may act as antimetabolites of pyrimidine bases and can accumulate in cancer cells <1967JME457>. *s*-Triazines are being investigated also as anticancer drugs. First examples of such boron-containing *s*-triazines **36**, **37**, **40**, **41** were prepared by reaction of propargyl esters **34**, **35**, **38**, **39** with decaborane (Scheme 3) <2003TL8689>.



Scheme 3

New rearrangements of the molecular ions of the 2-aminoderivatives of 4,6-dipropargyloxy-1,3,5-triazine **41** in mass spectrometry were found (**Scheme 4**).

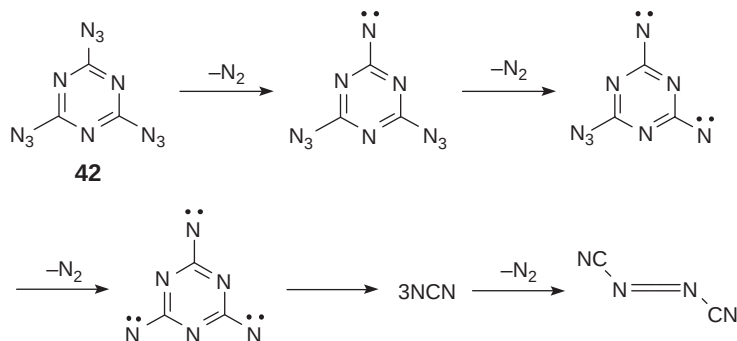


Scheme 4

9.03.3.5 IR/Raman Spectra

Since the publication of theoretical studies predicting that carbon nitride might be harder than diamond, a considerable amount of research has been directed toward the preparation of pure C_3N_4 <1989SCI841>. In contrast, carbon nitride molecules with the C_3N_4 formula have seldom been studied <2003AGE5206>.

Stepwise generation of mononitrene, dinitrene, and trinitrene by the matrix photolysis of 2,4,6-triazido-1,3,5-triazine **42** (cyanuric triazide) was observed by matrix IR and electron paramagnetic resonance (EPR) spectroscopy (**Scheme 5**). The generated species were identified by comparison of their matrix IR spectra with DFT computational results <2004JA7846>.



Scheme 5

2,4-Diamino-*s*-triazines form complexes with uracil derivatives that are as strongly associated as complexes of bis(acylamino)pyridines with uracils (**Figure 18**). 6-Substituted triazines are synthetically more accessible than 4-substituted bis(acylamino)pyridine derivatives; therefore, 2,4-diamino-*s*-triazine and uracil represent a convenient couple for supramolecular chemistry. Both units are synthesized and functionalized in the same fashion with substituents at the 6-position.

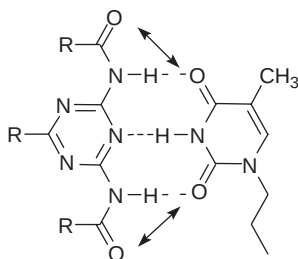
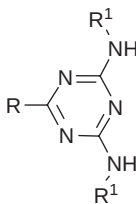


Figure 18

Bis(acylamino)triazines **44** and **46** each show an NH stretching vibration band at 3384 and 3395 cm^{-1} , respectively (**Figure 19**). The complexation behavior of compounds **43** and **45** with *N*-propylthymine in chloroform solution was studied also by means of IR spectroscopy <1996JOC6371>.



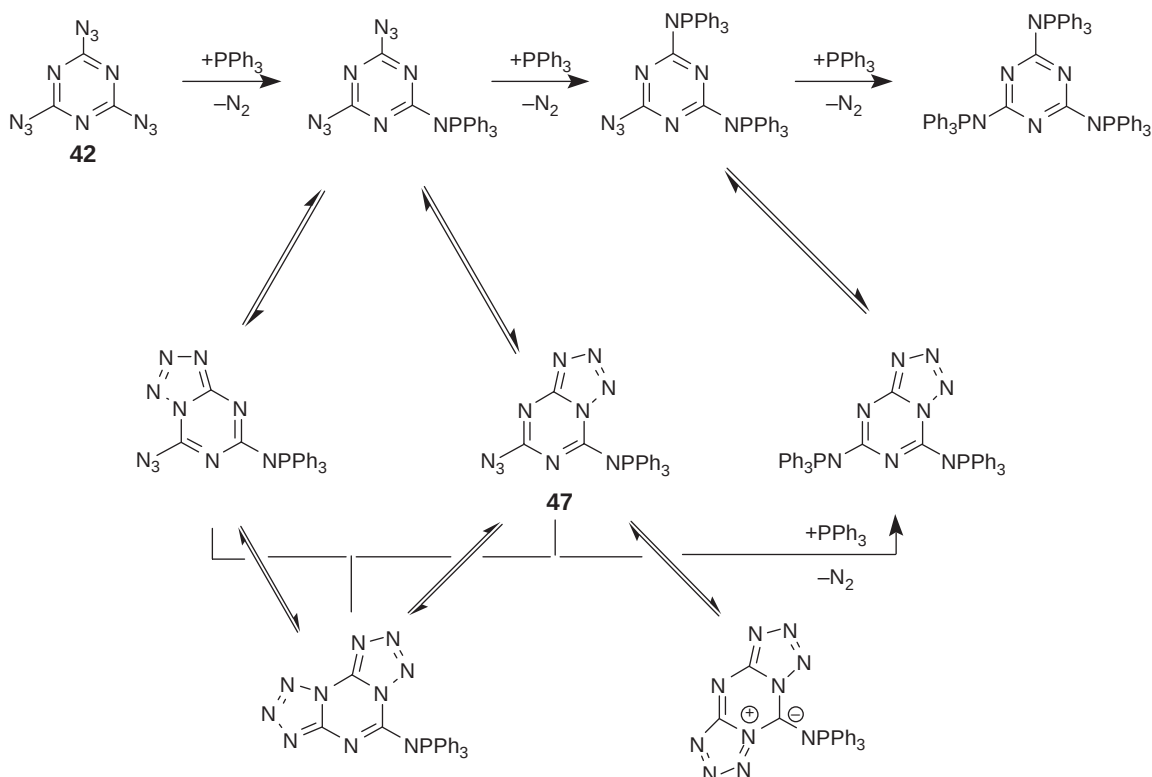
- 43**: $R = n\text{-C}_{12}\text{H}_{25}$; $R^1 = \text{H}$
44: $R = \text{CH}_2\text{OCH}_3$; $R^1 = (\text{CO})\text{CH}_3$
45: $R = \text{CH}_2\text{OCH}_3$; $R^1 = (\text{CO})n\text{-C}_{12}\text{H}_{15}$
46: $R = \text{CH}_3$; $R^1 = (\text{CO})^t\text{Bu}$

Figure 19

2-Triphenylphosphinimino-4-azidotetrazolo[5,1-*a*]-[1,3,5]triazine **47** was obtained by reaction of 2,4,6-triazido-1,3,5-triazine **42** with 1 equiv of triphenylphosphine (**Scheme 6**). Raman and X-ray data revealed that only one azide group formed a tetrazole ring system, whereas the second azide group did not undergo ring closure. The thermodynamics of different isomerization reactions and the activation barriers to cyclization were estimated <2001IC1102>.

9.03.3.6 Photoelectron Spectroscopy

Triamino-*s*-triazine derivatives **48–50** have been prepared, and their cationic states have been analyzed electrochemically by Blackstock and coworkers (**Figure 20**). At 298 K, **48**⁺ has a limited lifetime in CH_2Cl_2 solution; however, **49**⁺ and **50**⁺ are long-lived under such conditions, and quartet states of **49**³⁺ and **50**³⁺ are observed by electron spin resonance (ESR) spectroscopy. Variable-temperature ESR analysis and NMR shift susceptibility measurements indicate that **50**³⁺ is a doublet ground state with a populated quartet state <2000OL171>.



Scheme 6

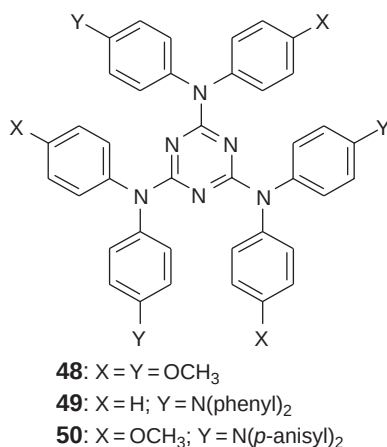


Figure 20

The photoelectron spectra of the mass-selected *s*-triazine (1,3,5-triazine, denoted Tz) cluster anions, Tz^-_n ($n = 1-6$), were obtained at various photon energies to investigate the electronic character of the clusters. This study provides the first direct observation of an isolated molecular anion of azabenzene, Tz^- . From the photoelectron spectrum taken at 1064 nm, the electron affinity (EA) of Tz was determined to be 0.03 eV. By examining the effect of the Jahn–Teller distortion in Tz^- , active vibrations associated with photodetachment were identified. A series of Ar-solvated clusters of Tz^- were also studied, which provided indirect evidence of asymmetric charge distribution in Tz^- caused by the Jahn–Teller distortion <2003JCP4320>.

9.03.3.7 Electron Spin Spectroscopy

The Ru precursor complex $\text{Ru}(\text{acac})_2(\text{CH}_3\text{CN})_2$ facilitates (1) the formation of an unprecedented bridging motif **51** of 2,4,6-tris(2-pyridyl)-1,3,5-triazine (tptz) and (2) the subsequent stabilization of a mixed-valent $\text{Ru}^{\text{II}}\text{Ru}^{\text{III}}$ configuration in the native state of **52–55** (Figure 21). The complexes displayed Ru(II)- and Ru(III)-based metal-to-ligand and ligand-to-metal CT transitions, respectively, in the vis region and ligand-based transitions in the UV region. In spite of reasonably high K_c values for **52–55**, the expected intervalence CT transitions did not resolve in the typical near-IR region up to 2000 nm.

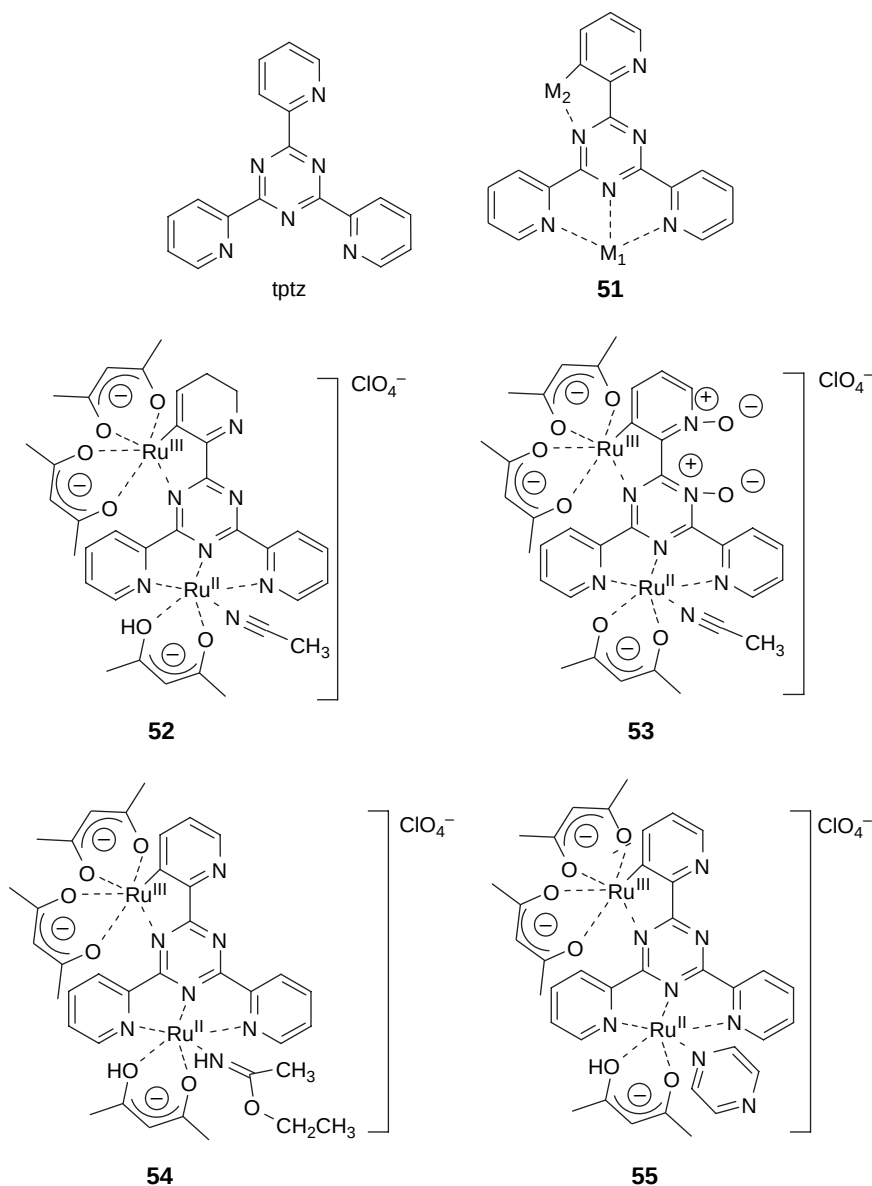
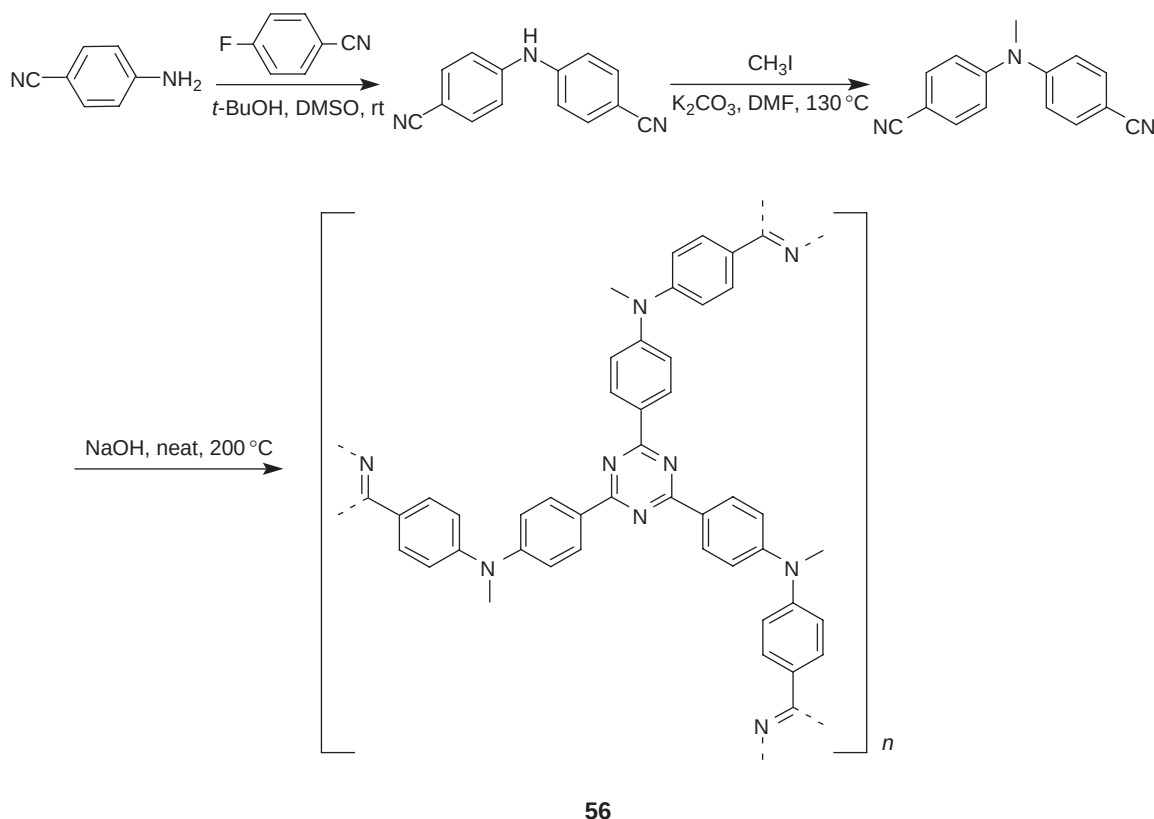


Figure 21

The paramagnetic $\text{Ru}^{\text{II}}\text{Ru}^{\text{III}}$ species **52–55** displayed rhombic EPR spectra at 77 K, typical of a low-spin Ru(III) ion in a distorted octahedral environment. The one-electron-reduced tptz complexes $[\text{Ru}^{\text{II}}(\text{tptz}^{\cdot-})(\text{acac})(\text{CH}_3\text{CN})]$ and $[(\text{acac})_2\text{Ru}^{\text{III}}(\mu\text{-tptz-H}^+)^{\cdot-2-}]\text{-Ru}^{\text{II}}(\text{acac})(\text{CH}_3\text{CN})$ **52**, however, show a free-radical-type EPR signal near $g = 2.0$ with partial metal contribution <2006IC2413>.

9.03.3.8 Fluorescence Spectroscopy

A novel synthetic strategy and optical properties of highly fluorescent, triazine-amine conjugated oligomers **56** were described by Fujita and Murase. The oligomers can be expressed as $(2n+1)$ -mer, where n represents the number of triazine rings in the oligomer (Scheme 7).



Scheme 7

The absorption maximum of an amine-conjugated trimer ($X = \text{NMe}$, $n = 1$) was outstandingly red-shifted as compared with those of the other trimers ($X = \text{CH}_2$, O). In acidic media, the amine-conjugated trimer showed two-step bathochromic shifts caused by protonation. The absorption maxima of the amine-conjugated $(2n+1)$ -mers ($X = \text{NMe}$, $n = 1-4$) did not depend on n ; instead, shoulder peaks appeared in the long-wavelength region when $n \geq 2$. The oligomers involving alternate conjugation of triazines and NMe groups through phenylene groups showed strong fluorescence in chloroform. In particular, the pentamer was the most efficient blue emitter ($\Phi_F = 0.82$). The other triazine-containing oligomers ($X = \text{CH}_2$, O) did not show fluorescence at all. Therefore, it was concluded that the emission properties are due to the strong electron-donating and accepting abilities of the NMe and triazine moieties, respectively <2005JOC9269>.

The total internal reflection (TIR) fluorescence decay profile of riboflavin (RF) in the absence of a guest in the CCl_4 phase was fitted satisfactorily by a single exponential function. On the other hand, in the presence of *N,N*-dioctadecyl-[1,3,5]triazine-2,4,6-triamine (DDT) as a guest in the CCl_4 phase, the fluorescence decay profiles were best fitted by double-exponential functions with the relevant amplitude (A_i) being varied with the concentration of DDT (Figure 22).

The slow rotational reorientation time of RF at the interface was ascribed to that of the RF-DDT complex formed at the water/ CCl_4 interface <2003ANC6035>.

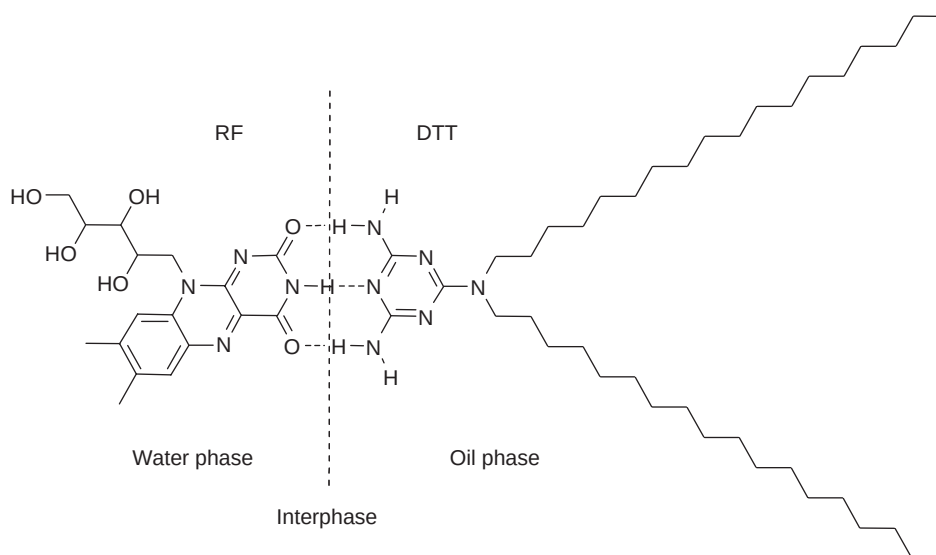
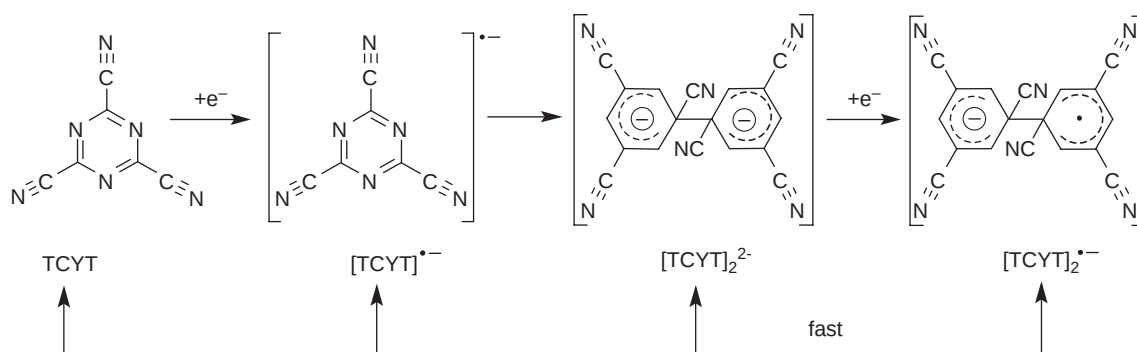


Figure 22

9.03.3.9 Other Methods

Chemical reduction of 2,4,6-tricyano-1,3,5-triazine, TCYT, results in the formation of an unstable radical anion that undergoes immediate dimerization at a ring carbon to form $[C_{12}N_{12}]^{2-}$, $[TCYT]_2^{2-}$, characterized by a long 1.570(4) Å central C–C bond. $[TCYT]_2^{2-}$ can decompose into the radical anion of 4,4',6,6'-tetracyano-2,2'-bitriazine, $[TCYBT]^-$, the one-electron reduced form of planar (D_{2h}) TCBT, which is also structurally characterized as the $[TMPD][TCYBT]$ CT complex (TMPD); (*N,N,N',N'*-tetramethyl-*p*-phenylenediamine) with a 1.492(2) Å central sp^2-sp^2 C–C bond (Scheme 8). Although crystals could not be obtained for the radical anion $[TCYBT]^-$, the electrochemistry, EPR, and theoretical calculations support the formation of $[TCYBT]^-$ <2003JOC3367>.



Scheme 8

Compounds with an intramolecular hydrogen bridge (IMHB), such as 2-(2-hydroxyaryl)-1,3,5-triazines, are used widely for the photostabilization of polymers. They absorb harmful UV radiation and transform it, via a very efficient ESIPT within the IMHB, into vibrational energy.

Both UV absorption and fluorescence maxima of 2-(2-methoxyaryl)-1,3,5-triazines show a marked bathochromic shift with increasing proton concentration. Well-defined isosbestic points establish an equilibrium between

protonated and nonprotonated species for the ground state. At higher proton concentrations, the twisted intramolecular charge transfer (TICT) fluorescence of the nonprotonated (2-methoxyaryl) triazines was shown to be replaced gradually by the much weaker fluorescence of the protonated species, which is shifted to still longer wavelengths <2000PCA8296>.

Various copolymers of 2,4-bis(2,4-dimethylphenyl)-6-[2-hydroxy-4-(2-hydroxy-3-[2-methylpropenoyloxy])propoxyphenyl]-1,3,5-triazine, with styrene, methyl methacrylate, and methacrylic acid have been synthesized by radical polymerization. Their absorption spectra in the long-wavelength UV region appear unchanged compared to those of the monomeric UV absorbers, indicating that the stabilizer chromophore remains unimpaired in the course of the polymerization.

9.03.4 Thermodynamic Aspects

9.03.4.1 Boiling Points and Melting Points

No new relevant data were found.

9.03.4.2 Chromatography

9.03.4.2.1 Thin-layer chromatography

A simple and rapid high-performance thin-layer chromatographic (HPTLC) determination of lamotrigine (LTG) in serum has been reported. The method involves extraction of the drug by ethyl acetate followed by separation on TLC silica plates using a mixture of toluene–acetone–ammonia (7:3:0.5), as eluting solvent. Densitometric analysis was carried out at 312 nm with LTG being detected at R_f of 0.54. The analytical method has excellent linearity ($r = 0.998$) in the range of 20–300 ng/spot. This assay range is adequate for analyzing human serum, as it corresponds to LTG concentrations measured in human serum from epileptic patients <2005JCH152>.

The traditional ‘one-pot’, three-component synthesis was adapted successfully for combinatorial mixture synthesis of dihydrophenyl triazines, which are nonclassical, dihydrofolate reductase (DHFR) inhibitors. The products precipitated out of the reaction mixture and could be collected easily and cleansed by washing. The reactions were monitored by TLC <1999BMC1255>.

Hydrogen-bonded tapes comprised of monomeric molecular precursors are used to define structural parameters for the design of related oligomers encoded with predetermined modes of assembly. Application of this ‘covalent casting’ strategy *vis-à-vis* the one-dimensional H-bonding motif expressed by 2-amino-4,6-dichlorotriazine has enabled the design of high-affinity duplex molecular strands.

Dimeric, trimeric, and tetrameric duplex oligomers are prepared through an iterative synthetic protocol involving sequential homologation of the oligo(aminotriazine). The use of fluorescent labels in conjunction with TLC analysis provides a qualitative test for duplex formation <2002JA5074>.

The selectivity of TLC systems was compared by use of correlations between $R_f(II)$ and $R_f(I)$ (by analogy with two-dimensional TLC). The greatest spread of points, indicative of individual selectivity, was obtained for nonaqueous mobile phases on silica and aqueous mobile phases on octadecyl silica adsorbent wettable with water (RP-18 W). The correlation of R_f values in normal- and reversed-phase systems was utilized in the practical separation of a mixture of 14 triazines and urea herbicides using 2-D TLC on a Multi-K CS5 dual phase (3 cm strip of octadecyl silica parallel to silica layer). The plate was videoscanned showing the real picture of the plate <2002JCH277>.

The mechanisms of the photodegradation of atrazine under direct photolysis, and in the presence of two different photocatalysts, TiO_2 and $Na_4W_{10}O_{32}$, were investigated by the means of TLC analysis on C-14 ring-labeled atrazine solutions. Integration of photo- and biodegradation processes was studied <1999T3401>.

Anaerobic biodegradation of atrazine by the bacterial isolate M91-3 was characterized with respect to mineralization, metabolite formation, and denitrification. The ability of the isolate to enhance atrazine biodegradation in anaerobic sediment slurries was also investigated. The organism utilized atrazine as its sole source of carbon and nitrogen under anoxic conditions in fixed-film (glass beads) batch column systems. Results of HPLC and TLC radiochromatography suggested that anaerobic biotransformation of atrazine by microbial isolate M91-3 involved hydroxyatrazine formation <1998AMB618>.

9.03.4.2.2 High-pressure liquid chromatography

Every year, over 250 million pounds of CYA **1** and chlorinated isocyanurates are produced industrially. The method developed for **1** using HPLC with UV detection simplifies and optimizes certain parameters of previous

methodologies by effective pH control of the eluent (95% phosphate buffer: 5% methanol, v/v) to the narrow pH range of 7.2–7.4. UV detection was set at the optimum wavelength of 213 nm where the cyanuric ion absorbs strongly <2000ANC5820>.

An *s*-triazine scaffold bearing a free and a protected amino group was synthesized and used for connecting two different and differently derivatized amino acids (Figure 23). Two diastereoisomeric chiral systems were obtained and, once linked to silica gel, they were used in the chromatographic resolution of structurally and electronically different racemic analytes, chosen among the racemates resolved by the isolated amino acid derivatives.

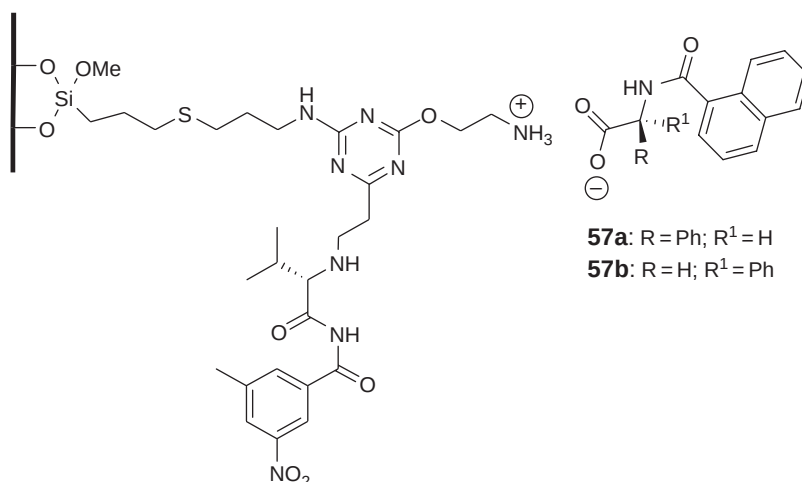


Figure 23

The collected results demonstrated the biselecting behavior of **57a** and **57b** in terms of enantiodiscriminating capability toward the class of racemic compounds resolved by both the isolated selectors as well as in terms of the independent action of the two chiral moieties of the system <2003TA1345>.

The use of LC–MS and LC–UV allowed determination of the degradation pathway of cyromazine under irradiation, with or without TiO₂. The formation of CYA prevented the complete mineralisation of cyromazine as previously observed for atrazine and other *s*-triazines by oxidative methods <2001JPH79>.

The metabolic fate of RDX was studied in a mixed culture incubated under methanogenic conditions. Analysis by HPLC confirmed the loss of RDX and the formation of mono-, di-, and trinitroso-RDX as transient biodegradation intermediates. An additional peak observed in the HPLC chromatogram was identified by LC–MS as hydroxylamino-dinitroso-1,3,5-triazine <2001ETC1874>.

9.03.4.2.3 Gas chromatography

Knopp and co-workers have developed a rapid and efficient method for the selective extraction of *s*-triazine herbicides in environmental samples using an immunosorbent of monoclonal antiatrazine antibodies, which were encapsulated in a sol–gel glass matrix. The method allows for the determination of the herbicides in linear ranges up to 1.5 µg l⁻¹ with correlation coefficients higher than 0.99 and relative standard deviations between 4% and 7% (*n* = 5). The LODs for 50 ml water samples were in the range 0.02 µg l⁻¹ (atrazine, propazine) to 0.1 µg l⁻¹ (desethyl atrazine) <2002EST3372>.

A GC/ion trap MS method was used for the trace analysis of atrazine and its deethylated degradation product deethylatrazine in environmental water and sediment samples. The isotope dilution technique was applied for the quantitative analysis of atrazine at parts-per-trillion levels <2003ANA263>.

The persistence of terbuthylazine, simazine, atrazine, and prometryn (*s*-triazine herbicides) was studied in sea, river, and groundwaters during long-term laboratory incubation (127 days) under different laboratory conditions (light–darkness at 20 °C). Analysis of herbicides was performed by GC–NPD and their identity was confirmed by GC–MSD (NPD = nitrogen phosphorus detector; MSD = mass selective detector) <2004SCT87>.

A GC method using phase-transfer catalysis for the simultaneous derivatization, extraction, and preconcentration of the highly polar CYA was developed recently. The method was based on the extractive N-methylation of the analyte of concern in two- and three-phase systems, whereby the 1,3,5-trimethyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione was

formed. The method is highly sensitive, almost free from interferences, and was easily applied to the determination of cyanuric acid in swimming pool water, surface water, human urine, and simulated air filter samples <2003ANC4034>.

9.03.4.2.4 Suppressed anion chromatography

Suppressed anion chromatography (SAC) <1975ANC1801> is generally recognized as a prominent technique for anion analysis at trace and ultratrace levels. The performance of CYA **1** (in the 1,3,5-triazine-2,4,6-trihydroxy form) as eluent for SAC has been investigated by Maurino and Minero. The distinctive features of this eluent are reported with respect to the others that are now routinely utilized. CYA-based eluents for SAC have several advantages over carbonate and tetraborate buffers: (1) wider range of eluent strength, (2) lower background conductivities, (3) good calibration linearities, (4) improved sensitivity for carboxylic acids, (5) the possibility to perform gradient analysis with limited baseline drifts, and (6) ease of eluent purification. This makes the **1**-based eluent well-suited for the analysis of strongly retained anions like chromate, thiosulfate, iodide, thiocyanate, and perchlorate with good limits of detection and reasonable capacity factors <1997ANC3333>.

9.03.4.3 Cyclic Voltammetry

The adsorption of organic molecules with different functional groups on Cu(111) in a 0.1 M HClO₄ solution was investigated *in situ* by cyclic voltammetry. The molecules of CYA and cyanuric chloride (CC) adsorb on the Cu(111) electrode surface and form well-defined adlayers with (3 × 3) structure in the double-layer potential region. The results were compared with those obtained on aromatic and heterocyclic molecular adlayers <2002PCB11272>.

9.03.4.4 Aromaticity

The statement that aromaticity is an elusive concept has been repeated again and again, so as to become commonplace. It happens, however, that there is no magnitude defining it unambiguously; it is not an observable property. An MO multicenter bond index involving the $\sigma+\pi$ electron population is proposed as a measure of aromaticity. It is related both to the energetical and to the magnetic criteria. Hexazine has the highest I (aromaticity index definition) ring value and 1,3,5-triazine the lowest one. The minimum bond order in a ring system is adopted as an aromaticity index definition based on ring current (RCI) <2000PCP3381>.

The compound 3,5-diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazine crystallizes with two methanol solvent molecules in the triclinic space group <P1, with $a = 7.372(4)$, $b = 10.476(4)$, $c = 11.863(11)$ Å, $\alpha = 72.18(5)$, $\beta = 79.73(6)$, $\gamma = 79.47(4)^\circ$. There is substantial distortion between the phenyl and triazine rings as illustrated by the value of the nonbonded angle C-3t-C-6t-C-4 of 173.60° and the C-4 atom being -0.4487 Å from the plane calculated for the triazine ring atoms. The lengths of the bonds of the triazine moiety suggest that there is a potential decrease in the degree of aromaticity of the ring. Comparisons were made between this structure, and other LTG analog structures that have been reported <1999JCX163>.

The basis for unprecedented noncovalent bonding between anions and the aryl centroid of electron-deficient aromatic rings has been demonstrated by an *ab initio* study of the interaction between 1,3,5-triazine and the fluoride, chloride, and azide ions at the MP2 level of theory. Minima are also located corresponding to C-H $\cdots$ X[−] hydrogen bonding, reactive complexes for nucleophilic attack on the triazine ring, and π -stacking interactions (with azide). Trifluoro-1,3,5-triazine also participates in aryl centroid complexation and forms nucleophilic reactive complexes with anions <2002JA6274>.

9.03.4.5 Conformation

Recently, the crystal structure of three derivatives of 2,4-dimethoxy-1,3,5-triazine has been described. In 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine **58**, the morpholine moiety adopts a chair conformation, and the dimethoxytriazine molecule adopts a butterfly conformation with respect to the two methoxy groups. In 3-(4,6-dimethoxy-1,3,5-triazin-2-yloxy)-2-methylphenol **59**, the dimethoxytriazine moiety adopts a propeller conformation with respect to the methoxy groups, and the molecules form dimers held together by O-H $\cdots$ N hydrogen bonds. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yloxy)phenyl phenyl ketone **60**, crystallizes with two crystallographically independent molecules in the asymmetric unit (Figure 24). The two molecules adopt different conformations with respect to the geometric relations between the phenyl ketone and triazine moieties <2003AXC687>.

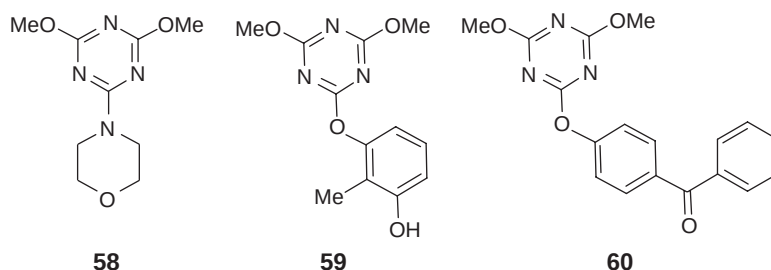


Figure 24

In the crystal structure of 4-chloro-6-morpholino-*N*-phenyl-1,3,5-triazin-2-amine **61**, there are intermolecular N–H···O hydrogen bonds which propagate infinite chains parallel to the *c*-axis (Figure 25). The morpholine ring adopts a chair conformation <2005AXE2345>.

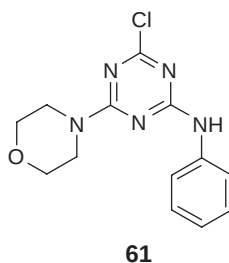


Figure 25

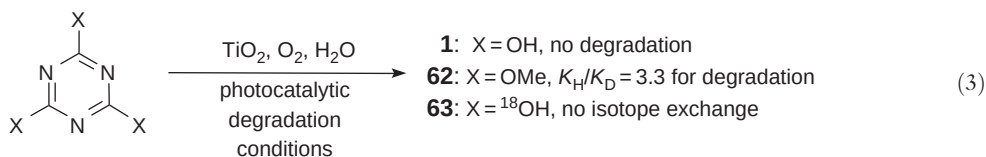
9.03.4.6 Tautomerism

The tautomeric equilibria of variously substituted 5-triazinones have been studied by comparing their mass spectra with those of their methylated derivatives. The results for 6-methyl-5-triazinone have been confirmed by comparison with the mass-analyzed ion kinetic energy spectra of ions generated from *N*-ethyl derivatives. The equilibria are dependent upon the nature of the substituents in the 3- and 6-positions <2005OMS347>.

9.03.5 Reactivity of Fully Conjugated Rings

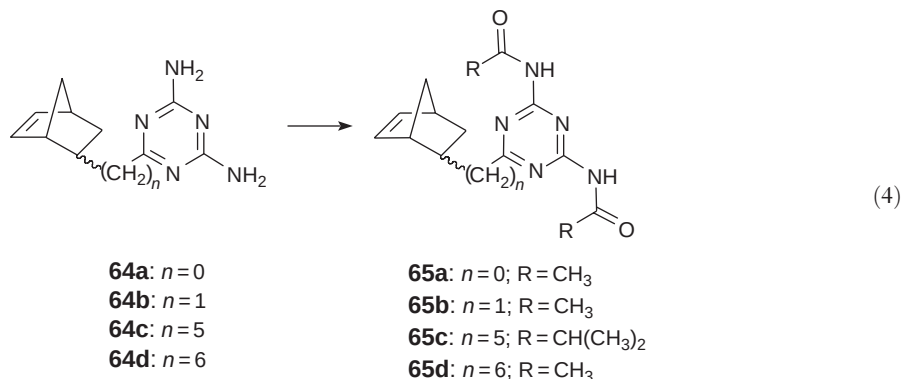
9.03.5.1 Unimolecular Thermal and Photochemical Reactions

CYA **1** is unique among organic molecules in being resistant to photocatalytic degradative conditions by TiO₂ in oxygenated water. Trimethyl cyanurate **62** shows an isotope effect of 3.1–3.3 on degradation selectivity when the methyl groups are deuterated, and cyanuric acid enriched in ¹⁸O, as in **63**, does not exchange hydroxyl groups with bulk water under these conditions (Equation 3). Thus, the tolerance of CYA to photocatalysis is not due to rapid and reversible addition to the aromatic nucleus <1999OL463>.

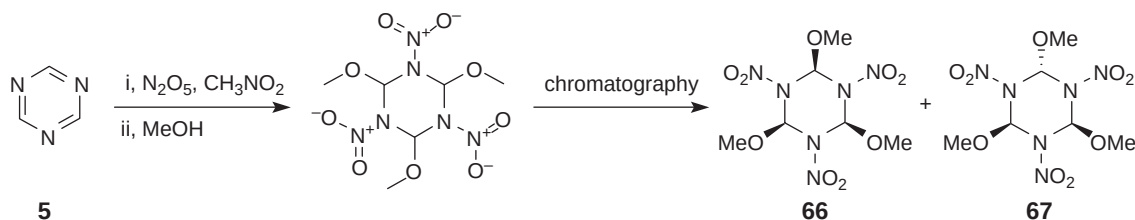


9.03.5.2 Electrophilic Attack at Nitrogen

Unsubstituted diaminotriazines **64a–d** are soluble only in highly polar solvents such as alcohols or dimethyl sulfoxide (DMSO; Equation 4). However, after acylation, monomers **65a**, **65b**, and **65d** are highly soluble in chloroform <2003CEJ992>.



When 1,3,5-triazine **5** is allowed to react with dinitrogen pentoxide and quenched with methanol, the product is indeed 1,3,5-trinitro-2,4,6-trimethoxyhexahydrotriazine (**Scheme 9**). However, upon chromatography, it was possible to isolate two isomers, the *cis*-**66** and *trans*-2,4,6-trimethoxy-1,3,5-trinitrohexahydrotriazine **67** in about an equimolar ratio <2000JOC4743>.



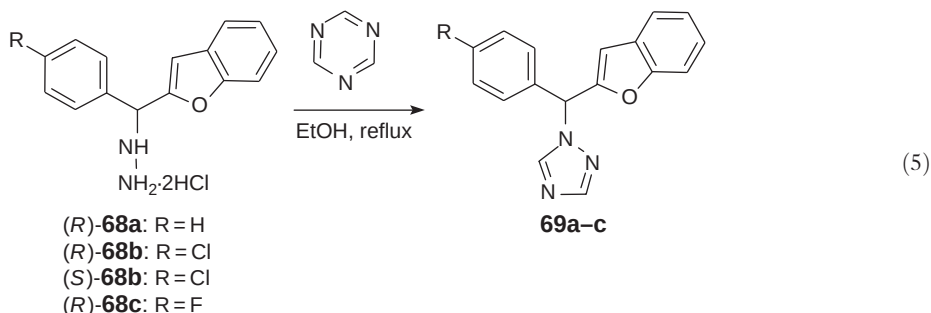
Scheme 9

9.03.5.3 Electrophilic Attack at Carbon

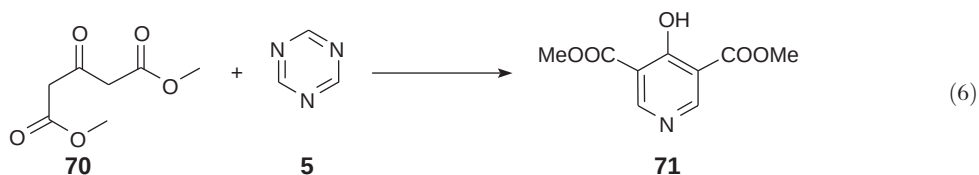
1,3,5-Triazines are resistant to electrophilic attack at carbon.

9.03.5.4 Nucleophilic Attack at Carbon

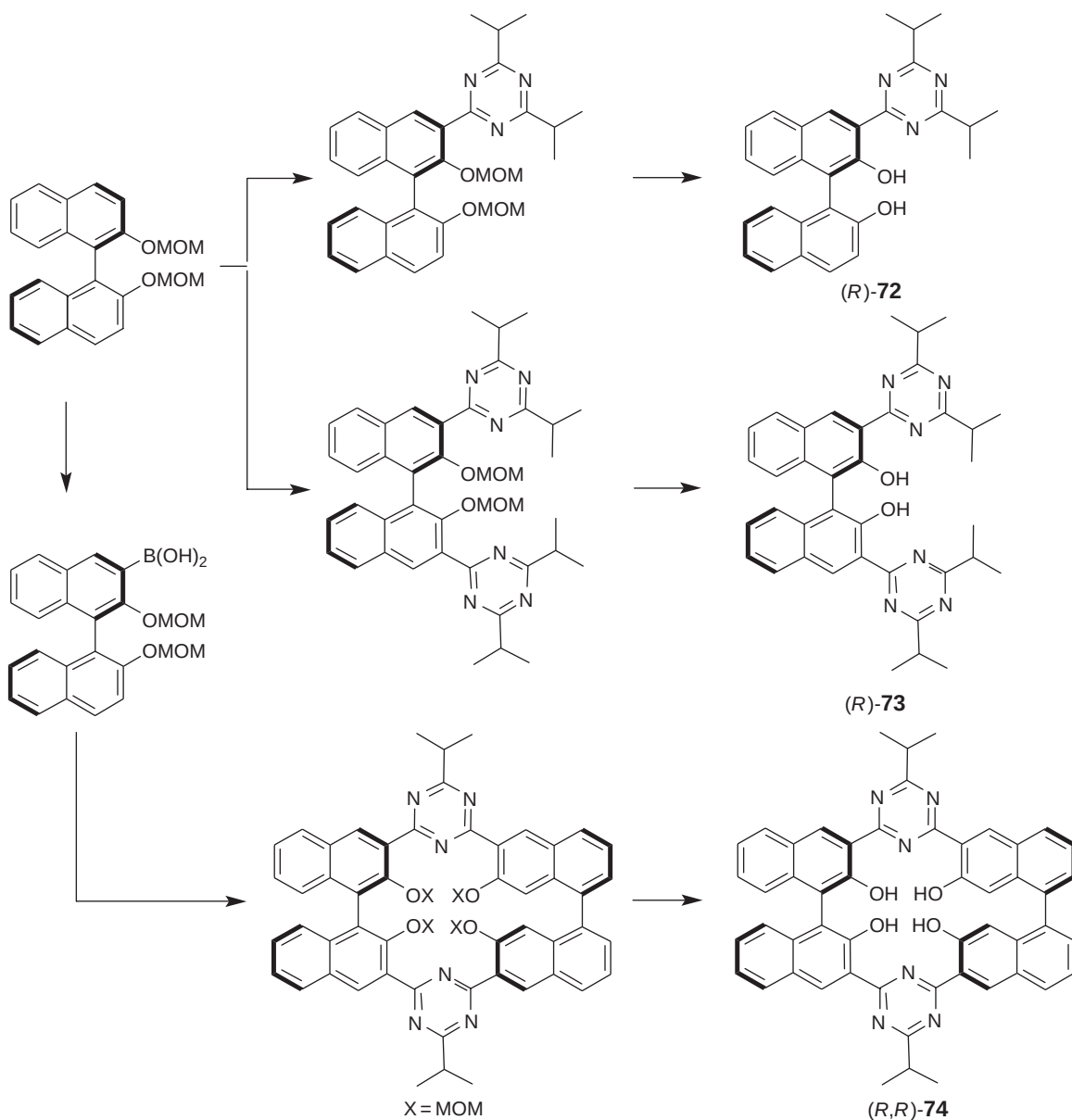
S-triazine **5** was used as the cyclization reagent in refluxing EtOH for conversion of (*R*)-**68a–c** and (*S*)-**68b** into the triazoles **69a–c** (Equation 5) <2000TA4895>.



Analogously, 1,3,5-triazine **5** was used for the conversion of dimethyl 1,3-acetonedicarboxylate **70** into the corresponding dimethyl 4-hydroxypyridine-3,5-dicarboxylate **71** (Equation 6) <2000JOC7432>.

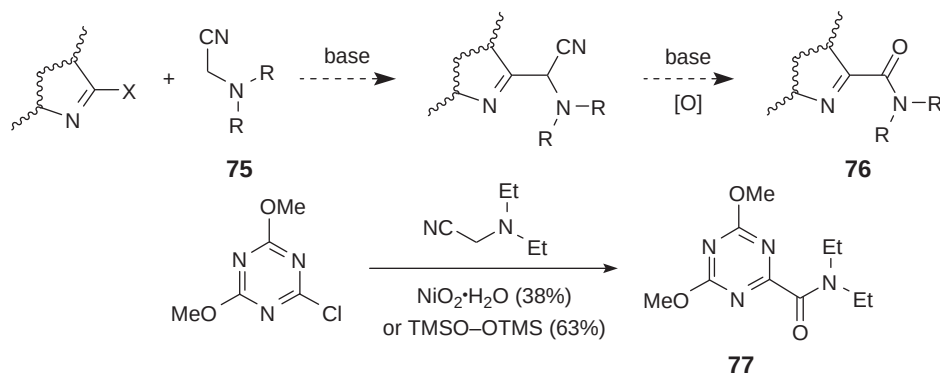


Three new substituted BINOL ligands, (*R*)-3-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-1,10-bi-2-naphthol (*R*)-(**72**), (*R*)-3,3'-bis[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-1,10-bi-2-naphthol (*R*)-(**73**), and 2,4-bis(2,2'-dihydroxy-1,10-binaphthalen-3-yl)-6-(*p*-tolyl)-1,3,5-triazine (*R,R*)-(**74**), have been obtained by directed *ortho*-lithiation and a Suzuki cross-coupling process (Scheme 10) <2005TA3667>. The titanium complex of (*R*)-**72** was found to be an effective catalyst in the asymmetric addition of diethylzinc to a variety of aromatic aldehydes.



Scheme 10

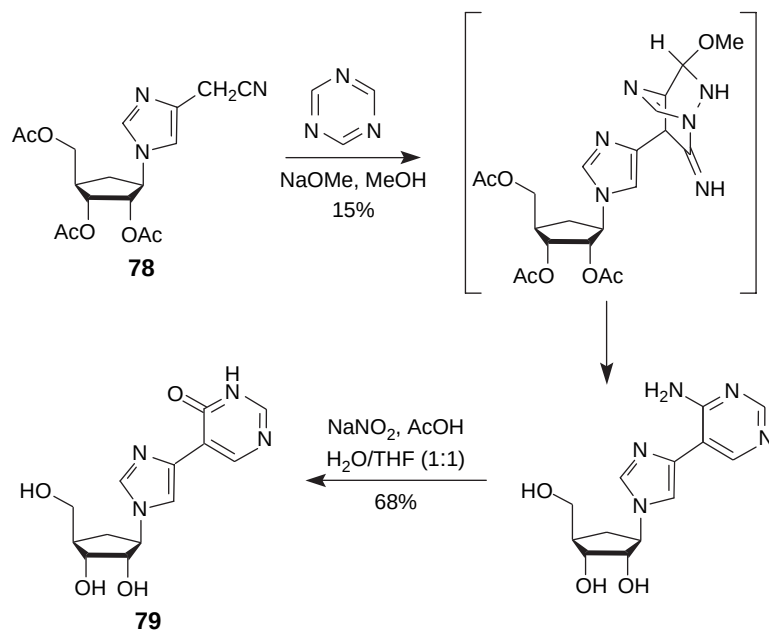
Dialkylamino acetonitrile derivatives **75** were utilized as alternatives to cyanohydrin synthons for preparation of the corresponding heteroaryl dialkyl amides **76** via a strategy of sequential base-mediated coupling and oxidation (**Scheme 11**). The most advantageous oxidant, $\text{NiO}_2 \cdot \text{H}_2\text{O}$, can readily oxidize 2-(diethylamino)ethanenitrile to the corresponding amide **77** under both basic and neutral conditions by forming cyanohydrins *in situ* <2004JOC1360>.



Scheme 11

9.03.5.5 Cycloaddition Reactions

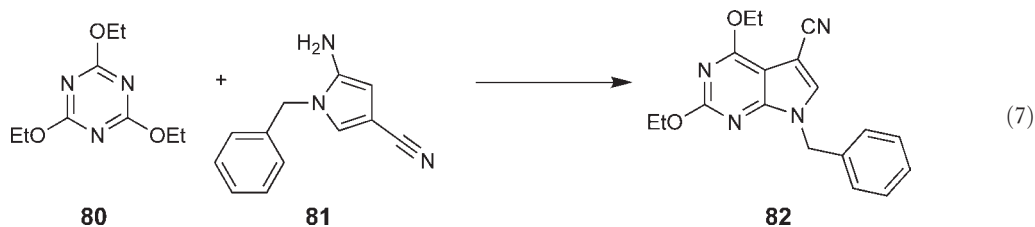
In situ formation of **79** from **78** was accomplished by a [4+2] Diels–Alder cycloaddition using sodium methoxide and 1,3,5-triazine, which was followed by a retro-Diels–Alder fragmentation of the intermediate that formed (**Scheme 12**) <2005OL63>. Inosine fleximer **79** was then realized in 68% yield, using standard diazotization conditions, followed by hydrolysis.



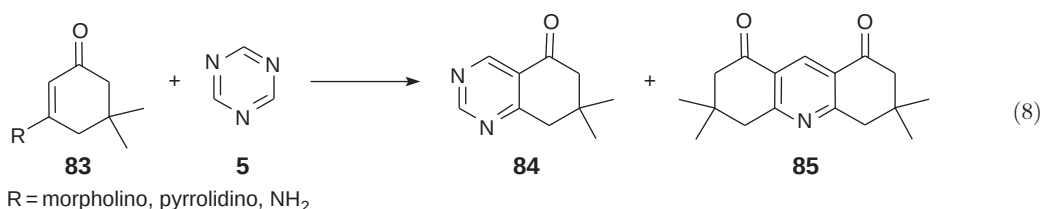
Scheme 12

2,4,6-tris(Ethoxycarbonyl)-1,3,5-triazine **80**, when treated with 2-amino-1-benzyl-4-cyanopyrrole **81**, underwent the inverse electron demand Diels–Alder (IDA) reaction, at room temperature, in just 2 h to efficiently generate

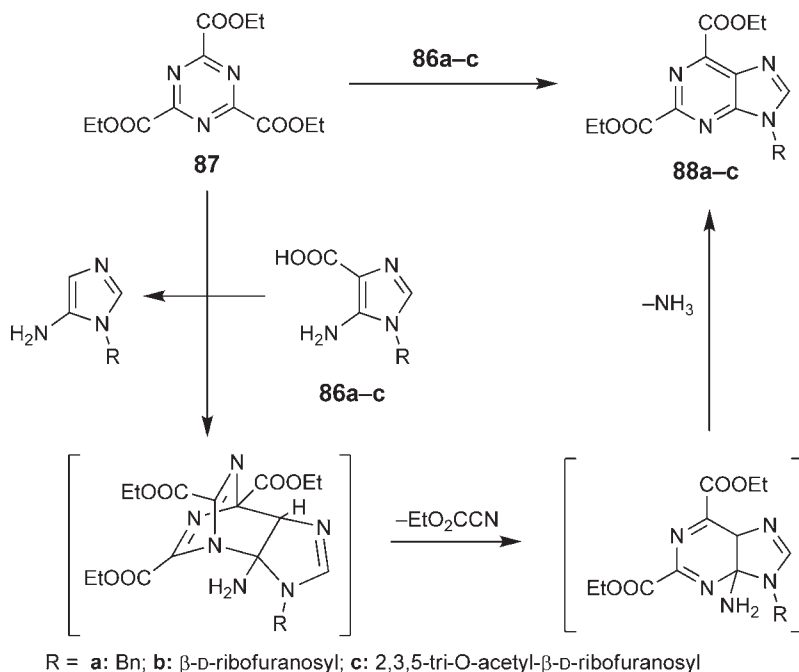
pyrrolo[2,3-*d*]pyrimidine **82** in high yield (Equation 7). This observation of high reactivity exhibited by pyrrole **81** is very unusual compared to other IDA reactions since most uncatalyzed IDA reactions were conducted under thermal conditions and sometimes required prolonged heating at elevated temperatures <2002JOC8703>.



Enaminones **83** undergo an IDA reaction with 1,3,5-triazine **5**, allowing access to functionalized quinazolinones as intermediates in the synthesis of CNS agents (Equation 8). This reaction is highly dependent upon the solvent: 1,3,5-triazine **5** undergoes single or double [4+2] cycloadditions with enaminones, and quinazolinones **84** or acridinediones **85** could be obtained selectively <2002TL3551>.

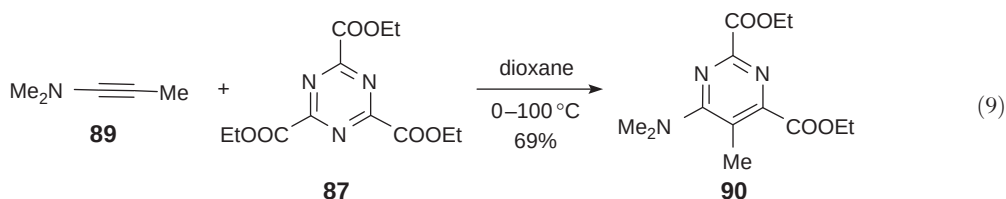


In an effort to find a more efficient synthesis of purine analogues, Dang *et al.* have explored the inverse electron demand Diels–Alder reaction between 5-aminoimidazoles **86a–c** and 1,3,5-triazines **87**. Reaction of 5-amino-1-benzyl-4-imidazolecarboxylic acid **86a** with **87** at 80 °C in DMF led to 9-benzyl-2,6-bis(ethoxycarbonyl)purine (**88a**) in 83% yield.

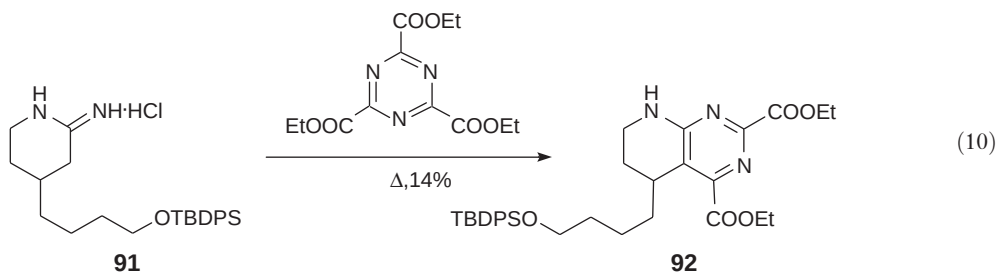


Scheme 13

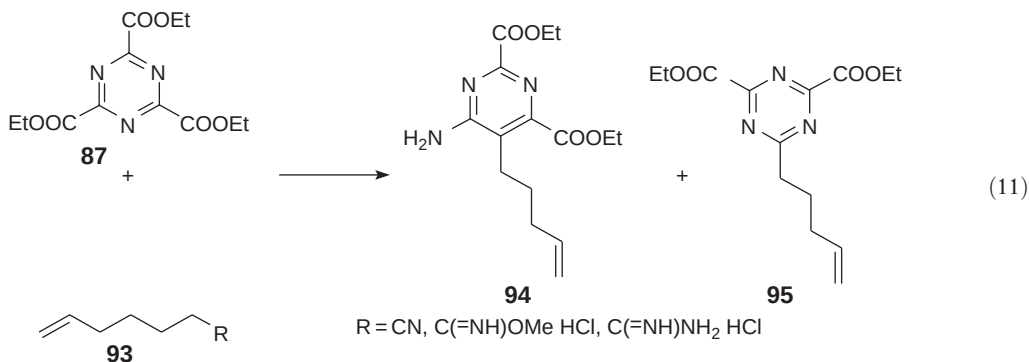
Preparation of **90** was accomplished from the [4+2] cycloaddition of 1-(dimethylamino)propyne **89** with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine **87** (Equation 9) <1998JA53>.



Thermal reaction of the amidine **91** with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine **87** provided only low conversion to the desired pyrimidine **92** and these results contrasted the effective conversion (75%) observed with the unsubstituted 2-iminopiperidine hydrochloride itself (Equation 10) <1998BMC643>.



Diels–Alder reaction of **93**, effected by treatment with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine **87**, provided the pyrimidine **94** together with a significant amount of the isomeric triazine **95** (Equation 11).



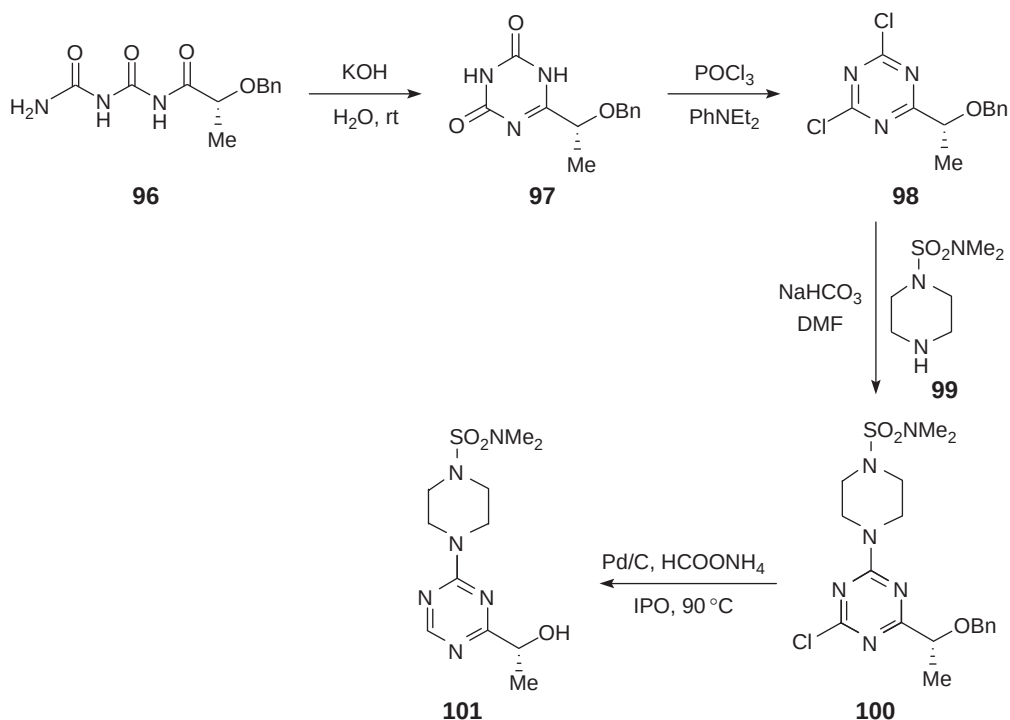
9.03.5.6 Reactions with Radicals

1,3,5-Tris[*p*-(*N*-oxy-*N*-tert-butylamino)phenyl]benzene is known as a persistent triradical with a quartet ground state. A new triradical with a triazine skeleton was synthesized and characterized. The nitroxide triradical with triazine derivative 2,4,6-tris[*p*-(*N*-oxy-*N*-tert-butylamino)phenyl]-1,3,5-triazine exhibited stronger intramolecular ferromagnetic interactions than those with the benzene derivative. The magnitude of the interactions depends on the planarity of the structures and/or the spin density of the center skeletons <1999CL545>.

9.03.6 Reactivity of Nonconjugated Rings

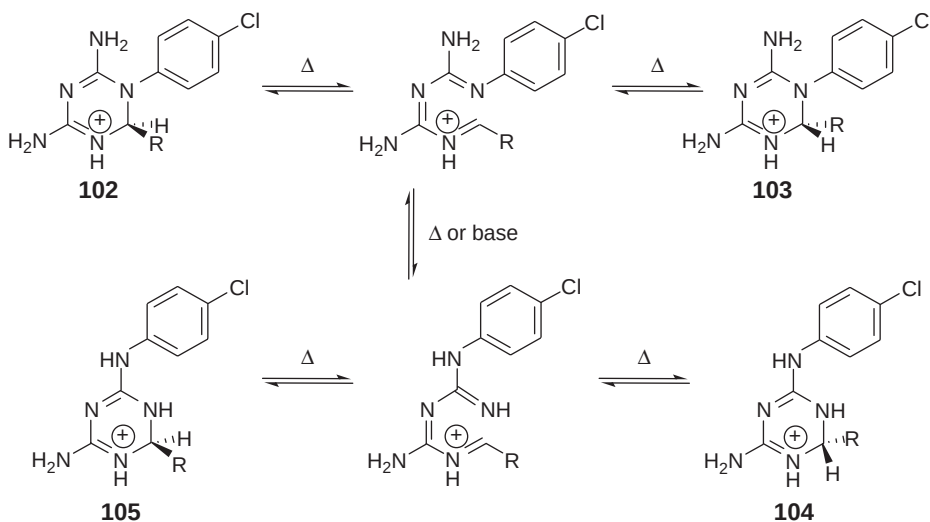
9.03.6.1 Dihydro-1,3,5-triazines

Base-promoted cyclization of **96** gave the triazinedione **97**, which was heated with phosphorus oxychloride to obtain the dichlorotriazine **98** (Scheme 14). Coupling of **98** with **99** gave **100**, which upon catalytic reduction over Pd/C underwent both dechlorination and debenzoylation to give the desired triazine, (*R*)-4-(4-(1-hydroxyethyl)-1,3,5-triazin-2-yl)-*N,N*-dimethylpiperazine-1-sulfonamide **101** <2003BMC4179>.



Scheme 14

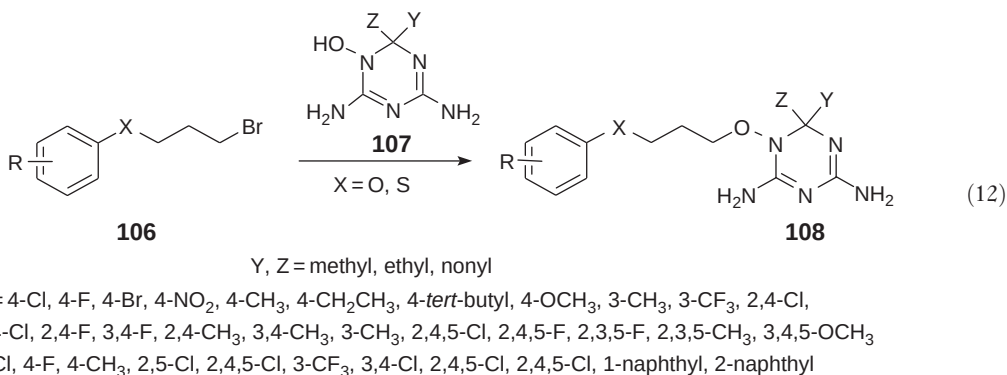
Chiral 1,2-diaryl-1,2-dihydro-4,6-diamino-1,3,5-triazines **102** undergo facile racemisation by a reversible thermal electrocyclic reaction mechanism; the transient intermediate can lead, after tautomerization, to rearranged racemic 2-aryl-1,2-dihydro-4-amino-6-anilino-1,3,5-triazines **103–105** (Scheme 15) <2001CC737>.



Scheme 15

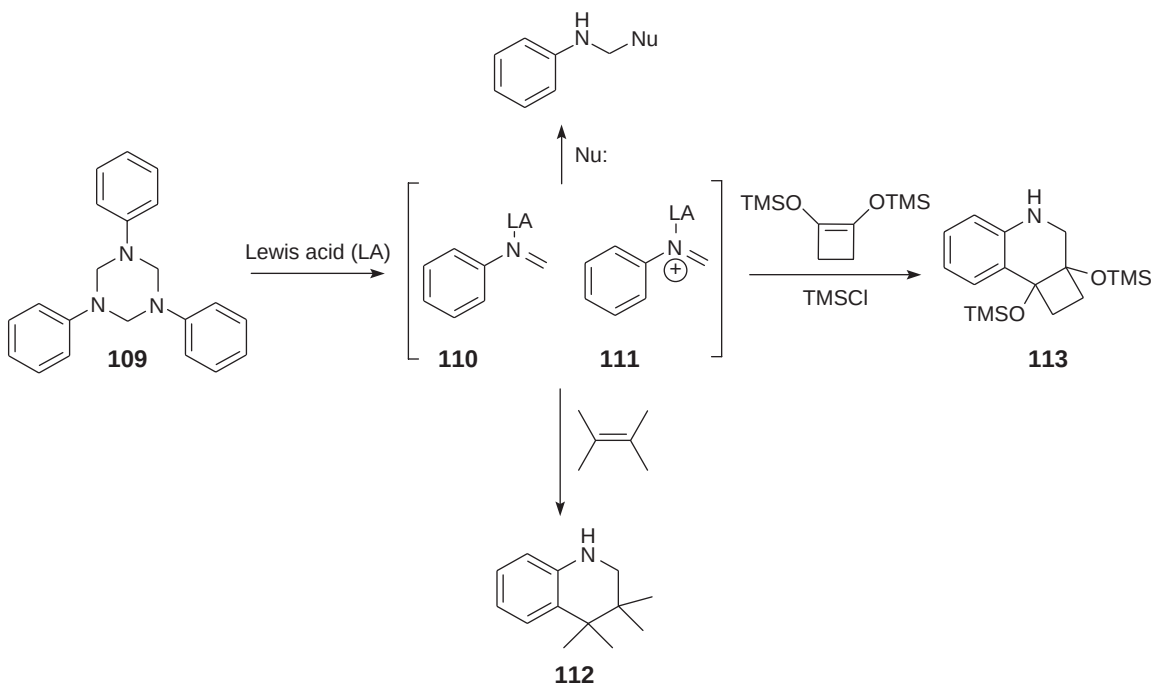
9.03.6.2 Tetrahydro-1,3,5-triazines

Utilizing the method of Mamalis, bromides **106** could be converted directly to the desired triazine products **108** by alkylation of an *N*-hydroxytriazine **107** (Equation 12) <2001JME3925>.



9.03.6.3 Hexahydro-1,3,5-triazines

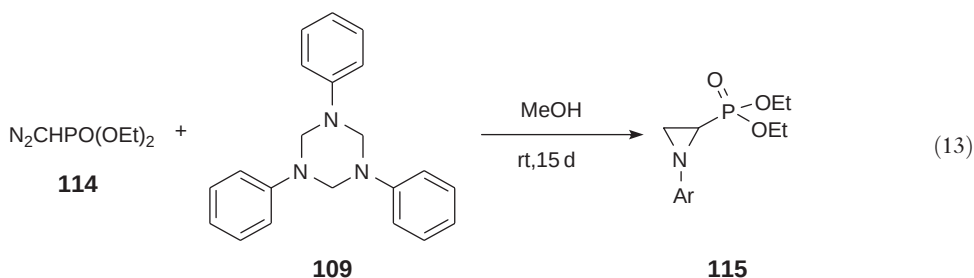
N-Methyleneamine equivalents can be generated from 1,3,5-trisubstituted hexahydro-1,3,5-triazines in the presence of a Lewis acid (LA) and used for aminomethylation reactions with various nucleophiles at the *R*-position of amines (Scheme 16). *N*-Methyleneaniline equivalents, as shown by **110** and **111**, result from the breaking of all three carbon–nitrogen bonds of 1,3,5-triphenylhexahydro-1,3,5-triazine **109**. They have characteristics of imine and iminium ions similar to Mannich bases and can be used for various aminomethylation reactions. However, there have been no reports of using *N*-methyleneamine equivalents as azadienes, which may react with olefins via $[4\pi+2\pi]$ cycloaddition to afford 1,2,3,4-tetrahydroquinolines **112** <2000T5259>.



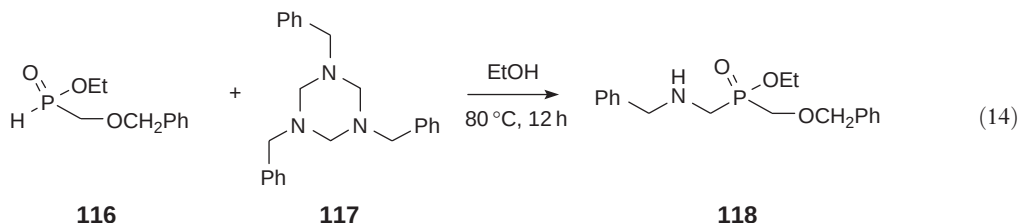
Scheme 16

Lee and co-workers have succeeded in using *N*-methyleneaniline equivalents generated from 1,3,5-triphenylhexahydro-1,3,5-triazine **109** as azadienes with electron-rich 1,2-bis(trimethylsilyloxy)cyclobutene to give $[4\pi+2\pi]$ cycloadducts 2a,8b-bis(trimethylsilyloxy)-1,2,2 α ,3,4,8 β -hexahydrocyclobuta[*c*]quinoline **113** <2000JOC8384>.

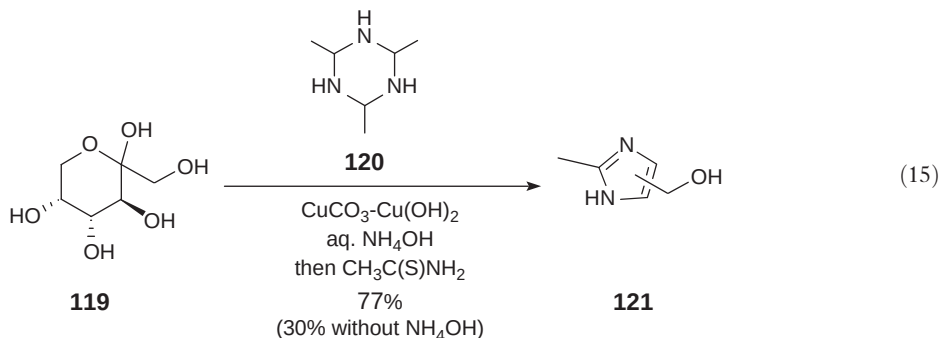
During a parallel investigation, Lesniak and coworkers have observed the cycloaddition reactions of **114** with hexahydro-1,3,5-triazines **109** as precursors of reactive *N*-methylenamines (Equation 13). The results showed that the cycloaddition of **114** onto a C=N bond, formed *in situ*, afforded the corresponding triazolines, which underwent a spontaneous extrusion of N₂ to aziridines **115** <2004TL7301>.



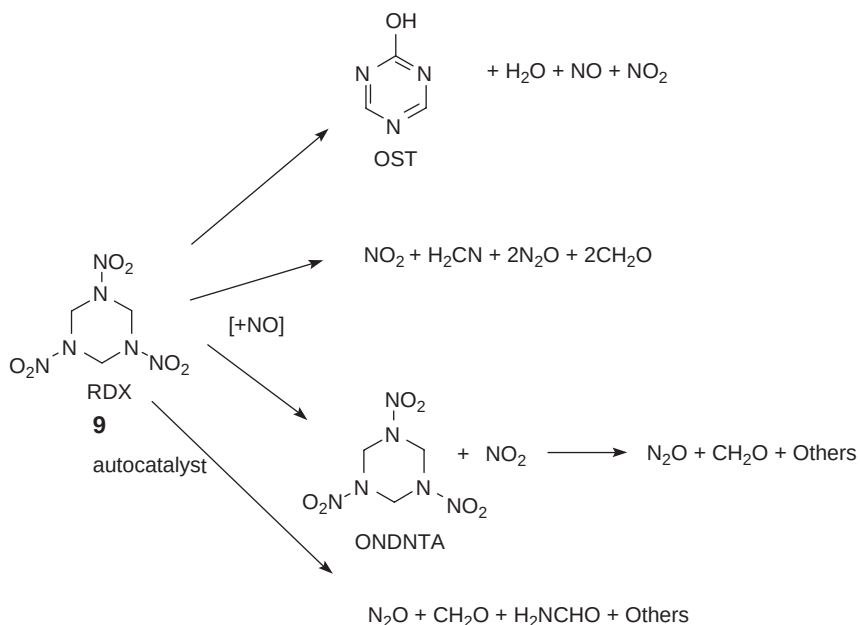
The reaction of ethylphosphinate **116** with 1,3,5-*N*-benzyl-1,3,5-hexahydrotriazine **117** afforded an analog of phosphonoglycine **118** (Equation 14) <2004T877>.



The degradation/condensation reaction of fructose **119** with trimer **120** in place of formaldehyde and ammonium hydroxide is a promising route for the synthesis of 2-methylimidazole derivative **121**, a key intermediate for the preparation of a 2-methylfructose-derived ionic liquid (Equation 15). Unfortunately, while this approach did afford the desired C-2 methyl product **121**, it was in modest yield (30%). Performing the same reaction, but with the addition of ammonium hydroxide, the yield of **121** improved to 77% <2005JOC1915>.



Through the use of simultaneous thermogravimetry modulated beam mass spectrometry, optical microscopy, hot-stage time-lapsed microscopy, and scanning electron microscopy measurements, the physical and chemical processes that control the thermal decomposition of RDX **9** below its melting point (160–189°C) have been identified (Scheme 17) <2005PCA11236>.

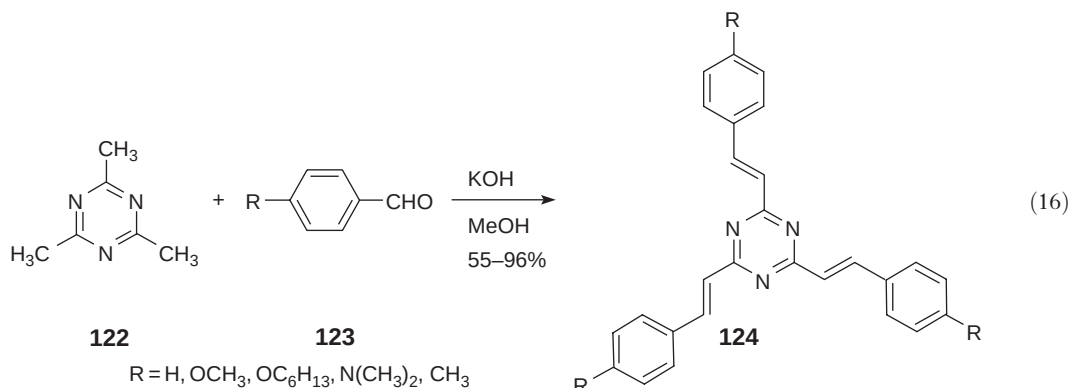


Scheme 17

9.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

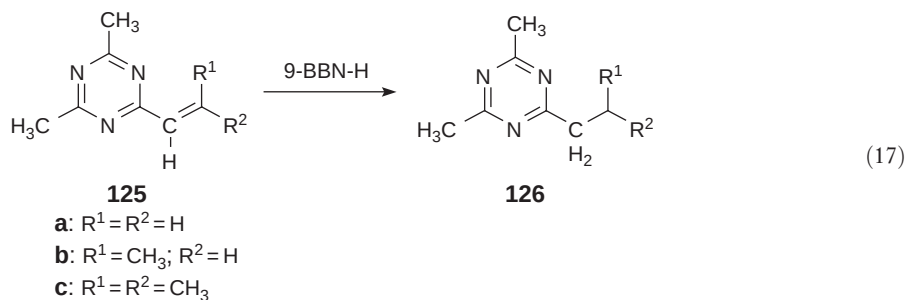
9.03.7.1 Reactivity of Carbon Substituents

The high reactivity of 2,4,6-trimethyl-1,3,5-triazine **122** in alkaline condensation reactions with aldehydes is well known. Meyer *et al.* have reported the preparation of the *para*-substituted derivatives **124** by treating **122** with aromatic aldehydes **123** (Equation 16).



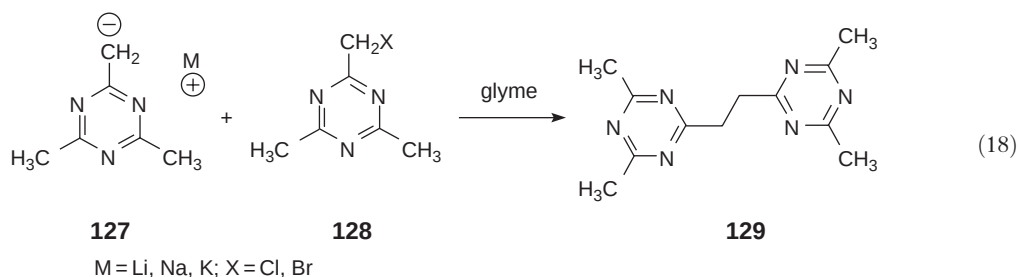
The reaction times at room temperature amounted to several days, with aromatic aldehydes reacting particularly slowly because of the low nucleophilicity of **122** <2003EJO4173>.

Hydroboration of the conjugated alkenes **125** with 9-BBN-H was reported to give the corresponding alkanes **126** under normal workup conditions, with or without oxidation (9-BBN = 9-borabicyclo[3.3.1]nonane; Equation 17).



With time and without workup, the hydroboration of **125** gave spectral evidence for the formation of intermediates resulting from the migration of the 9-BBN moiety from the R-carbon to a ring nitrogen, with concurrent formation of an exocyclic double bond to an R-carbon of the ring <2002JOC3202>.

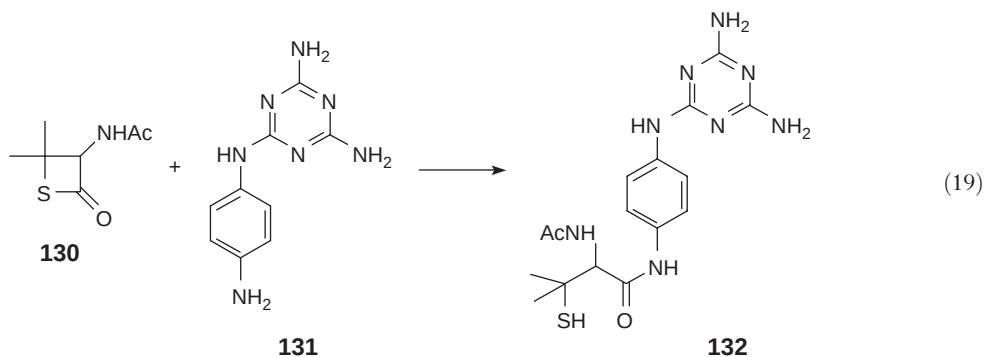
Reactions of lithium, sodium, and potassium salts of 2,4,6-trimethyl-*s*-triazine **127** with 2-halomethyl-4,6-dimethyl-*s*-triazine **128** ($X = \text{Cl}, \text{Br}$) in glyme have been studied and found to give a complex mixture of triazine derivatives, in which the product **129** is formed primarily via an $\text{S}_\text{N}2$ reaction (Equation 18) <2002JOC3202>.



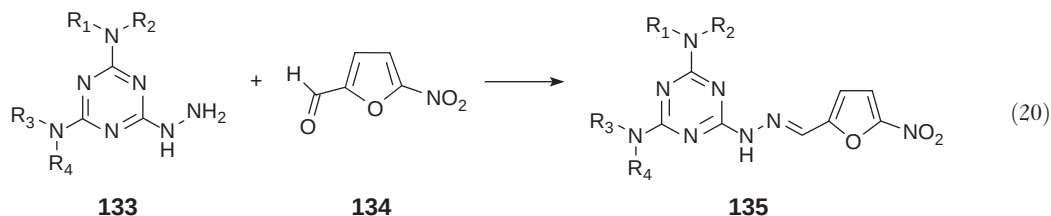
9.03.7.2 Reactivity of Nitrogen Substituents

Recently, Sharpless and co-workers have reported an enantioselective procedure for the vicinal addition of a hydroxyl group and amino-substituted heterocycles to olefins. They have found that simple aminopyrimidines and aminotriazines function as excellent reagents for the asymmetric aminohydroxylation. Stilbene is converted into either enantiomer of the corresponding amino alcohol with high ee's with 2-aminotriazines as the nitrogen source <1999AGE1080>.

Reaction of thietanone **130** with 2-(4-aminophenylamino)-4,6-diamino-1,3,5-triazine **131** gave the thiol **132** (Equation 19) <2000BML1347>.

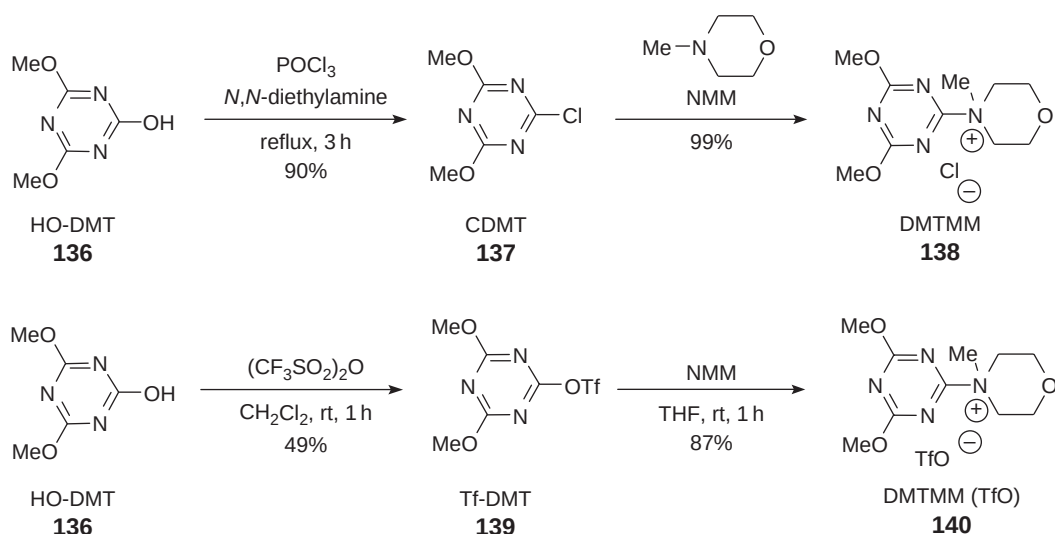


Reaction of the hydrazine derivatives **133** with 5-nitro-2-furaldehyde **134** afforded the corresponding 4,6-disubstituted-2-(5-nitrofurfurylidenehydrazino)-1,3,5-triazines **135** (Equation 20). The products had low solubility in most organic solvents, except DMSO. However, purification was achieved by recrystallization from methanolic and ethanolic water solutions.



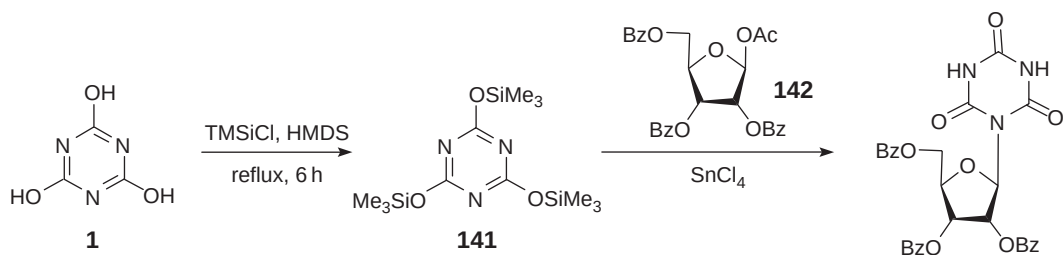
9.03.7.3 Reactivity of Oxygen Substituents

A simple procedure for the isolation of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine **136** (HO-DMT), a co-product arising from dehydrative condensation using DMTMM chloride **138**, has been established. HO-DMT **136** can be recycled by treatment with POCl₃ to give 2-chloro-4,6-dimethoxy-1,3,5-triazine **137** (CDMT), which is further converted to DMTMM **138**. Alternatively, reaction with triflic anhydride, followed by addition of *N*-methylmorpholine, gives DMTMM triflate **140** (Scheme 18) <2002TL3323>.



Scheme 18

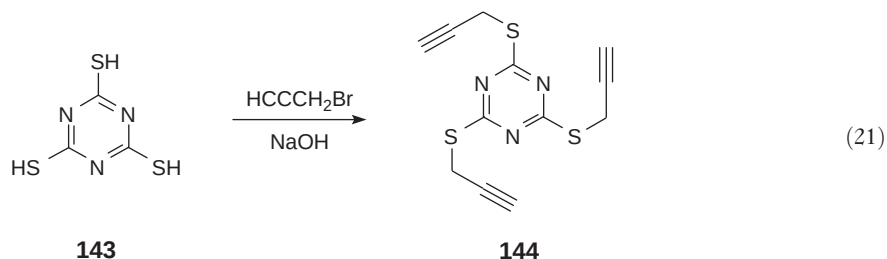
CYA **1** was persilylated by refluxing with trimethylchlorosilane and hexamethyldisilazane, and the resulting tris(trimethylsilyl) derivative **141** was treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose **142** in the presence of SnCl₄ to afford the corresponding nucleoside (Scheme 19) <2004CAR2641>.



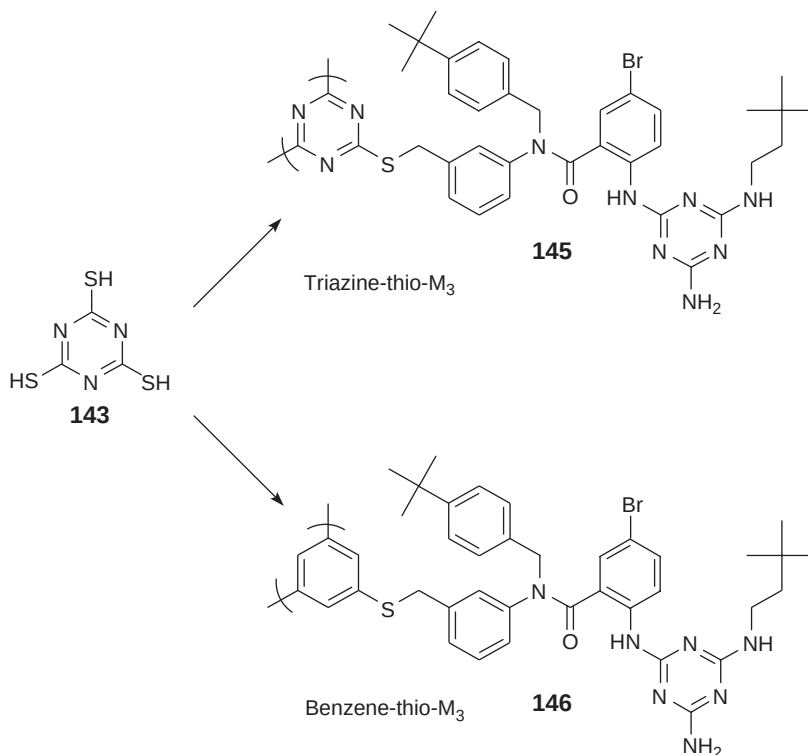
Scheme 19

9.03.7.4 Reactivity of Sulfur Substituents

Gabel and co-workers have synthesized the 2,4,6-tripropargyl thioderivative **144** by interaction of the thiocyanuric acid **143** with propargyl bromide in 2% aqueous NaOH at room temperature for 3 h (Equation 21) <2003TL8689>.



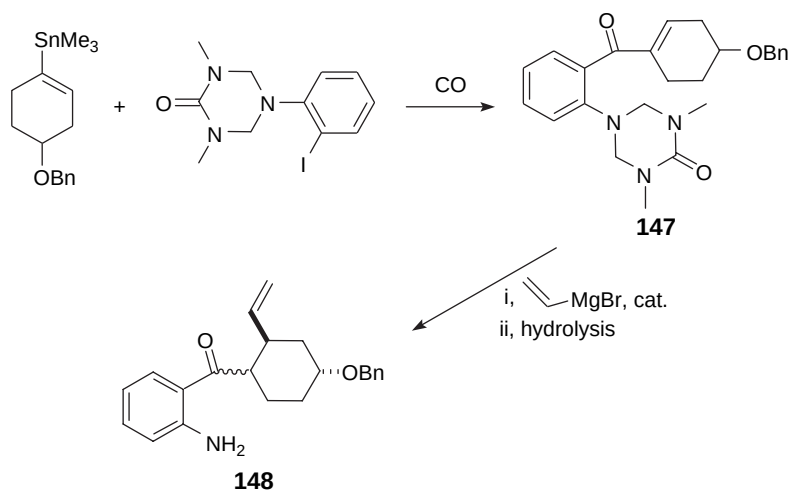
2,4,6-Trithiocyanuric acid **143** was reported to react with 1,3,5-trimercaptobenzene and a benzylic bromide melamine derivative to yield triazine-thio-M₃ **145** and benzene-thio-M₃ **146** (Scheme 20) <1996JOC1779>.



Scheme 20

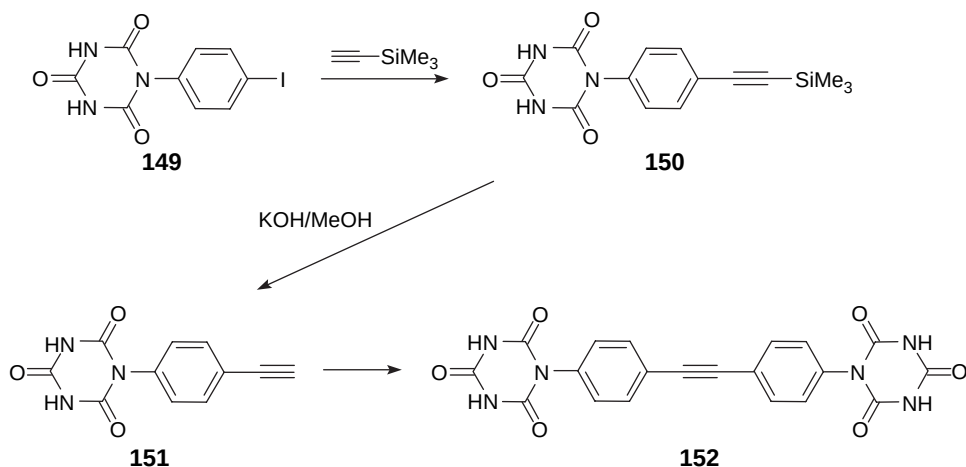
9.03.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms

Perhydro-1,3-dimethyl-1,3,5-triazin-2-one **147** was used as protecting group in the preparation of a mixture of diastereomeric (2-aminophenyl)[4-(benzyloxy)-2-vinylcyclohexyl]ketones **148** by reaction with vinyl MgBr under Lipshutz' conditions and successive hydrolysis (Scheme 21) <2001JA6724>.



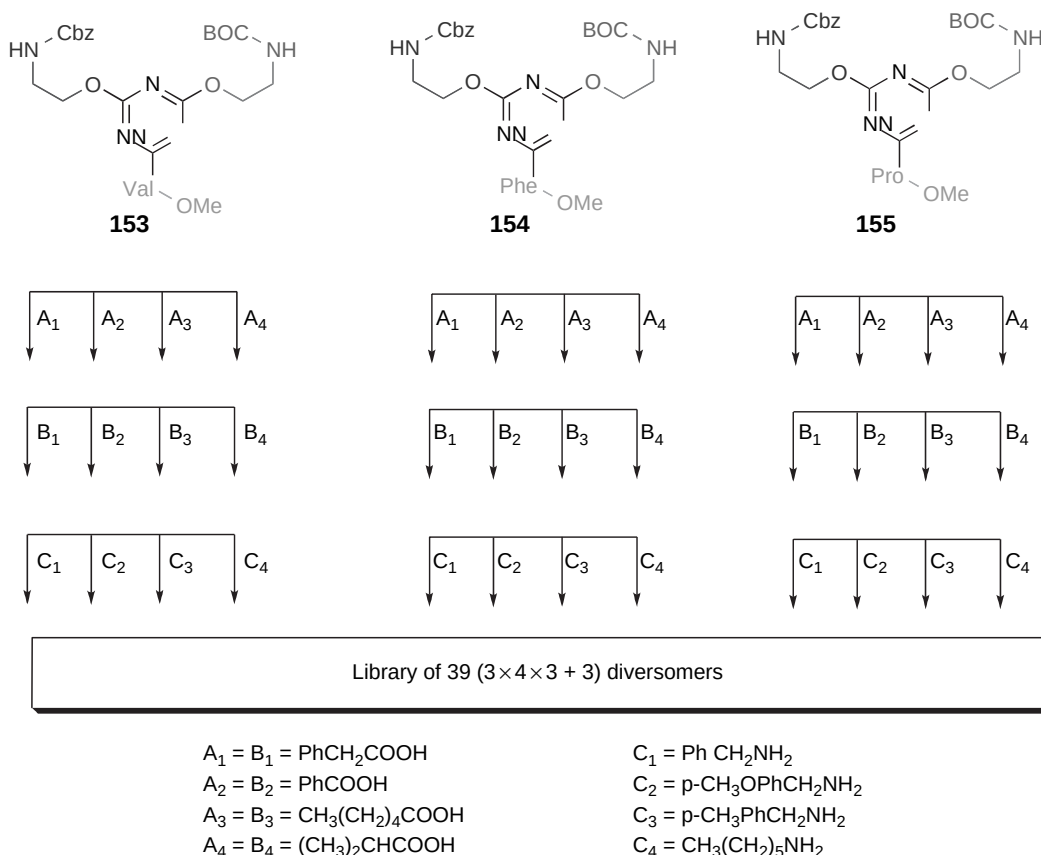
Scheme 21

1-(4-Iodophenyl)-1,3,5-triazine-2,4,6-trione **149** was reported to undergo Sonogashira coupling with trimethylsilylacetylene despite possessing the acidic functionality of the isocyanuric acid group. Removal of the trimethylsilyl group with KOH/MeOH and coupling of the resulting compound **151** with **149** gave the first isocyanuric acid dimer **152** (Scheme 22) <2004T6385>.



Scheme 22

Falorni *et al.* have developed a simple procedure to prepare trifunctionalized orthogonally protected CRAB (chemical rigid amide building) templates **153–155** based on the triazine skeleton (Scheme 23). Starting from the CRAB products **153–155** and using four acids (A_1 – A_4) in the first and second steps (B_1 – B_4), and four amines (C_1 – C_4) in the third coupling, they obtained an array of 39 diversomers. With this protocol, they have prepared a class of simple polyfunctionalized scaffolds for liquid-phase synthesis of libraries of small organic molecules <1998TL7607>.

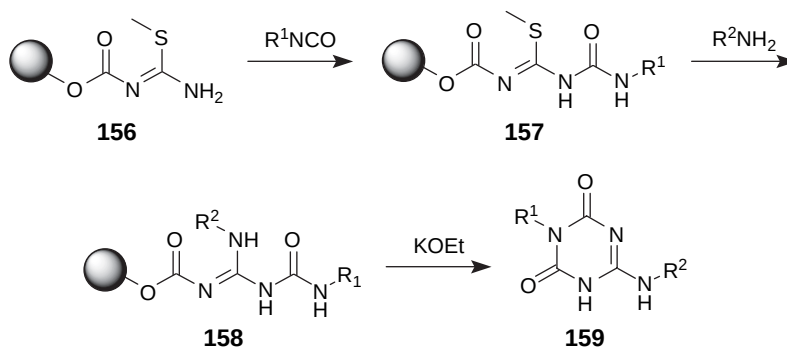


Scheme 23

9.03.9 Ring Syntheses from Acyclic Compounds

9.03.9.1 Synthesis by Formation of One Carbon–Nitrogen Bond

Reaction of resin-bound *S*-methylisothiourea **156** with isocyanates yielded resin-bound iminouras **157**, which reacted with amines to afford the corresponding guanidines **158** (Scheme 24). Following intramolecular cyclizative cleavage of the resin-bound guanidines using potassium ethoxide as a base, the 6-amino-1,3,5-triazine-2,4-diones **159** were obtained in good yields and high purities [\[2002JCO484\]](#).



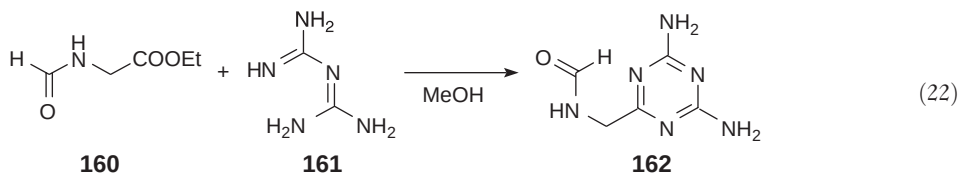
Scheme 24

9.03.9.2 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [5+1] Atom Fragments

Synthetic methods leading to 2,4-diamino-1,3,5-triazines include the reaction of biguanide with esters or acid chlorides.

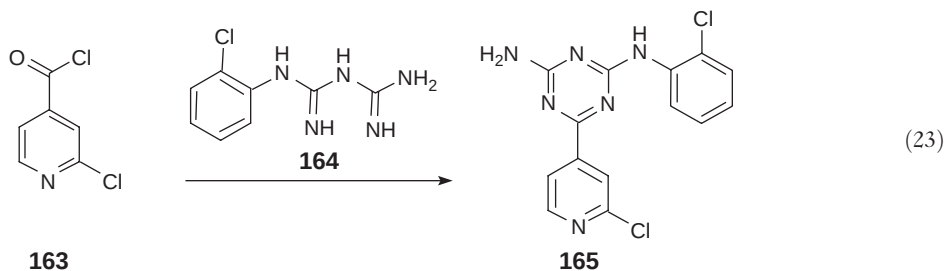
9.03.9.2.1 Synthesis with biguanidines as the five-atom fragment

N-Formylglycine ethyl ester **160** and biguanide **161** condense smoothly in methanolic solution to afford the triazine derivative **162** (Equation 22) <2003OL2067>.



9.03.9.2.2 Synthesis from other five-atom fragments

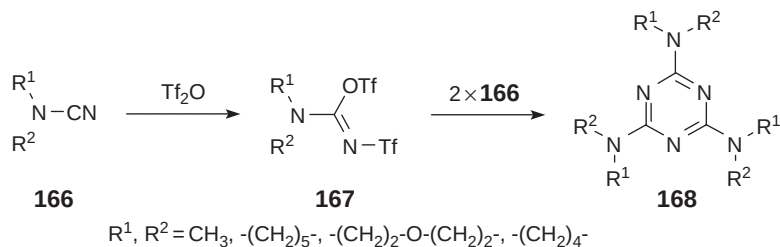
Cyclocondensation of **163** with (3-chlorophenyl)biguanide **164** gave *N*-2-(3-chlorophenyl)-6-(2-chloropyridin-4-yl)-1,3,5-triazine-2,4-diamine **165** (Equation 23) <2005JME4535>.



9.03.9.3 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [4+2] Atom Fragments

9.03.9.3.1 Synthesis from cyanamide

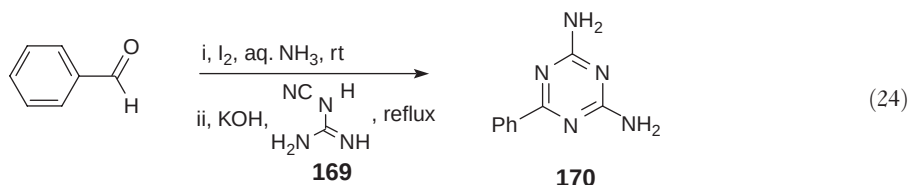
Triflic anhydride was found to be efficient for the cyclotrimerization of dialkylcyanamides **166** under mild conditions. The same reaction can be applied to aryl nitriles and thiocyanates. The reaction involves the formation of the bistrifluoroisourea intermediates **167**, which react quickly with two molecules of cyanamide to afford the triazines **168** (Scheme 25) <2004S503>.



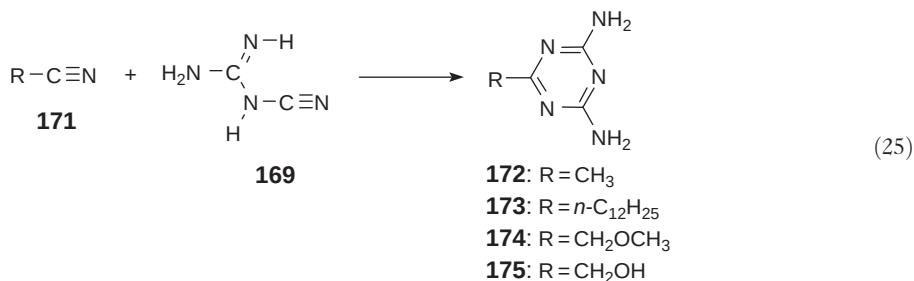
Scheme 25

9.03.9.3.2 Synthesis from dicyandiamide

The most convenient synthetic approach to 2,4-diaminotriazines utilizes the addition reactions of nitrile compounds with dicyandiamide (also called cyanoguanidine). The reaction is catalyzed by base. Benzonitrile, resulting from the reaction of benzaldehyde with $I_2/aq. NH_3$ *in situ*, was treated with dicyandiamide **169** to afford 2,6-diamino-4-phenyl-1,3,5-triazine **170** in 78% yield (Equation 24) <2003JOC1158>.

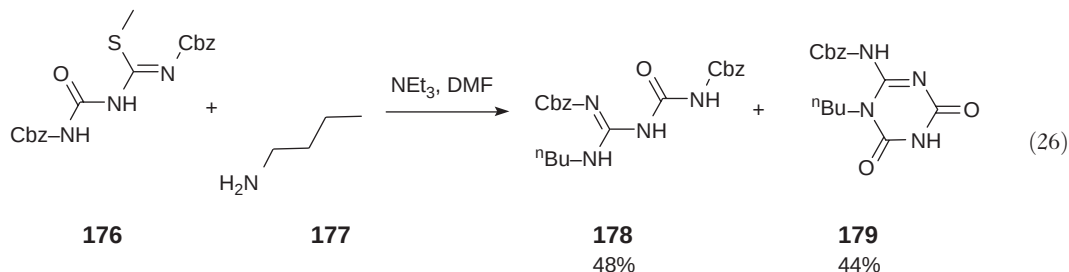


2,4-Diamino-*s*-triazines **172–175** were prepared by condensation of the appropriate nitrile **171** with dicyandiamide **169** (Equation 25). 6-(Hydroxymethyl)-2,4-diamino-*s*-triazine **175** was prepared according to the method of Sims by protection of glycolonitrile as its butyl vinyl ether, subsequent conversion to the corresponding 2,4-diamino-*s*-triazine, and deprotection with acid <1996JOC6371>.



9.03.9.3.3 Synthesis from other four-atom fragments

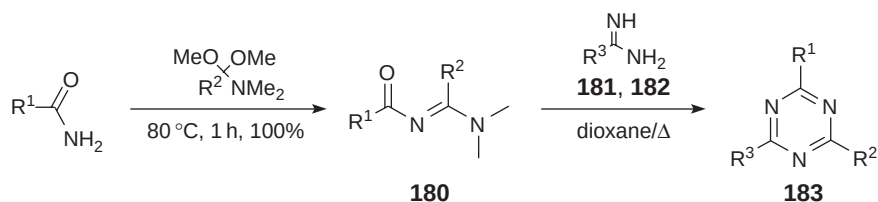
N-(Benzyloxycarbonyl)ureido-*N'*-benzyloxycarbonyl-*S*-methylisothiurea **176** was condensed with butylamine **177** in the presence of triethylamine (TEA) in DMF to give a 1:1 ratio of amidinourea **178** and triazine **179** (Equation 26). If the reaction was allowed to proceed longer, the triazine **179** was the only product isolated. It is believed that the initially formed **178** cyclizes to the triazine in the presence of excess TEA to form the more stable 1,3,5-triazine-2,4-dione <1996TL1945>.



9.03.9.4 Synthesis by Formation of Two Carbon–Nitrogen Bonds from [3+3] Atom Fragments

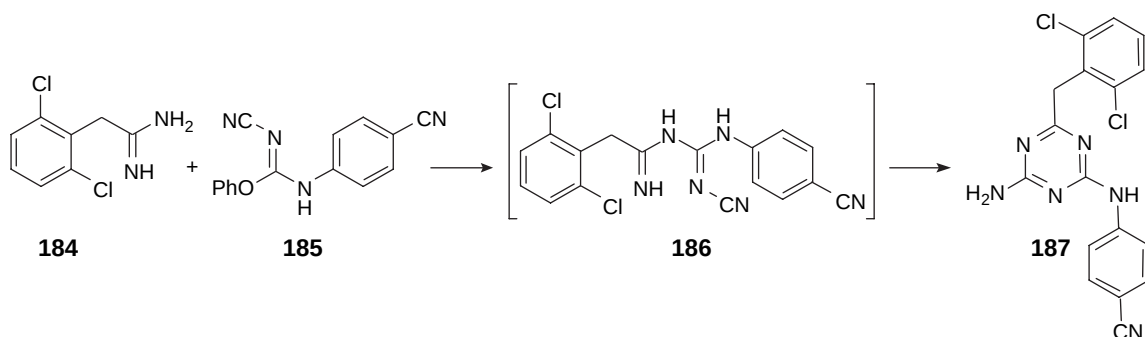
9.03.9.4.1 Synthesis from amidines

Cyclizations of acylamidines **180** with amidines **181** or guanidines **182** in aprotic solvents gave *s*-triazines **183** bearing three different substituents (Scheme 26) <1995JOC8428>.



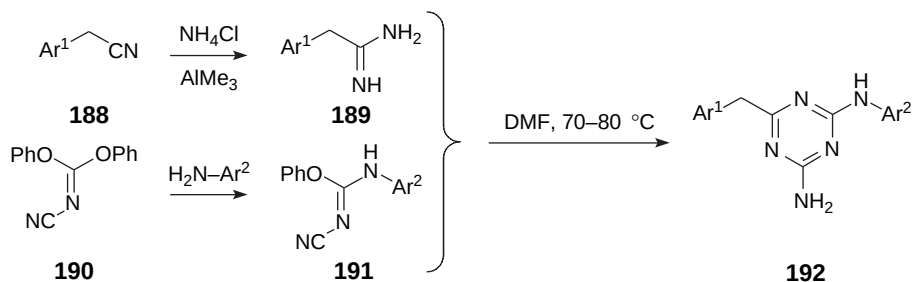
Scheme 26

The reaction of amidine **184** with *N*-cyano-*O*-phenyl isourea **185** resulted in clean conversion to a single product that was revealed by spectral analysis to be triazine **187**, and not the expected product **186** (Scheme 27).



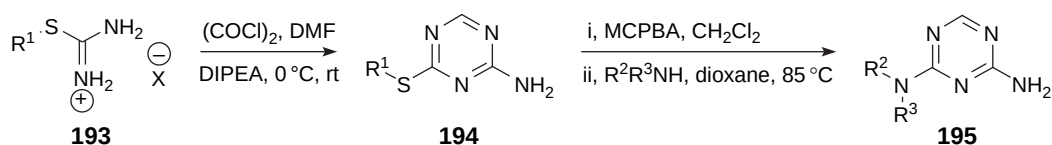
Scheme 27

The chemistry that led to the formation of **187** was adapted readily to the preparation of triazine analogs **192** in which both Ar^1 and Ar^2 could be varied (Scheme 28) <2001BML2229>.



Scheme 28

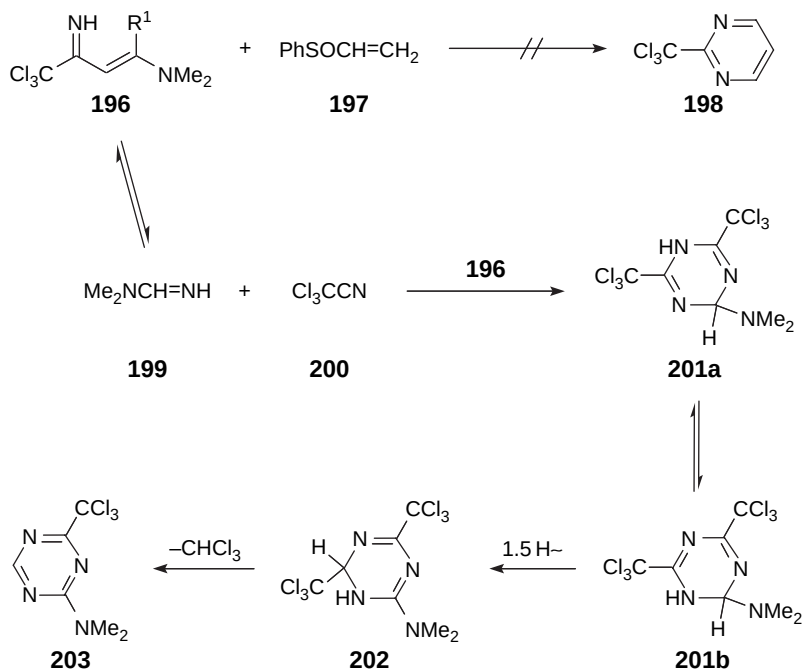
Masquelin has presented a facile preparation of 2,6-disubstituted triazines **194** through base-catalyzed cyclization of the corresponding thiuronium salts **193** (Scheme 29).



Scheme 29

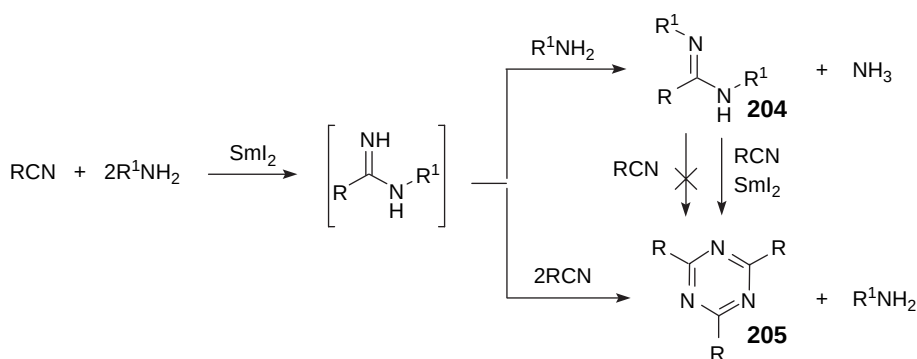
Since 2-alkylsulfinyl [1,3,5] triazines **194** can be substituted easily in various ways, this approach constitutes a novel and efficient synthesis of 2,6-disubstituted triazines **195** <1998TL5725>.

An attempt to generate 2-(trichloromethyl)pyrimidine **198**, from **196** and phenyl vinyl sulfoxide **197**, failed and produced 2-(trichloromethyl)-4-(dimethylamino)-1,3,5-triazine **203** as the only isolable product (20%) (**Scheme 30**). This compound is suggested to arise as a consequence of a partial fragmentation of **196** to *N,N*-dimethylformamidine **199** and trichloroacetonitrile **200** <1996JOC2470>.



Scheme 30

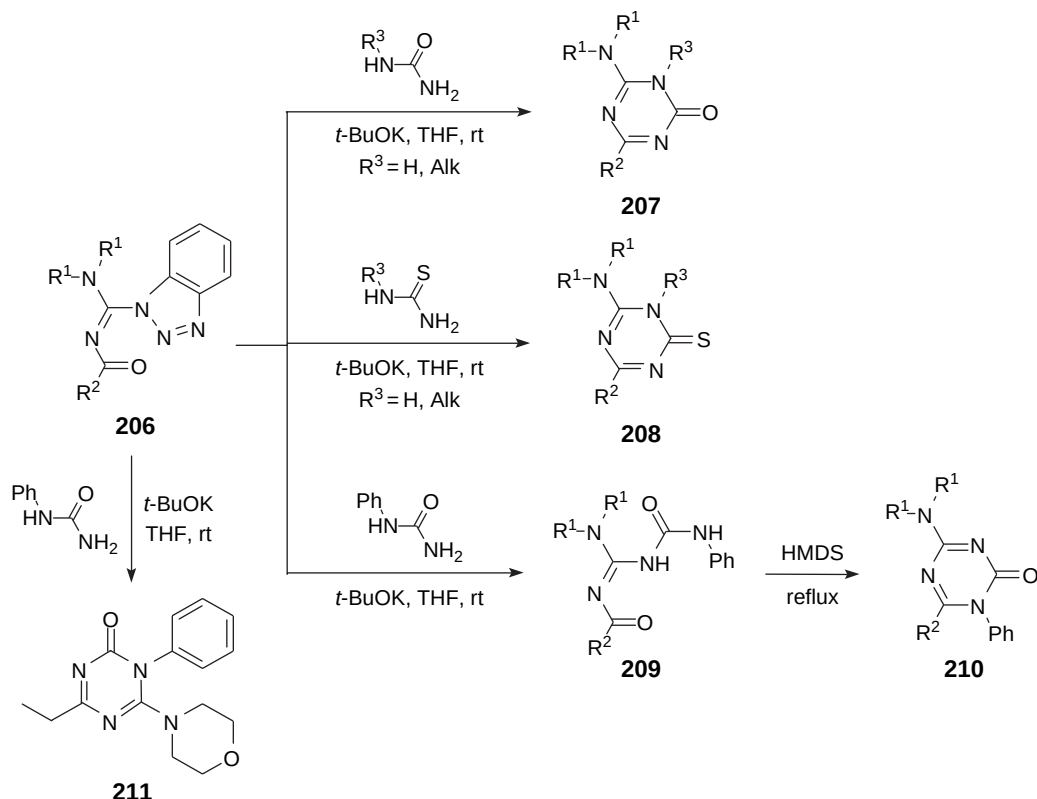
SmI₂ has been found to be an efficient catalyst for the condensation of nitriles with amines to form *N,N*-disubstituted amidines **204** under mild reaction conditions and in good yields (**Scheme 31**). The *N,N*-disubstituted amidine alone cannot be transformed into *s*-triazine **205** whether SmI₂ is used or not. *s*-Triazine **205** is obtained only in the presence of the corresponding nitrile and a catalytic amount of SmI₂ <2002TL1867>.



Scheme 31

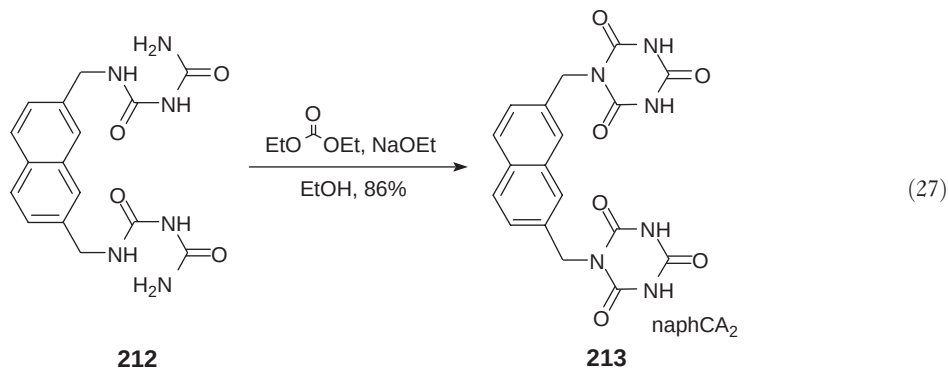
9.03.9.4.2 Synthesis from carbonate, urea, thiourea, and guanidine derivatives

Katritzky *et al.* have developed a new, efficient procedure for the preparation of 4(6)-amino-1,6(4)-disubstituted-1,3,5-triazin-2-ones **207**, **210**, and **211**, and 4(6)-amino-1,6(4)-disubstituted-1,3,5-triazin-2-thiones **208** (Scheme 32) <2001JOC6797>. Their method allows the introduction of a variety of amino group substituents, which is not possible by direct reactions with cyanoguanidines or is limited by the availability of N,N-disubstituted formamide diacetals. Use of acyl cyanoguanidines could provide diversity in the 4(6)-position but, once again, it would not allow the introduction of a substituent in the amino group at the same time. The proposed protocol did not need rigorous control of the reaction conditions in comparison to the protocol for the condensation of CC with amines. The option of introducing the thione group increases the usefulness of the reported protocol.

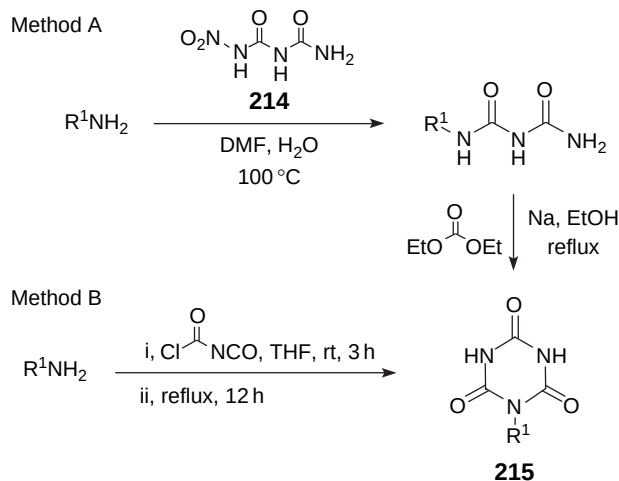


Scheme 32

The reaction of **212** with diethyl carbonate produced naphCA₂ **213** (Equation 27). This compound is not soluble in most nonpolar solvents, but slightly soluble in methanol and very soluble in dimethylformamide (DMF) <1999CM684>.

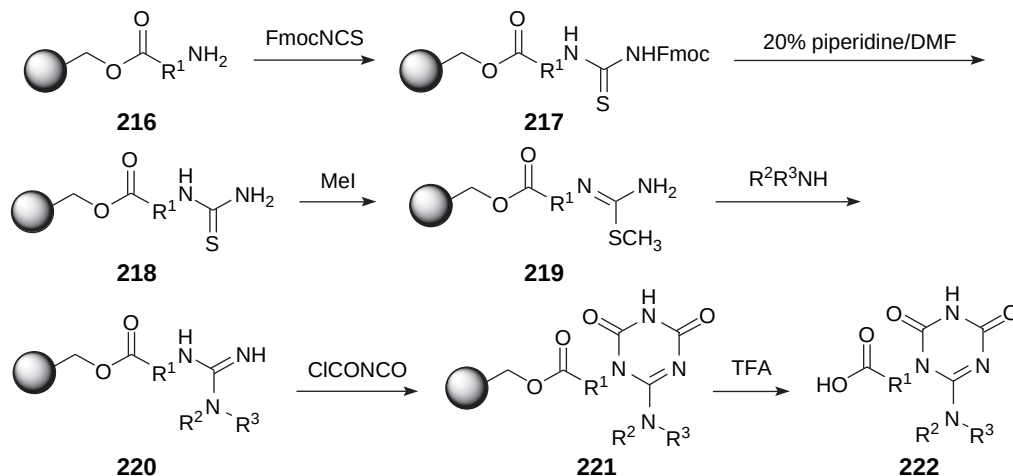


The synthesis of cyanurates **215** started with condensation of the corresponding amines with an excess of nitrobiuret **214** (method A, [Scheme 33](#)). Subsequent ring closure with diethyl carbonate and sodium ethoxide gave compound **215** in good yields. Similar results could be obtained by the reaction of the same amines with *N*-chlorocarbonyl isocyanate (method B, [Scheme 33](#)) [<2002CEJ2288>](#).



Scheme 33

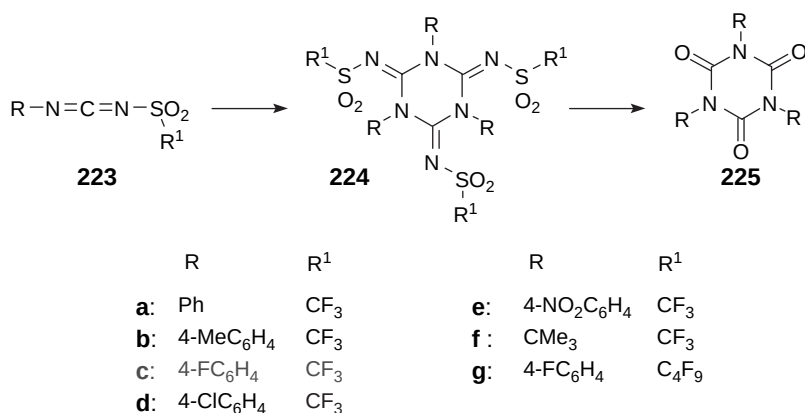
A new solid-phase synthesis of trisubstituted 6-amino-2,4-dioxo-3,4-dihydro-1,3,5-triazines **222** from a resin-bound amine component **216** was described by Gopalsamy *et al.* ([Scheme 34](#)). The amine was converted readily to the corresponding polymer-bound *S*-methylthiopseudourea **219**, which, upon reaction with secondary amines, gave the disubstituted guanidines **220**. Cyclization of the polymer-bound guanidines with chlorocarbonylisocyanate and cleavage from the polymer afforded the triazinediones **222**. A third point of diversity could be introduced by the Mitsunobu reaction. The method is amenable to iterative combinatorial library generation [<2001JCO278>](#).



Scheme 34

9.03.9.4.3 Synthesis from carbodiimides

On long storage at room temperature or on heating in glyme solutions, compounds **223** converted into high-melting dimers or trimers (cf. **224**). In the course of recrystallization and column chromatography on silica gel, the trimer of **223c** was hydrolyzed by atmospheric moisture into triazinetrione **225c**, which was identified by X-ray diffraction analysis ([Scheme 35](#)) [<2001EJO1225>](#).



Scheme 35

9.03.9.5 Synthesis of Symmetrical 1,3,5-Triazines by Formation of Three Carbon-Nitrogen Bonds from [2+2+2] Atom Fragments

9.03.9.5.1 Synthesis from nitriles

The mono- and diesters **226** and **227** were employed as precursors to *s*-triazine derivatives **228** and **229**, respectively (Figure 26). The latter, **229**, was formed in low yield (21%) and was accompanied by a product **230** (29%), formed through incomplete condensation with ensuing ester exchange <2000T1233>.

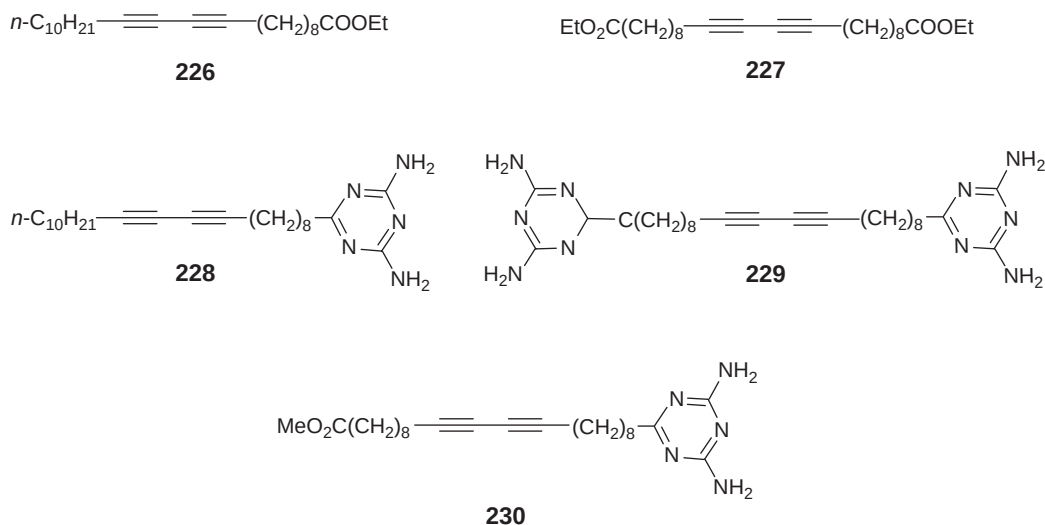
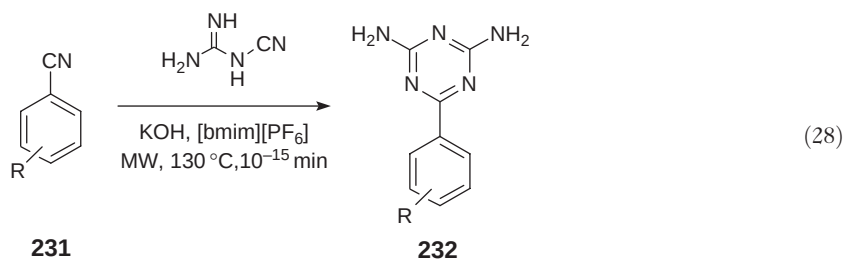


Figure 26

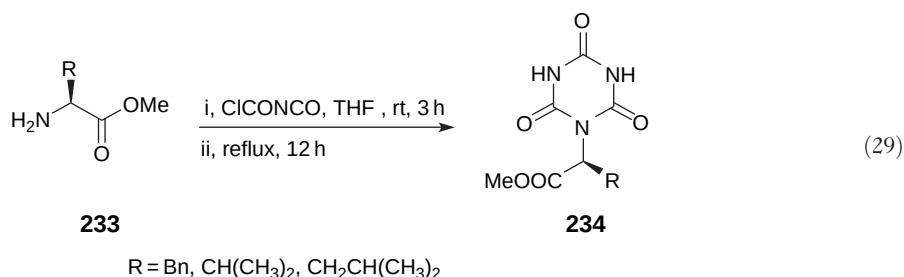
An efficient and green approach was developed to prepare 6-aryl-2,4-diamino-1,3,5-triazines **232** from the corresponding aryl nitriles and dicyandiamide **231** in an ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]) under computer-controlled microwave irradiation (Equation 28). Particularly valuable

features of this method included the short reaction time, good yield, convenient operation, and ecofriendly solvent <2004TL5313>.

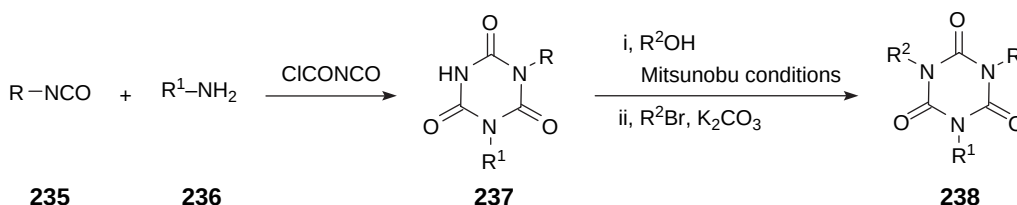


9.03.9.5.2 Synthesis from isocyanates

The cyanurates **234** were prepared in one step by treatment of the corresponding methyl ester-protected amino acids **233** with *N*-chlorocarbonyl isocyanate, in yields varying between 50% and 65% (Equation 29) <2002CEJ2288>.

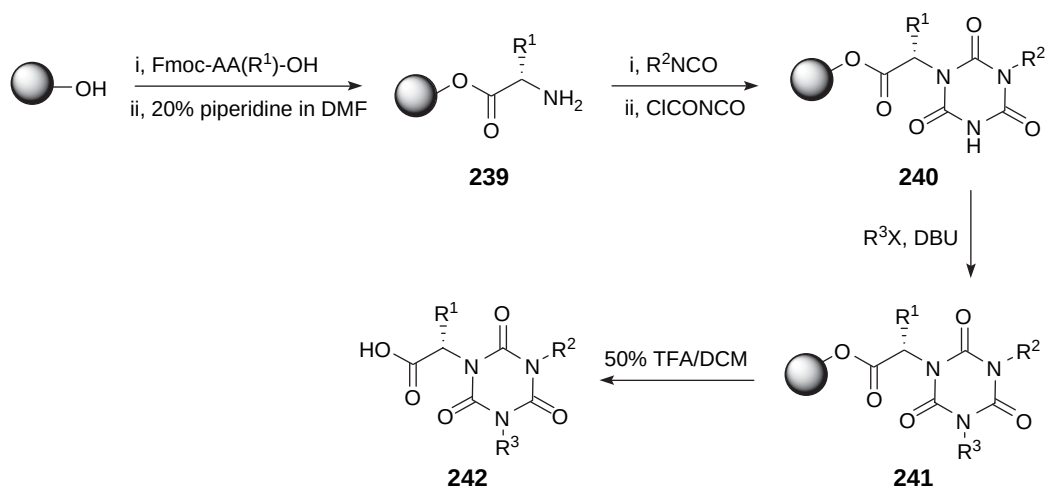


Guo *et al.* have developed a convenient one-pot synthetic route for the preparation of asymmetric 1,3-dialkyl-1,3,5-triazine-2,4,6-triones **237** from readily available alkyl or aryl isocyanates **235**, primary amines **236**, and *N*-chlorocarbonyl isocyanate in excellent yields (Scheme 36). Subsequent alkylation with *N*-protected amino alcohols afforded the desired 1,3,5-triazine-2,4,6-triones **238** in good yields <2005BML693>.



Scheme 36

Reaction of resin-bound amino acids **239** with isocyanates yields resin-bound ureas, which react further with chlorocarbonyl isocyanate to afford the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **240**, selectively (Scheme 37). Subsequent, selective alkylation at the N-5 position, to yield the resin-bound 1,3-disubstituted 1,3,5-triazine-2,4,6-triones **241**, was accomplished by treatment with alkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The desired products **242** were cleaved from the solid support and obtained in good yield and purity <2002JCO484>.



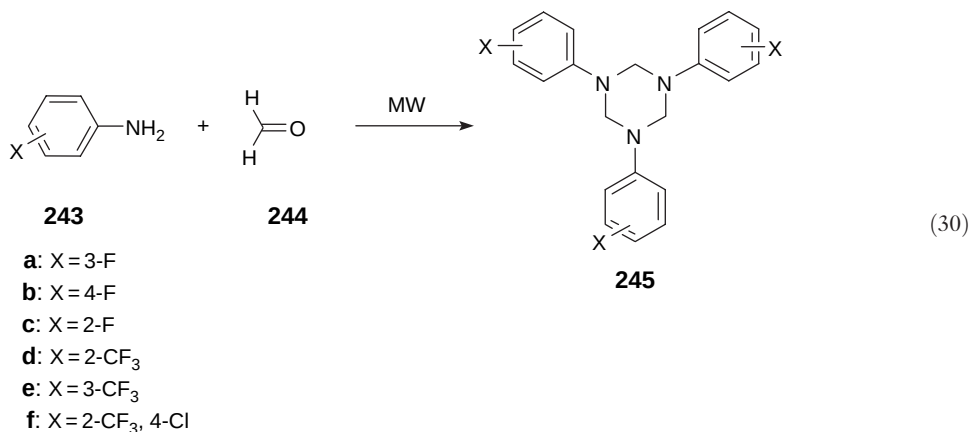
Scheme 37

9.03.9.5.3 Synthesis from isothiocyanates, imidates, and carbodiimides

5,6-dihydro-1,3,5-trimethyl-6-methylimino-1,3,5-triazine-2,4-(1*H*,3*H*)-dithione was synthesized by the reaction of methyl isothiocyanate under high pressure in the presence of NEt_3 and H_2O . The yield and selectivity were affected by pressure, reaction temperature, solvent, and the amount of H_2O <1993CL1097>.

9.03.9.5.4 Synthesis of symmetrical 1,3,5-triazines from aldehydes and ammonia or amines

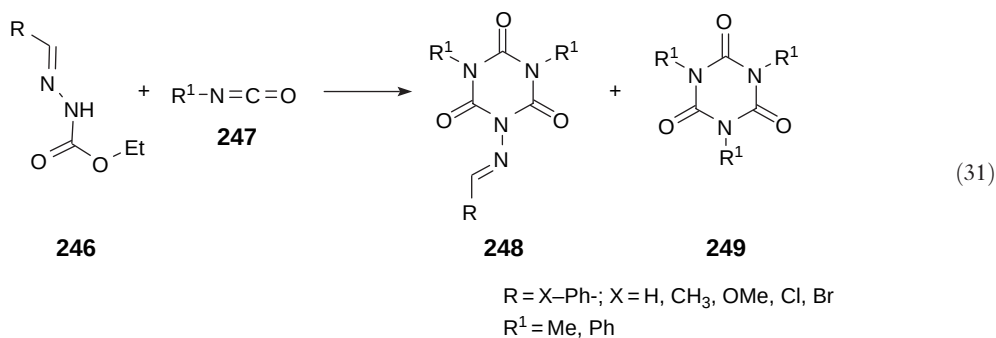
Dandia *et al.* have reported for the first time the economic, ecofriendly, facile, one-pot synthesis of fluorinated 1,3,5-triaryl hexahydro-1,3,5-triazines **245** by the condensation of fluorinated amines **243** with formaldehyde **244** under microwave irradiation in an aqueous medium (Equation 30) <2004JFC1273>.



9.03.9.6 Synthesis of Unsymmetrical 1,3,5-Triazines by Formation of Three Carbon–Nitrogen Bonds from [2+2+2] Atom Fragments

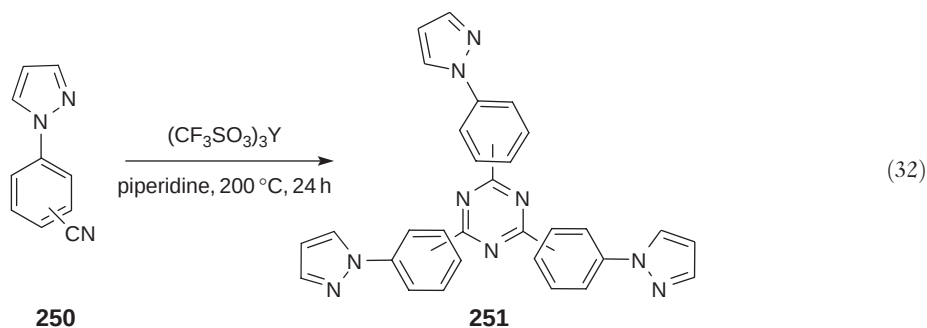
9.03.9.6.1 Synthesis from imino derivatives

The 3,5-disubstituted 1-amino-1,3,5-triazine-2,4,6-triones **248** and **249** were synthesized in good yields from aromatic aldehyde or ketone ethoxycarbonylhydrazones **246** by treatment with aryl or methyl isocyanates **247** in boiling TEA, followed by hydrolysis with hydrochloric acid (Equation 31) <1998JHC261>.

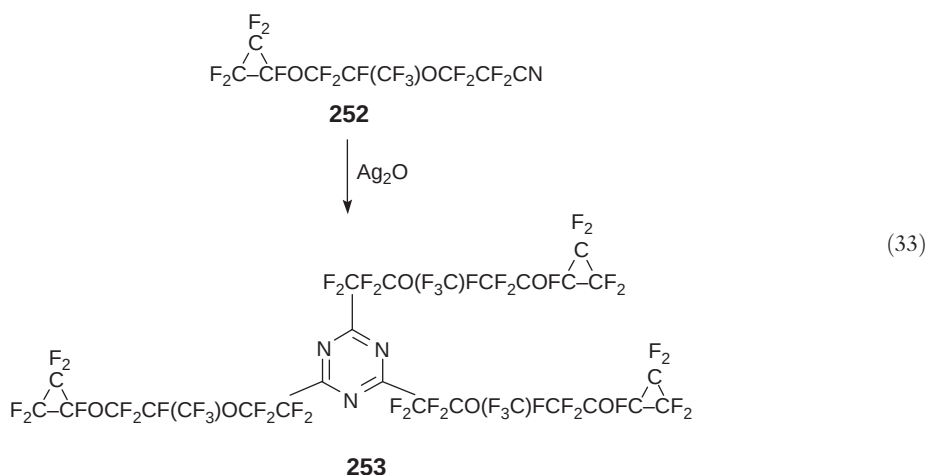


9.03.9.6.2 Synthesis by co-trimerization of nitriles

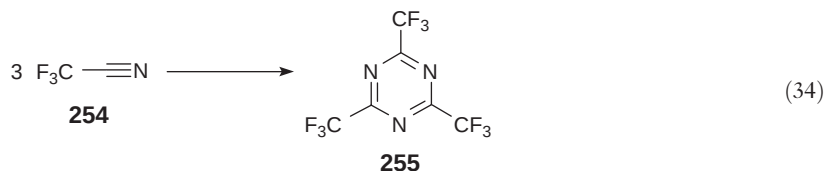
Trimerization of aromatic nitriles requires harsh reaction conditions, high temperatures, long reaction times, and pressure. In order to obtain the desired 1,3,5-triazines under milder reaction conditions, de la Hoz *et al.* have performed the cyclotrimerization of cyanopyrazole **250** in the absence of solvent using yttrium trifluoromethanesulfonate as catalyst (Equation 32). Cyclotrimerization of pyrazolylcarbonitriles **250** produces pyrazolyl-substituted 1,3,5-triazines **251** with interesting structures, which could be used in coordination chemistry and crystal engineering <2001T4397>.



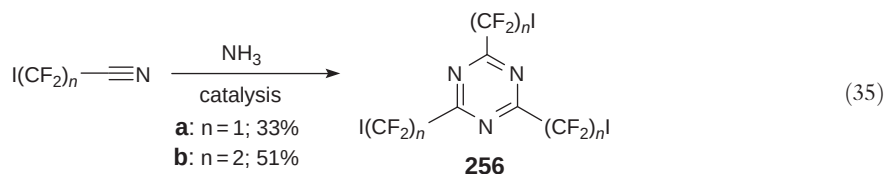
Fluorinated nitrile compounds can be trimerized into fluorinated *s*-triazines in high yields. When *c*-C₃F₅OCF₂-CF(CF₃)OCF₂CF₂CN **252** was treated with catalytic amounts of Ag₂O at 120–140 °C neat for 10 h, the corresponding *s*-triazine **253** was formed in 80% isolated yield (Equation 33) <2003JOC4410>.



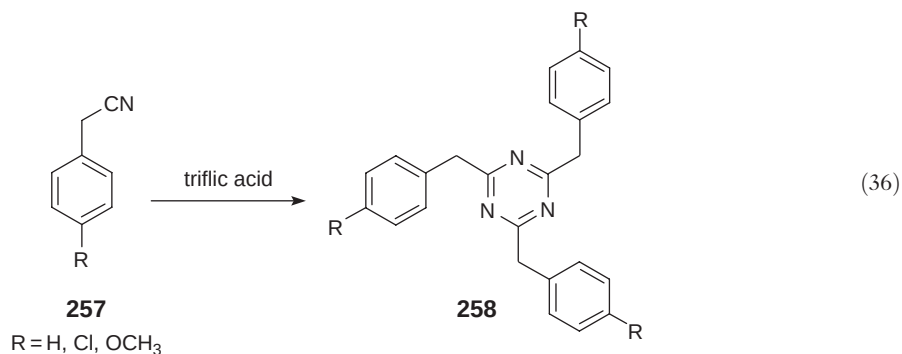
Trifluoroacetonitrile **254** trimerizes to give 2,4,6-tris-(trifluoromethyl)-1,3,5-triazine **255** (Equation 34) <1997JOC9070>.



$\text{I}(\text{CF}_2)_n\text{CN}$ may be used to make iododifluorinated triazines **256** by catalysis with NH_3 gas at 40–130 °C. The triazine **256**, containing an extremely thermally stable triazine core and multiple reactive sites (C–I bond), is useful in building networks for highly thermally stable specialty materials (Equation 35) <2004JOC198>.



2,4,6-Trisubstituted *s*-triazines **258** were synthesized using the trimerization reaction of phenyl acetonitrile derivative **257** with triflic acid (Equation 36) <2005BML1121>.



9.03.9.7 Synthesis by Formation of Four Carbon–Nitrogen Bonds

Treatment of 3-benzyl-6-methyl-1,3-oxazine-2,4(3*H*)-dione with thioureas under phase-transfer catalytic conditions gave 6-thioxo-1,3,5-triazine-2,4(1*H*,3*H*,5*H*)-dione. In analogous reactions with ureas, the substituents influence the mode and the nature of the products <1992J(P1)1139>.

Several substituted triazones were prepared by a three-component condensation of *N,N*-dimethylurea, aqueous formaldehyde, and primary amines under microwave irradiation <2001IJB612>.

9.03.10 Ring Synthesis by Transformations of Another Ring

9.03.10.1 Synthesis from Three-Membered Rings

No new relevant data were found.

9.03.10.2 Synthesis from Four-Membered Rings

No new relevant data were found.

9.03.10.3 Synthesis from Five-Membered Rings

Irradiation of a solution of 5-phenyl-1,2,4-thiadiazole in acetonitrile for 150 min was accompanied by the consumption of 53% of the reactant and the formation of 2-phenyl-1,3,5-triazine, 2,4-diphenyl-1,3,5-triazine, and other (gas-liquid chromatography) (GLC)-volatile products. Diphenyl-1,2,4-thiadiazole was observed also to undergo photofragmentation and triazine formation. Thus, irradiation of a solution of diphenyl-1,2,4-thiadiazole in cyclohexane resulted in the formation of benzonitrile and triphenyl-1,3,5-triazine in yields of 26% and 52%, respectively <2003JOC4855>.

9.03.10.4 Synthesis from Six-Membered Rings

No new relevant data were found.

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

9.03.11.1 Synthesis of 1,3,5-Triazines

No new preparation of the parent 1,3,5-triazine has appeared since the mid-1980s. The synthesis due to Maier and Bredereck, which involves the reaction of ammonium acetate with triethyl orthoformate, remains the main route <1979S690>.

9.03.11.2 Synthesis of Monosubstituted 1,3,5-Triazines

No new synthetic route to monosubstituted 1,3,5-triazines has been reported. The reaction of 1,3,5-triazine with imidates gives monoalkyl- or aryl-1,3,5-triazines <1961JOC2784>. 2-Amino-1,3,5-triazines are best prepared by reaction of triformidomethane with a formyl guanidine <1963AGE655>.

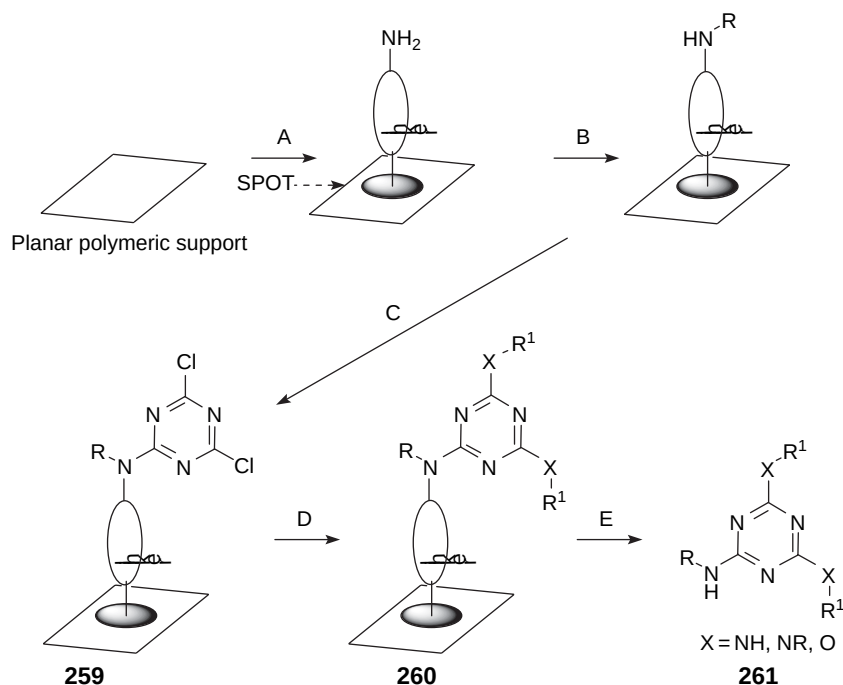
9.03.11.3 Synthesis of 2,4-Disubstituted 1,3,5-Triazines

New, general synthetic approaches to 2,4-disubstituted 1,3,5-triazines have not been described.

9.03.11.4 Synthesis of Trisubstituted 1,3,5-Triazines

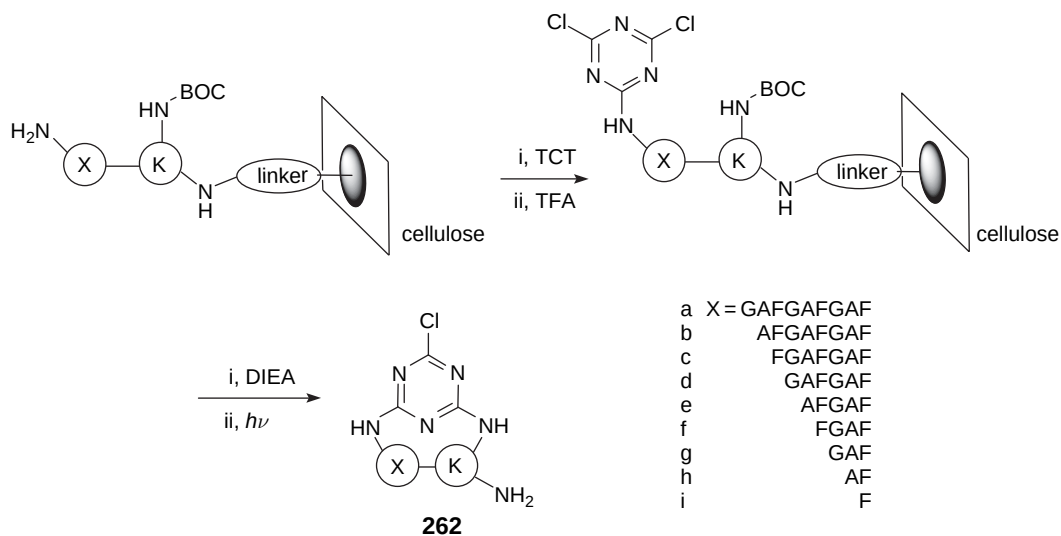
Catalytic 18-crown-6, already successfully used for the selective mono- and dialkoxylation of CC, can be employed conveniently for the selective amination of the same substrate in the presence of K_2CO_3 . This procedure is particularly convenient for the preparation of symmetrically di- and trisubstituted, optically active alkylamino-1,3,5-triazines without loss of expensive materials, as well as for the preparation of asymmetric di- and trisubstituted alkylamino-1,3,5-triazines by a time-saving one-pot procedure <2002EJO1551>.

Effective spatially addressed parallel assembly of tris-amino- and amino-oxy-1,3,5-triazines **259** was achieved by applying the SPOT-synthesis technique on cellulose and polypropylene membranes (Scheme 38). In addition to developing a suitable linker strategy and employing amines and phenolate ions as building blocks, a highly effective microwave-assisted nucleophilic substitution procedure at membrane-bound monochlorotriazines was developed. The 1,3,5-triazines **260** obtained could be cleaved in parallel from the solid support by trifluoroacetic acid (TFA) vapor to give compounds **261** adsorbed on the membrane surface in a conserved spatially addressed format for analysis and screening. The reaction conditions developed were employed for the synthesis of 8000 cellulose-bound 1,3,5-triazines **261**, which were probed in parallel for binding to the antitransforming growth factor-R monoclonal antibody in order to identify epitope mimics <2000JCO361>.



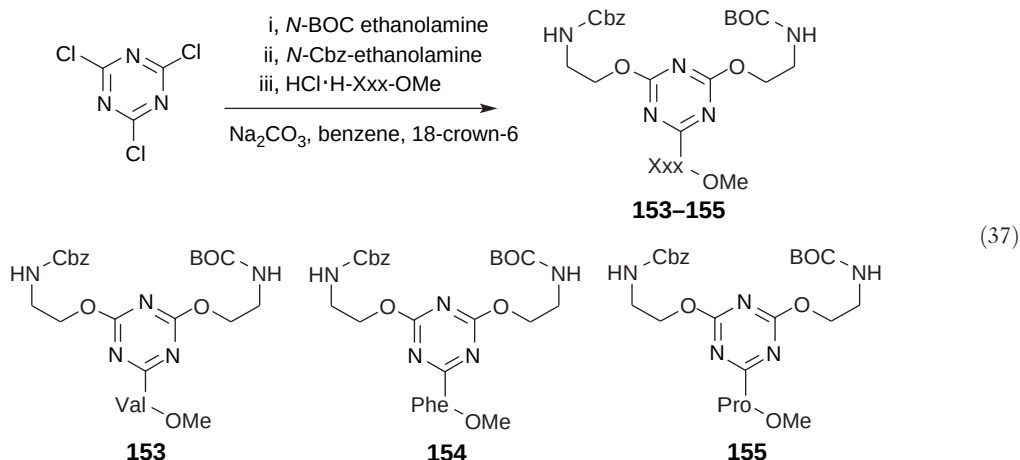
Scheme 38

A novel concept for the synthesis of macrocyclic peptidomimetics **262**, which incorporate heteroaromatic units, was reported (Scheme 39). This method involves sequential S_NAr reactions of orthogonally protected amino groups of peptides and other linear oligomers on halogenated heterocycles such as 2,4,6-trichloro[1,3,5]triazines. The scope of this novel solid-phase approach was evaluated systematically by means of the SPOT-synthesis methodology on planar cellulose membranes <2000JCO361>.

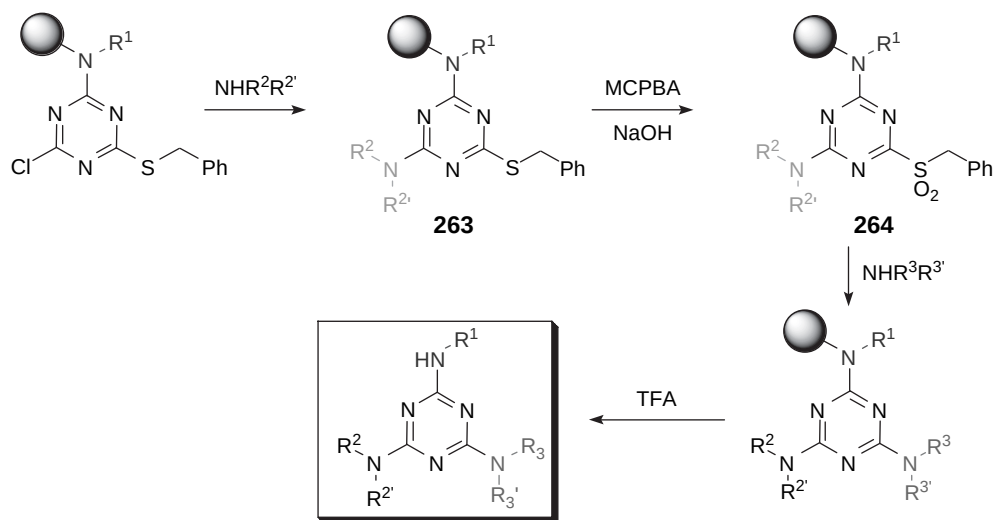


Scheme 39

The synthesis of trifunctionalized orthogonally protected CRAB templates based on the triazine skeleton has been studied by Falorni *et al.* Pure CRABs **153–155** were obtained in 31–35% overall yields (Equation 37) <1998TL7607>.



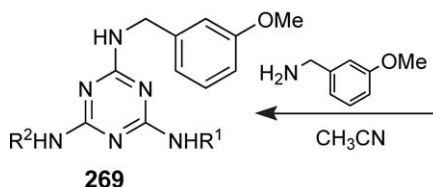
To improve upon the previous orthogonal method for synthesis of a triazine library, an alternative strategy has been developed by Bork and co-workers via oxidation/activation of the thioethers **263** to the sulfones **264** (Scheme 40). Through a comparison between these two methods, the sulfone strategy was demonstrated as an enhanced method for the generation of highly pure triazine library compounds <2003OL117>.



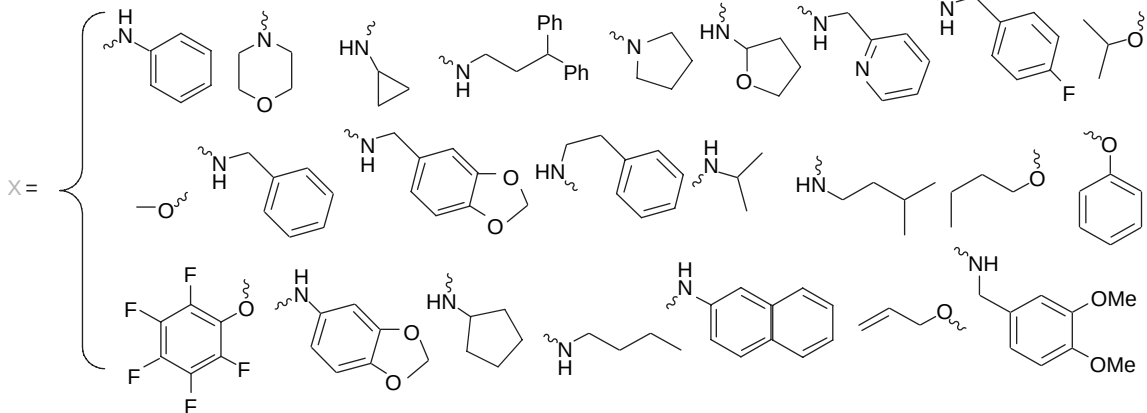
Scheme 40

More recently, an original safety-catch method for the synthesis of highly pure trisubstituted triazines has been designed. PS-Thiophenol resin **265** was used to anchor the monosubstituted triazines giving **266** (Scheme 41). The second chlorine site was aminated at 120 °C in the presence of *N,N*-diisopropylethylamine to yield **267**. Khersonsky and Chang then have taken advantage of a thioether's propensity to oxidation by *m*-chloroperbenzoic acid (MCPBA) to an activated sulfone, affording **268** <2004JCO474>. Finally, a nucleophile was used to displace the activated sulfone solid support and release the trisubstituted triazines **269**.

A novel and highly diverse tagged triazine library incorporating a triethylene glycol-based linker was synthesized using an orthogonal combinatorial approach on the solid phase and covalent immobilization on a glass substrate as a small molecule microarray (SMM) (Scheme 42). The SMM was screened with a fluorophoreconjugated human immunoglobulin G (IgG), and four novel binders from a library of 2688 compounds were identified from the fully spatially addressable array without the need for compound decoding <2004JCO862>.

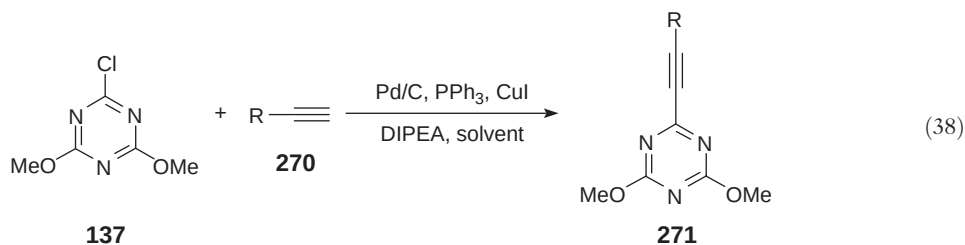


Scheme 41

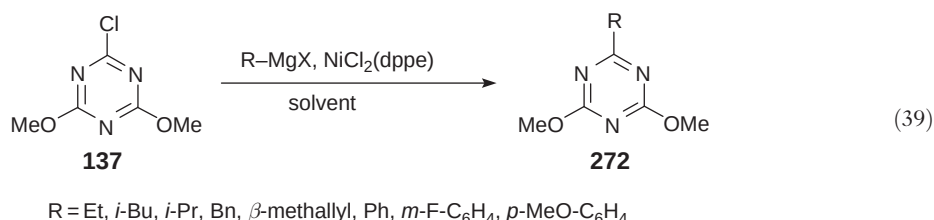


Scheme 42

2-(1-Alkynyl)-4,6-dimethoxy-1,3,5-triazines **271** have been synthesized in satisfactory yields by (Pd/C)/PPh₃/CuI-catalyzed cross-coupling between terminal alkynes **270** and 2-chloro-4,6-dimethoxy-1,3,5-triazine **137**, carried out in the presence of diisopropylethylamine or K₂CO₃/18-crown-6 (Equation 38) <2002T1381>.



The reactivity of 2-chloro-4,6-dimethoxy-1,3,5-triazine **137** has been investigated in Pd- or Ni-catalyzed cross-coupling processes with organostannanes, Grignard reagents, organoalanes, and organozinc halides (Equation 39). All of these organometallic reagents formed new C–C bonds on the heteroaromatic ring and afforded the corresponding 2-alkyl-4,6-dimethoxy-1,3,5-triazines **272** in moderate to very good yields <2005T4475>.



9.03.11.5 Synthesis of 1,3,5-Triazin-2-(1*H*)-ones

1,3,5-Triazin-2-(1*H*)-ones were prepared from reactions of *N*-acyl-1*H*-benzotriazole-1-carboximidamides with urea or its *N*-monoalkyl derivatives in the presence of 3 equiv of potassium *tert*-butoxide (see Section 9.03.9.4.2). This method allows the introduction of several amino group substituents, which is not possible by direct reactions with cyanoguanidines or is limited by the availability of *N,N*-disubstituted formamide diacetals. Use of acyl cyanoguanidines provided diversity in the 4(6)-position, but, once again, it did not allow the introduction of a substituent in the amino group at the same time.

9.03.11.6 Synthesis of 1,3,5-Triazin-2,4-(1*H*,3*H*)-diones

1,3,5-Triazin-2,4-(1*H*,3*H*)-diones have been prepared on the solid phase from isocyanates and amines via a novel traceless approach (see Section 9.03.9.1). An alternative solid-supported synthesis of 1,3,5-triazine-2,4-dione derivatives was developed by Gopalsamy and Yang. The synthetic design includes four variable groups, which are added in the scaffold from a primary amine component, from a secondary amine component, and from an alcohol component (see Section 9.03.9.4.2). 1,3,5-Triazin-2,4-(1*H*,3*H*)-diones were prepared also by condensation of *N*-(benzyloxycarbonyl)ureido-*N'*-benzyloxycarbonyl-*S*-methylisothioureia **176** with butylamine **177** in the presence of TEA in DMF (see Section 9.03.9.3.2).

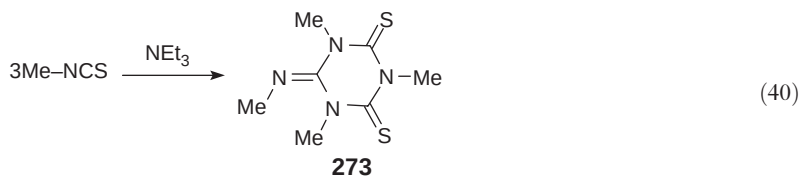
9.03.11.7 Synthesis of 1,3,5-Triazin-2,4,6-(1*H*,3*H*,5*H*)-triones

1,3,5-Triazin-2,4,6-(1*H*,3*H*,5*H*)-triones were best prepared from readily available alkyl or aryl isocyanates **235**, primary amines **236**, and *N*-chlorocarbonyl isocyanate. The one-pot synthetic route developed by Guo *et al.* gives access to asymmetric 1,3,5-triazine-2,4,6-triones **238** in good yields (see Section 9.03.9.5.2).

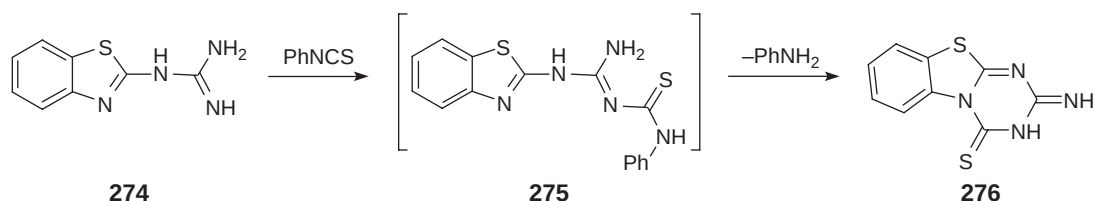
Using the concept of 'libraries from libraries', 1,3-disubstituted and 1,3,5-trisubstituted 1,3,5-triazine-2,4,6-triones were prepared on two different solid supports from common building blocks such as amino acids, isocyanates, and alkyl halides (see Section 9.03.9.5.2).

9.03.11.8 Synthesis of 1,3,5-Triazinethiones

5,6-Dihydro-1,3,5-trimethyl-6-methylimino-1,3,5-triazine-2,4-(1*H*,3*H*)-dithione **273** was synthesized by the reaction of methyl isothiocyanate under high pressure in the presence of Et₃N and H₂O (Equation 40). Yield and selectivity were seriously affected by pressure, reaction temperature, solvent, and the amount of H₂O <1993CL1097>.



When the benzoza(thia)zoyl-2-guanidine **274** was reacted with phenyl isothiocyanate, instead of the expected addition product **275**, 2-imino-3,4-dihydro-2*H*-benz[1,3]oxa(thia)zolo-[3,2-*a*]-1,3,5-triazin-4-one (thione) **276** was obtained (Scheme 43). Obviously, the urea **275** is formed as an intermediate in the first reaction step and then undergoes ring closure to the triazinone (thione) **276** with elimination of aniline <2001CHE524>.



Scheme 43

The compound **277** was prepared as a by-product during an effort to synthesize a Mg(II) complex with trithiocyanurate (ttcH₃) and 1,10-phenanthroline (phen) (Figure 27). Compound **277** consists of [Na(phen)₃]⁺ and [ttcH₂][−] moieties. The Na⁺ ion is 6-coordinated by the N-atoms of the three phen ligands <2003AXC399>.

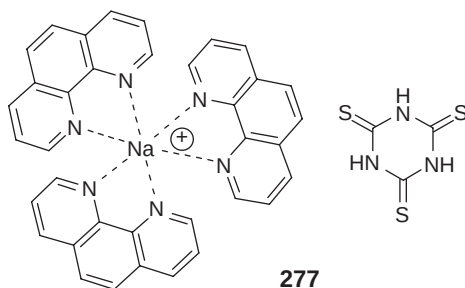


Figure 27

9.03.11.9 Synthesis of Reduced 1,3,5-Triazines

New, general synthetic approaches to reduced 1,3,5-triazines have not been described.

9.03.11.10 Synthesis of Triazinetriimines

A facile and efficient one-pot reaction for the preparation of triazinetriimines involves the cyclotrimerization of dialkylcyanamides in the presence of triflic anhydride. The same reaction can be applied to aryl nitriles and thiocyanates (see Section 9.03.9.3).

9.03.11.11 Synthesis of *N*-Aminotriazines

N-Aminotriazines **248** were synthesized in good yields from aromatic aldehyde or ketone ethoxycarbonylhydrazones **246** by treatment with aryl or methyl isocyanates **247** in boiling TEA followed by hydrolysis with hydrochloric acid (see Section 9.03.9.6.1).

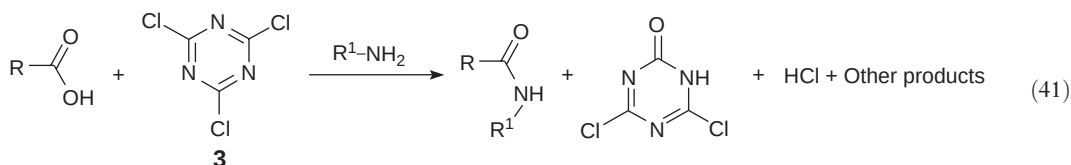
9.03.11.12 Synthesis of Triazine *N*-Oxides

New, general synthetic approaches to triazine *N*-oxides have not been described.

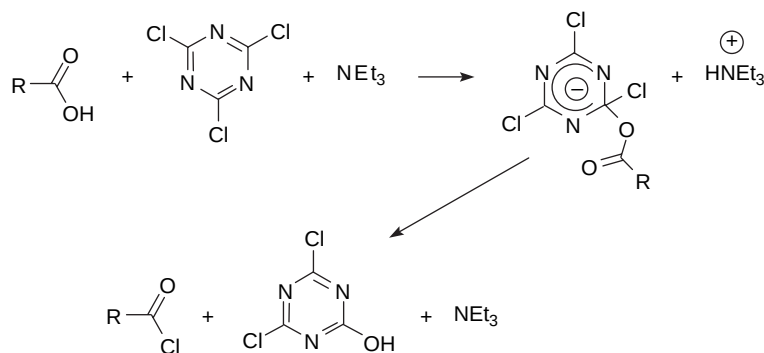
9.03.12 Important Compounds and Applications

9.03.12.1 2,4,6-Trichloro-1,3,5-triazine

The reactions of CC **3** (2,4,6-trichloro-[1,3,5]triazine, TCT) until 1937 have been summarized by Fierz-David and Matter <1937JDC424>. However, aside from its reaction with ammonia and a few amines <1944JA1775>, mainly aromatic, the first extensive report on CC derivatives was not published until 1951 <1951JA2981>. One of the first uses of **3** for synthetic purposes was as an activator of carboxylic acids for the preparation of amides (Equation 41) <1969CIM287>.



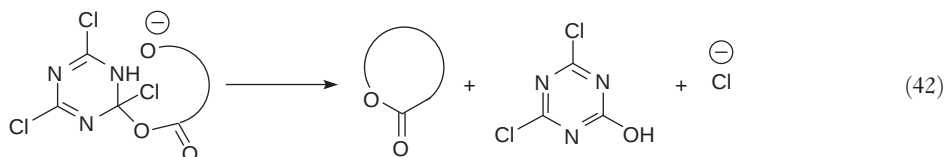
Later, Venkataraman and Wagle <1979TL3037> reported the use of TCT as a useful reagent for the conversion of carboxylic acids into chlorides, esters, amides, and peptides: the authors proposed the formation of the acyl chloride as shown in Scheme 44.



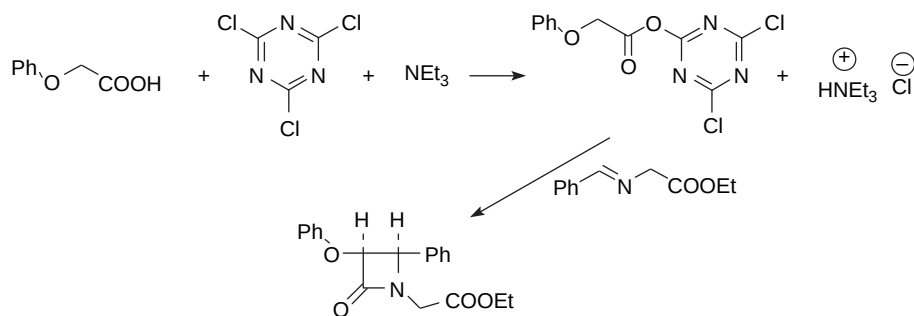
Scheme 44

The reactions were carried out in acetone at room temperature and the hydroxy dichloro-[1,3,5]-triazine separated as an insoluble product; the solution containing the acyl chloride and the residual unreacted acid could be used directly for further transformations. The acyl chloride was formed rapidly, presumably via the σ -adduct resulting from the nucleophilic attack of the carboxylic group on TCT.

The same authors described the use of TCT for macrocyclic lactonization <1980TL1893> (Equation 42). The reactions were carried out in acetone at room temperature employing TEA as a base. The lactones were recovered in good isolated yields (40–70%) depending on the ring dimensions.

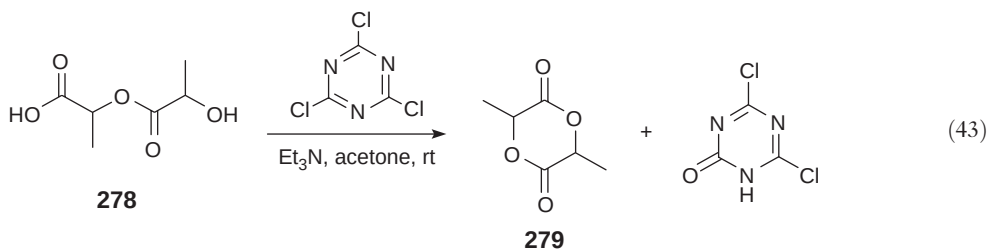


Further, CC has been used for the synthesis of β -lactams [<1981S209>](#). The procedure involves the reaction of an imino compound with a substituted acetic acid in the presence of TCT and TEA: β -lactams are obtained in good yields ([Scheme 45](#)).

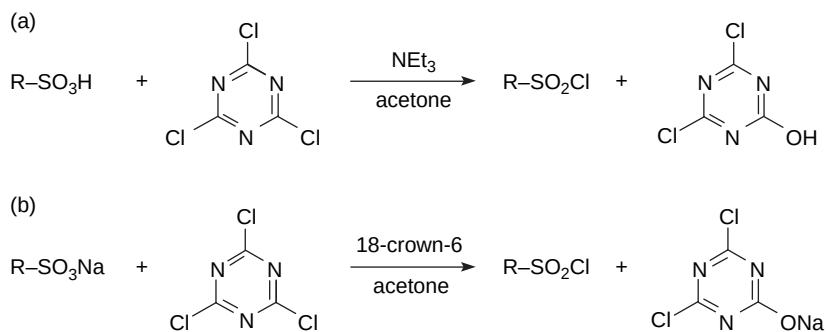


Scheme 45

Polyhydroxy acids such as polylactic acid and polyglycolic acid can be synthesized by a polycondensation reaction of lactic acid at high temperature. This route, however, yields relatively low molecular weight polymers. A synthetic pathway to functionalized six-membered dilactones structurally analogous to lactide was described by Hennink and co-workers ([Equation 43](#)). Through the use of orthogonal protecting groups, the synthesis of functionalized dilactones **279** was performed in a straightforward way by CC-mediated cyclization of the corresponding linear α -hydroxy acid dimers **278** [<2003EJO3344>](#).

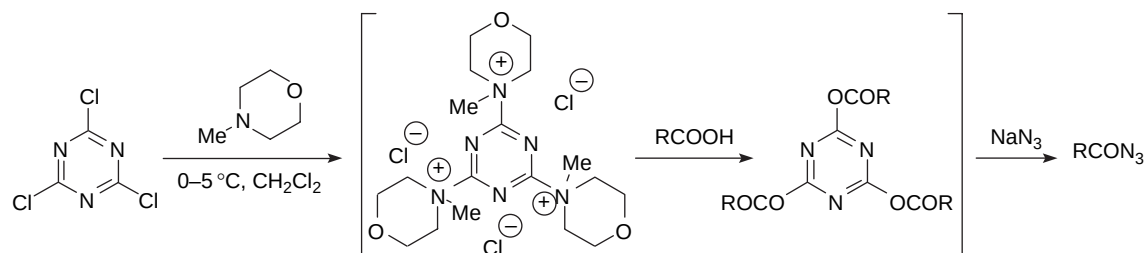


In 2003, Blotny presented a new method for the preparation of sulfonyl chlorides that involves treatment of sulfonic acids with 2,4,6-trichloro-1,3,5-triazine in refluxing acetone under neutral conditions ([Scheme 46](#)) [<2003TL1499>](#).



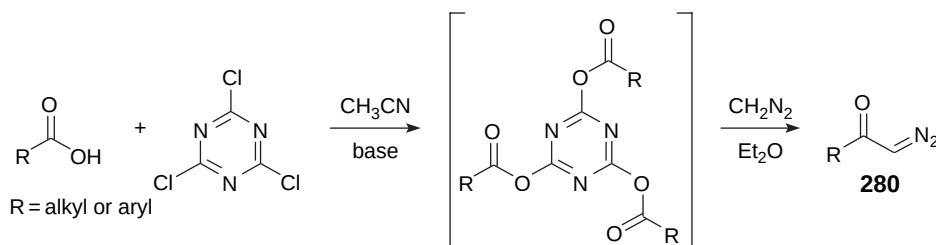
Scheme 46

Recently, Bandgar and Pandit have described a mild, efficient, and general method for the preparation of acyl azides from carboxylic acids and sodium azide using CC (**Scheme 47**). Various aryl, heteroaryl, alkylaryl, and alkyl carboxylic acids, on reaction with CC in the presence of sodium azide and *N*-methylmorpholine, undergo smooth conversion to the corresponding acyl azides in excellent yields <2002TL3413>.



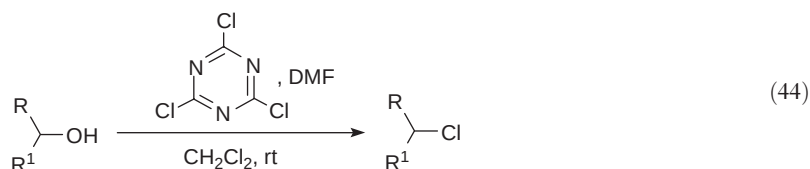
Scheme 47

2,4,6-Trichloro-1,3,5-triazine is an excellent coupling reagent, allowing for the efficient transfer of diazomethane to a carboxylic acid (**Scheme 48**). Preparation of diazo ketones **280** using carboxylic acids and triazine reagents was considerably more convenient than classical diazo transfer protocols because H₂O did not have to be removed. Electron-deficient and neutral aryl carboxylic acids were found to give better results than electron-rich or aliphatic carboxylic acids <2000TL943>.

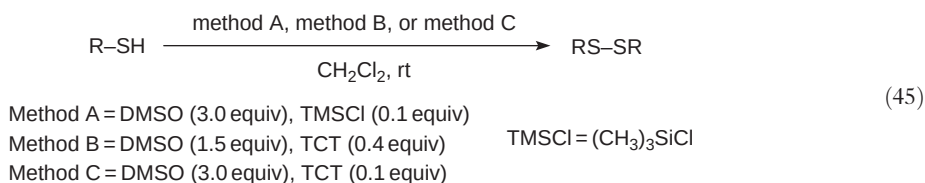


Scheme 48

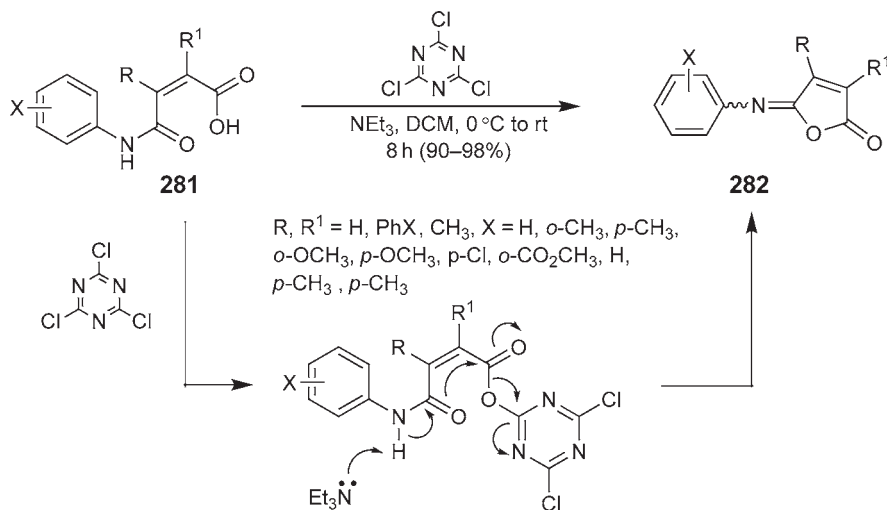
Efficient conversion of alcohols and α -amino alcohols to the corresponding chlorides can be carried out at room temperature in methylene chloride, using 2,4,6-trichloro[1,3,5]triazine and *N,N*-dimethyl formamide (**Equation 44**). This procedure can also be applied to optically active carbinols. Alkyl bromides can be obtained by addition of sodium bromide and the alcohol to the TCT/DMF mixture in CH₂Cl₂. Use of sodium iodide did not lead to formation of the alkyl iodide <2002OL553>.



Different types of thiols were converted rapidly and efficiently to disulfides using DMSO in the presence of catalytic amounts of either trimethylchlorosilane (TMSCl) or CC (**Equation 45**) <2002S2513>.

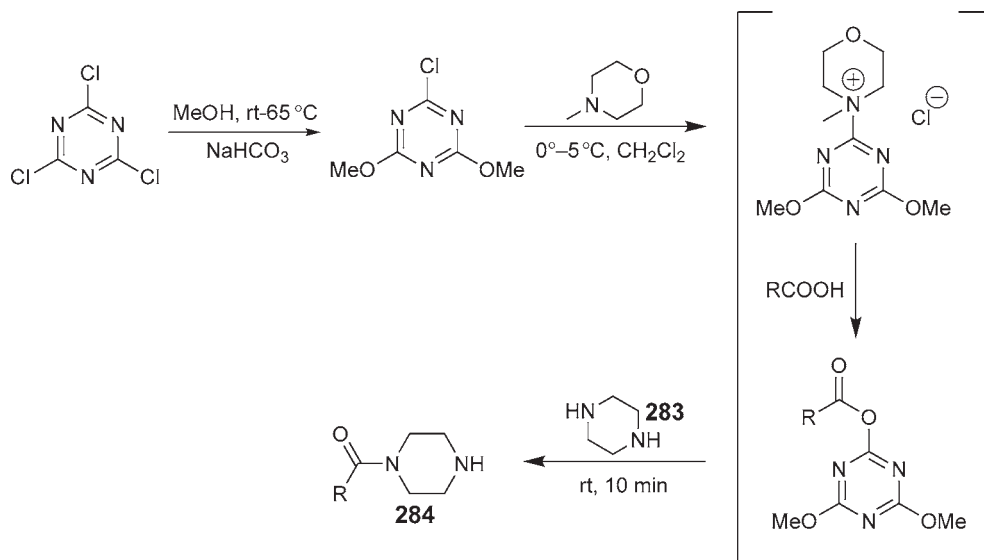


Starting from maleanilic and maleamic acids **281**, a facile, general approach to kinetically controlled isomaleimides **282** has been described for the first time by Argade and co-workers using CC as a dehydrating agent with 85–98% yields (Scheme 49) <2006T937>.



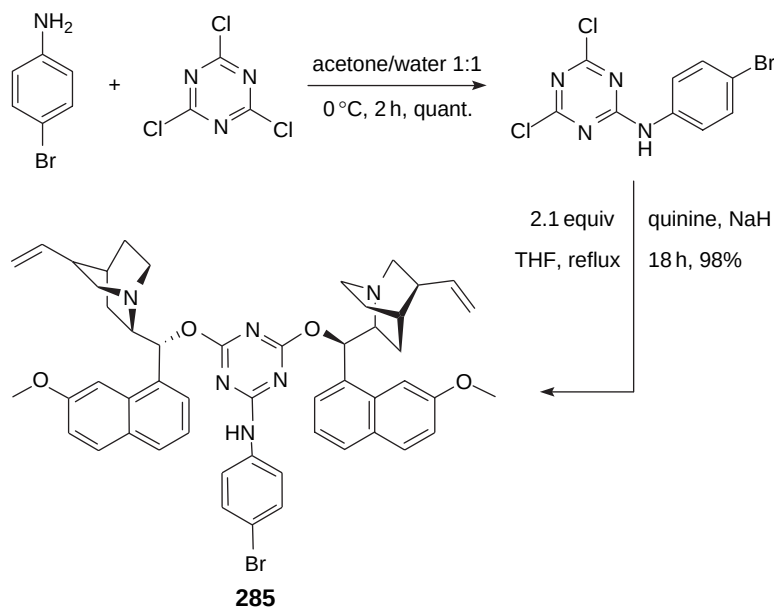
Scheme 49

In 2003, a convenient and straightforward protocol was developed to convert piperazine **283** into monosubstituted acyl piperazine derivatives **284** starting from CC (Scheme 50). Furthermore, this process is amenable to scaleup <2003TL3855>.



Scheme 50

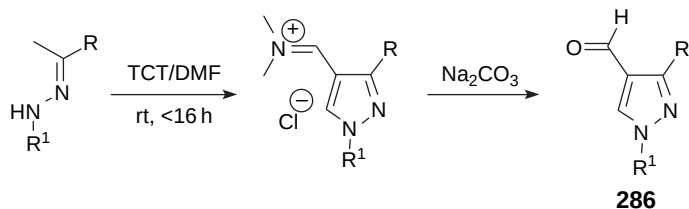
A novel Sharpless-type asymmetric dihydroxylation ligand with a triazine core **285** was prepared by Bradley and co-workers in two, easy, high-yielding steps from readily available starting materials, and offered an economic alternative to other systems (Scheme 51). The catalyst was found to be active in the asymmetric dihydroxylation of alkenes, especially those of *trans*-geometry.



Scheme 51

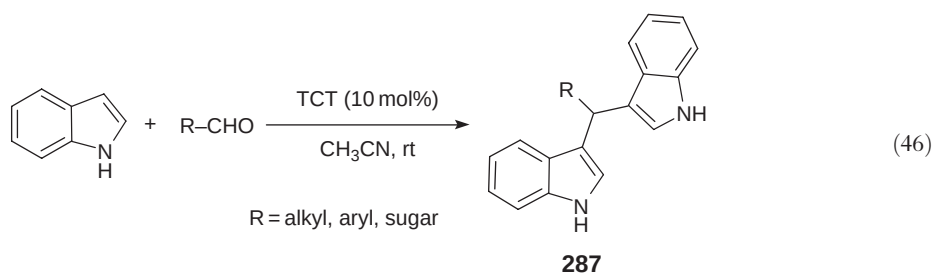
It was observed that the incorporation of an aniline moiety is crucial for the catalytic activity of such a ligand [\(2004TL8527\)](#).

A variety of 3-aryl-4-formylpyrazoles **286** can be prepared easily in good yields from the corresponding methyl ketones, upon treatment with 2,4,6-trichloro[1,3,5]triazine in *N,N*-dimethylformamide at room temperature ([Scheme 52](#)). The reactions occur with good yields in all cases examined, varying from 65% to 90% [\(2004SL2299\)](#).

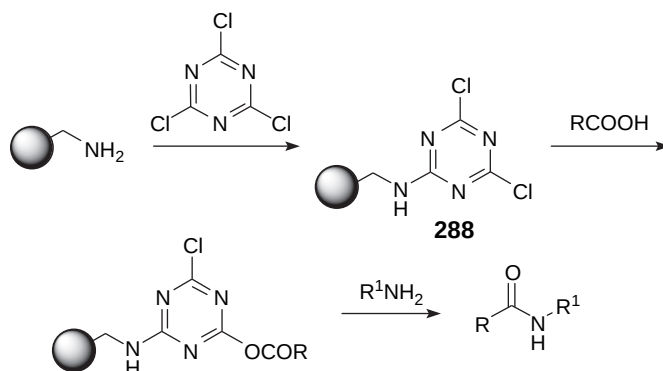


Scheme 52

A practical and efficient electrophilic substitution reaction of indoles with a variety of aldehydes was carried out using catalytic trichloro-1,3,5-triazine (10 mol%) in acetonitrile to furnish the corresponding bis(indolyl)methanes **287** in excellent yields ([Equation 46](#)) [\(2004TL7729\)](#).

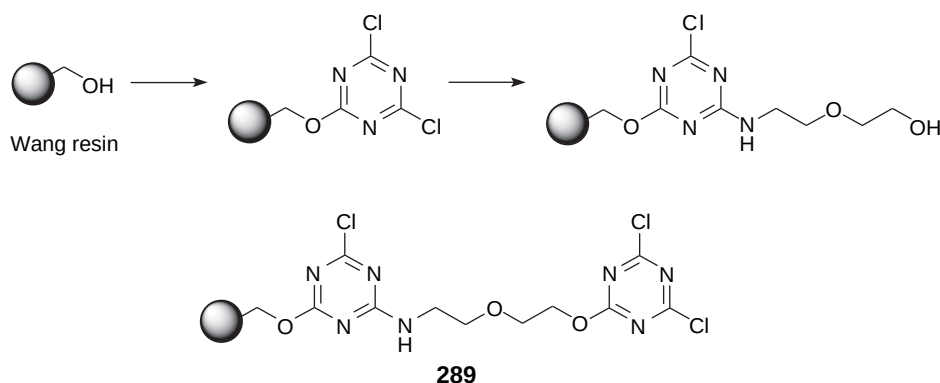


Polymer-supported reagents and auxiliaries have found increasing applications for the preparation of small organic molecules during the past few years. 2,4,6-Trichloro[1,3,5]triazine was loaded on different types of NH_2 -functionalized resins to give new supported reagents. The best results, in term of yields, were obtained using the chlorotriazine linked to a polystyrene-poly(ethylene glycol) resin **288** (Scheme 53). This reagent was employed for the solution-phase synthesis of different amides and dipeptides <1999OL1355>.



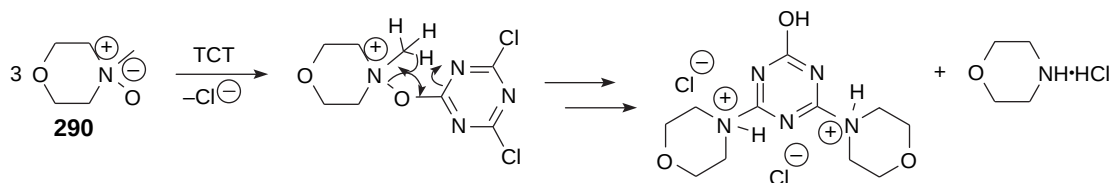
Scheme 53

A new resin-supported chlorinating reagent **289**, based on CC, has been developed and used in the facile preparation of acyl chlorides (Scheme 54). Compared to the conventional synthesis of acyl chlorides using thionyl or oxalyl chloride, the solid-phase methodology is odorless, and the handling process is very convenient since purification can be affected by simple filtration <2002TL8909>.



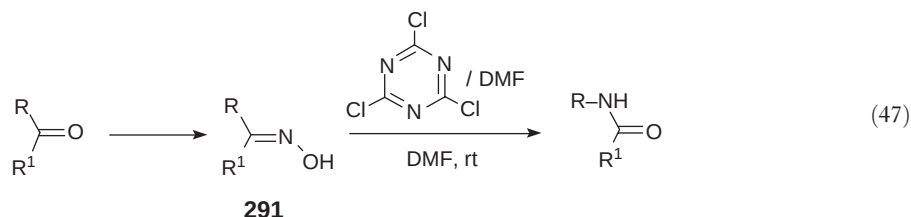
Scheme 54

The course of the reaction between *N*-methylmorpholine-*N*-oxide **290** (NMMO) and cyanuric chloride is strictly dependent on the hydrate water content of the amine oxide (Scheme 55). The reaction can be conducted in such a way that a clean deoxygenative demethylation is achieved <2002T9809>.



Scheme 55

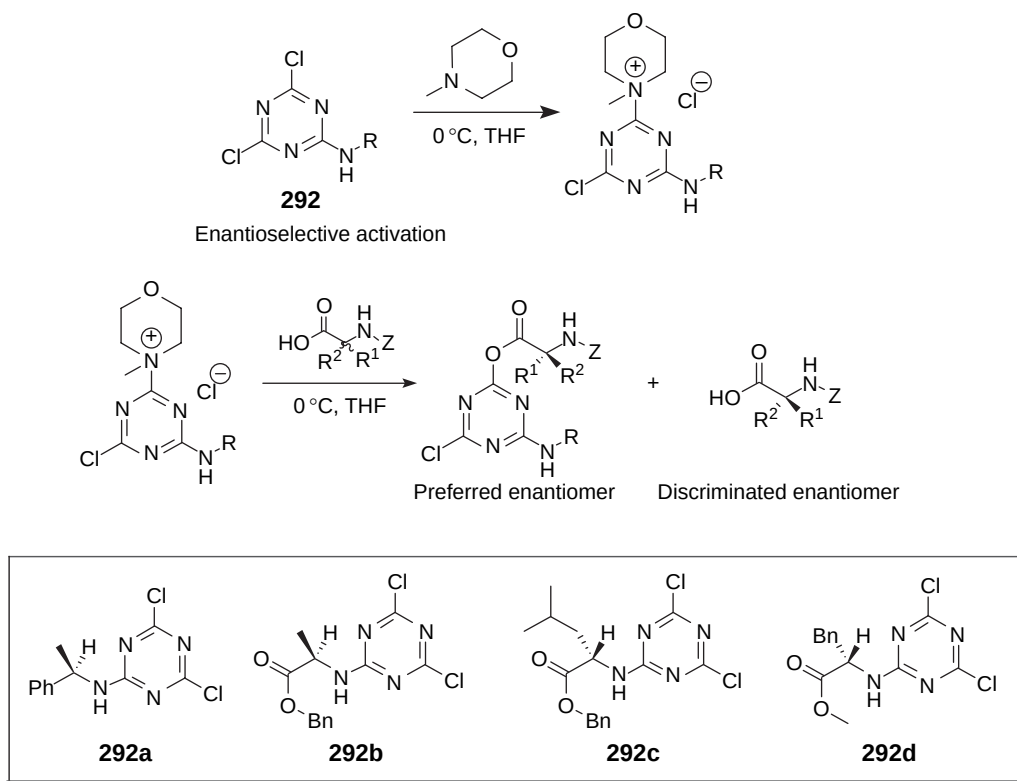
A variety of ketoximes **291**, easily prepared from the corresponding ketones, undergo the ‘Beckmann rearrangement’ upon treatment with 2,4,6-trichloro[1,3,5]triazine in *N,N*-dimethylformamide at room temperature in excellent yields (Equation 47). This method can be applied successfully on a large scale and no deoximation of the oximes to carbonyl compounds occurs. This procedure can be applied also to aldoximes for the preparation of the corresponding nitriles <2002JOC6272>.



Very recently, Yamamoto and co-workers realized the first general organocatalytic Beckmann rearrangement of ketoximes into amides <2005JA11240>. Commercially available CC (TCT) was the most effective organocatalyst, and acids such as HCl and ZnCl₂ were effective as cocatalysts for TCT. Acetal and ester groups in ketoximes were tolerated under these conditions. Large cycloalkanone oximes were very reactive also and were transformed to the corresponding lactams, which were useful as starting materials for nylons. Unfortunately, the reaction of six- to eight-membered cycloalkanone oximes gave the desired lactams in poor yield.

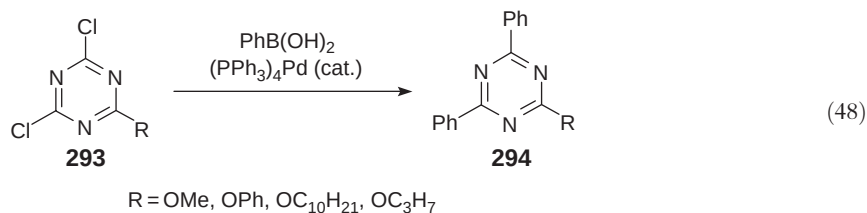
9.03.12.2 2,4,-Dichloro-6-methoxy-1,3,5-triazine

Chiral triazines **292a–d** have been found to be very efficient enantioselective condensing reagents (Scheme 56). Their application enables the synthesis of optically active products from racemic substrates with ee's exceeding 98% <2001ABP1143>.



Scheme 56

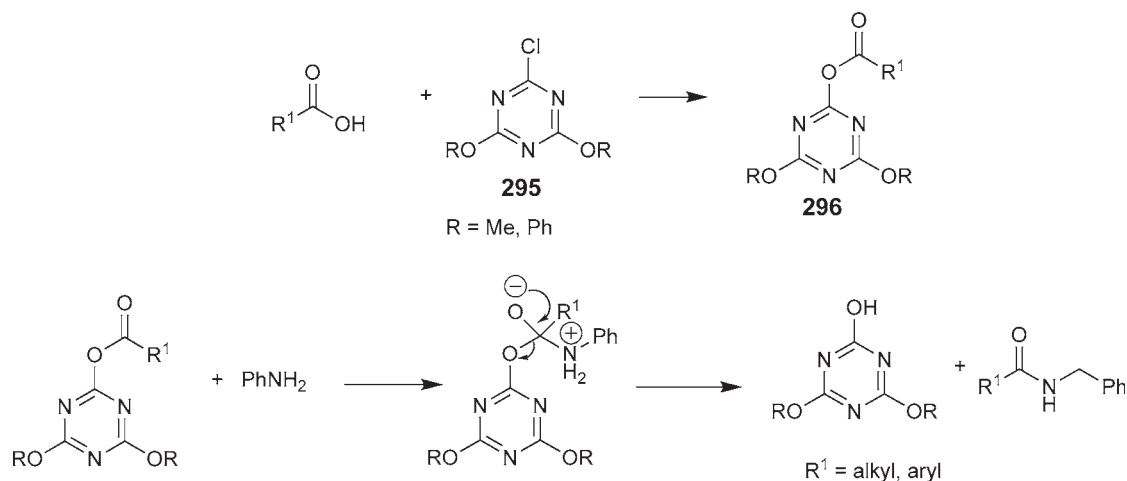
In 1993, Janietz and Bauer reported that 2-substituted 4,6-diphenyl-1,3,5-triazines **294** could be obtained easily in high yield by palladium(0)-catalyzed reaction of the corresponding chloro-1,3,5-triazines **293** with phenyl boronic acid (Equation 48) <1993S33>.



Anhydrides of carboxylic acids were obtained in 53–95% yield by treatment of appropriate carboxylic acids with CDMT or 2,4-dichloro-6-methoxy-1,3,5-triazine (DCMT) in the presence of *N*-methylmorpholine <1985TL2901>.

9.03.12.3 2-Chloro-4,6-dimethoxy-1,3,5-triazine

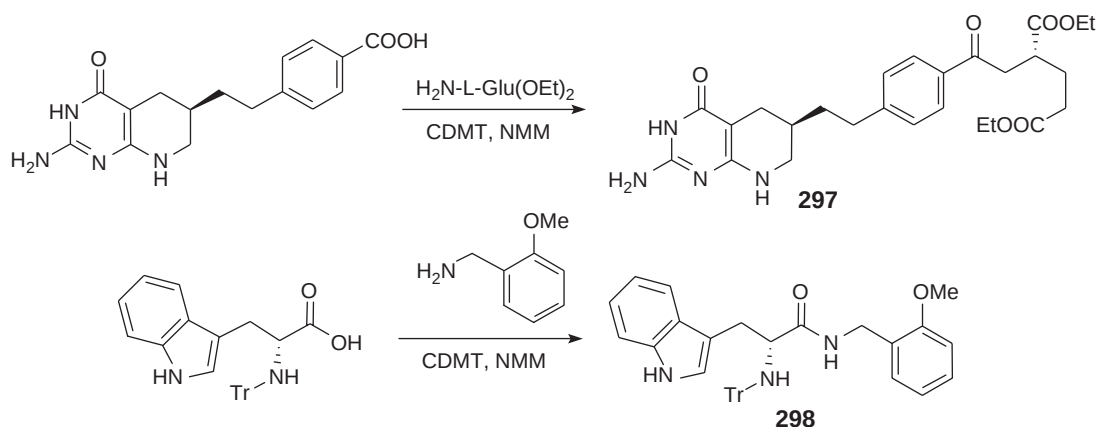
Kamiński has noted that partial substitution of chlorine atoms in TCT **3** by methoxy or phenoxy groups changes the course of the reaction with carboxylic acids <1985TL2901>. In fact, instead of the expected acyl chlorides, the reaction between 2-chloro-4,6-dialkoxy-[1,3,5]-triazine **295** and carboxylic acids gave highly reactive 2-acyloxy-4,6-dialkoxy-[1,3,5]-triazine **296**, which, under further treatment with amines, alcohols, and carboxylic acid anions, afforded amides, esters, and anhydrides, respectively (Scheme 57).



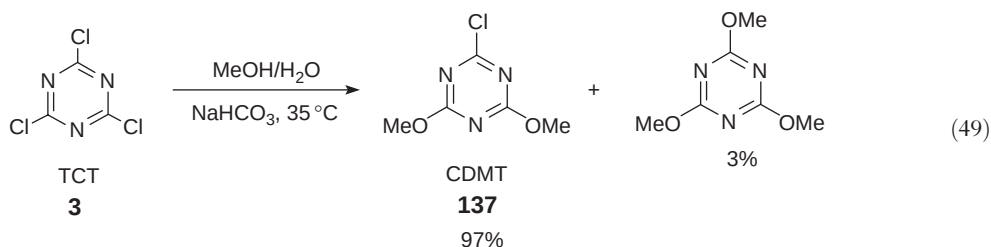
Scheme 57

These results prompted the researchers to investigate the application of 2-CDMT **137** in synthetic applications, such as in the asymmetric synthesis of Lometrexol **297** ((6*R*)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid) <1994JOC7036>, or in the synthesis of **298**, a precursor of LY303870, an NK-1 antagonist <1995JOC7033> (Scheme 58).

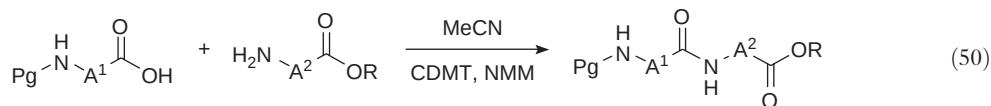
An improved procedure for the large-scale synthesis of CDMT **137** has been reported by Copp and co-workers <1996SC3491>. The authors noted that the previous procedure <1951JA2986, 1994SC2153> was not successful for the preparation of kilogram quantities of CDMT owing to the formation of appreciable amounts of 2,4,6-trimethoxy-[1,3,5]-triazine (Equation 49). They observed that a significant exothermic process was associated with the conversion of CDMT into the trimethoxy derivative. However, the yield in CDMT can be controlled by using 3 equiv of sodium bicarbonate, operating at 35 °C and stopping the reaction after 12 h.



Scheme 58



This novel triazine derivative **137** was proposed as a new coupling reagent for peptide synthesis, mainly in order to facilitate the purification of peptides (Equation 50). Owing to the weakly basic properties of the triazine ring, the side products and excess coupling reagent can be removed easily by washing the crude reaction mixture with dilute acids <1987S917>.



The presence of three chlorine atoms prone to substitution reactions makes TCT an interesting virtual chiral auxiliary if the 4- and 6-positions were bound with optically active alkoxy substituents. This possibility has been tested by employing chiral 2-chloro-4,6-dimethoxy-[1,3,5]-triazine **299** as a differentiating coupling reagent (Figure 28).

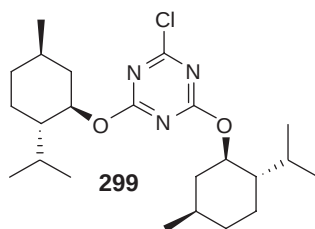
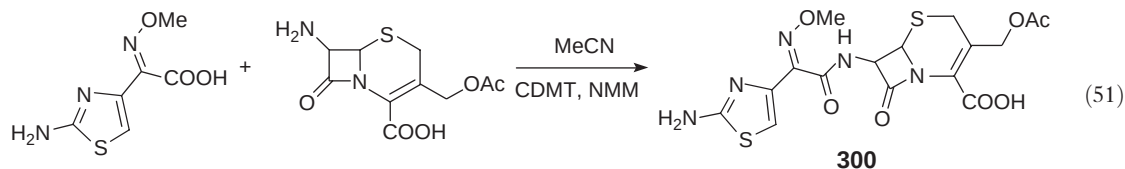
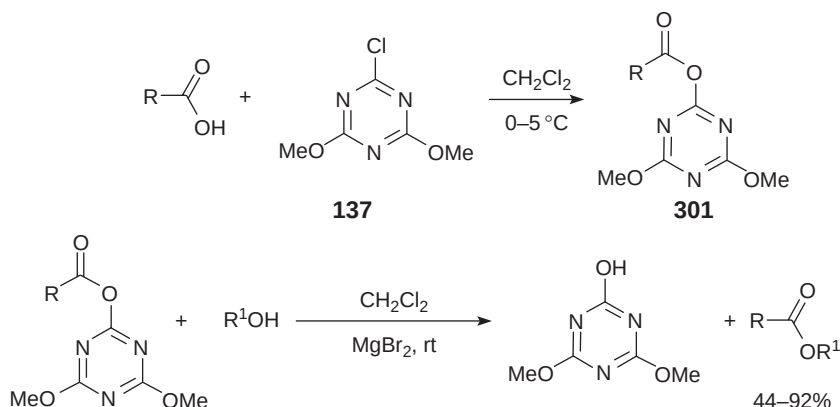


Figure 28

CDMT **137** was employed also as a convenient coupling reagent for cephalosporin derivatives (Equation 51): for this process, use of CDMT was simpler and more versatile than 1-hydroxybenzotriazole (HOBT); since the desired cephalosporin derivative **300** could be obtained in a shorter time without undesirable side reactions <1998SC1339>.



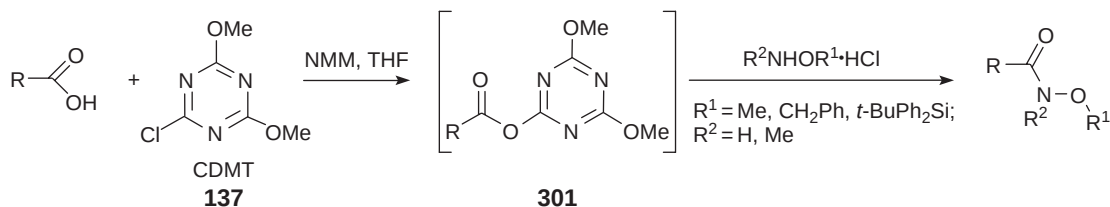
2-Acyloxy-4,6-dimethoxy-[1,3,5]-triazines **301**, obtained by reaction between carboxylic acids and CDMT **137**, have been used as acylating agents for the synthesis of esters from primary, secondary, and tertiary alcohols (Scheme 59). Because of the mild acylation conditions, the method could be applied to esterification of labile alcohols with aromatic and aliphatic acids in good yields <1999S593>.



Scheme 59

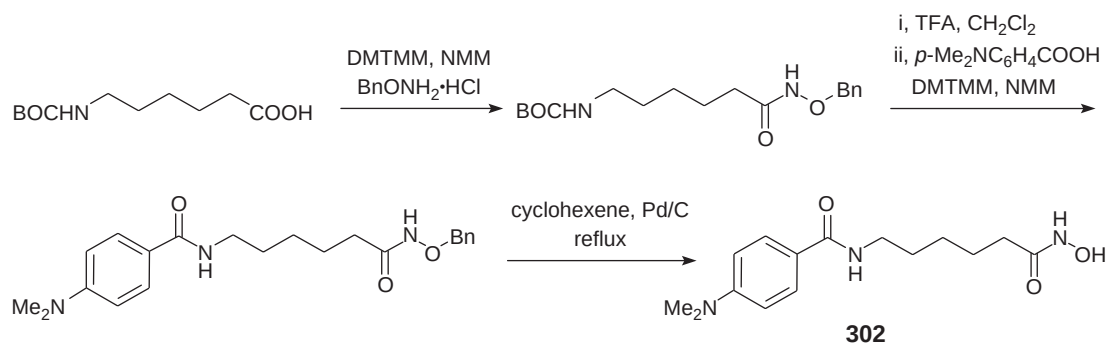
However, the reaction requires the presence of catalytic amounts of MgBr_2 , and the final ester in some cases has to be purified by flash-chromatography.

An easy and convenient one-pot procedure for the synthesis of Weinreb amides <1981TL3815> and hydroxamates has been reported more recently <2001JOC2534>. The method avoids the use of expensive and toxic coupling reagents such as benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), dicyclohexylcarbodiimide (DCC), and, in addition, the nonfacile removal of their excess from the reaction mixtures (Scheme 60).



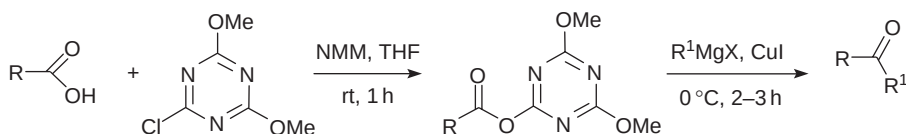
Scheme 60

This method can be applied also to the preparation of hydroxamic acids as demonstrated by the synthesis of the Trichostatine A analog **302** (Scheme 61), a powerful cytodifferentiating agent, which appears to be very promising as a potential cancer chemotherapeutic <1999JME4669>.



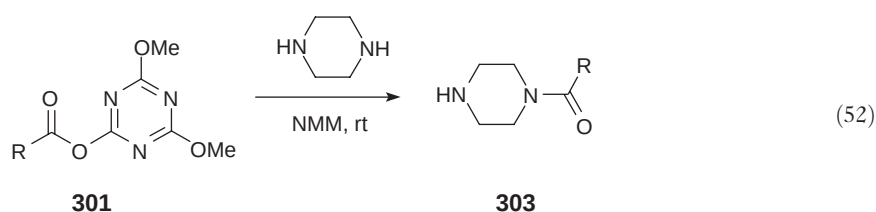
Scheme 61

A valuable method to obtain ketones and, in particular, N-protected α -amino ketones is based on the reaction between Grignard or organolithium reagents and N-protected α -amino Weinreb amides. An alternative approach to the direct synthesis of ketones was reported that avoids the formation of the Weinreb amide [<2001JOC2534>](#) and provides an efficient and cheap conversion of acids and, in particular, of α -amino acids into the corresponding ketones via direct reaction with Grignard/CuI reagents ([Scheme 62](#)) [<2001OL1519>](#). This methodology is applicable to NH-BOC- and *N*-Cbz-protected α -amino acids having secondary amino groups (BOC = *t*-butoxycarbonyl; Cbz = carbobenzyloxy).

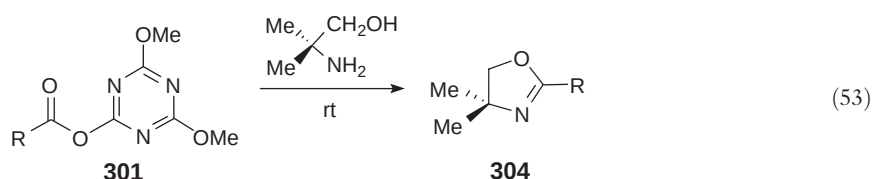


Scheme 62

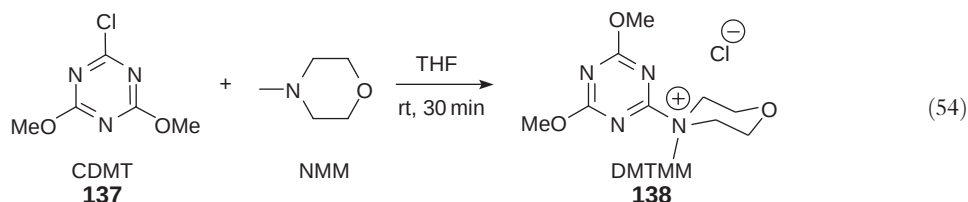
More recently, a series of monoacylated piperazine derivatives **303** were obtained by the reaction of the activated ester **301** (from CDMT and the carboxylic acid) with piperidine. The reactions were carried out in dichloromethane, using 1 equiv of NMM ([Equation 52](#)) [<2003TL3855>](#).



Using analogous procedures and reaction conditions, the same authors have developed a valuable procedure for the direct synthesis of 2-alkyl-5,5-dimethyl-2-oxazolines **304** from carboxylic acids ([Equation 53](#)) [<2003TL2331>](#).

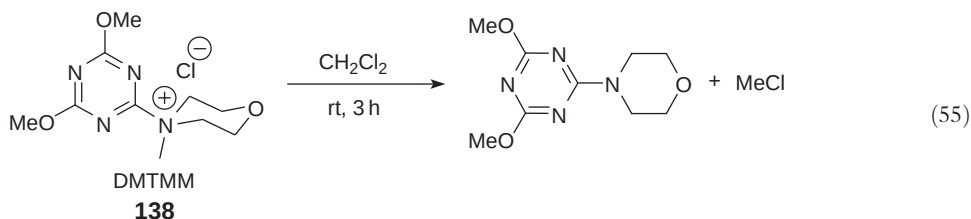


DMTMM chloride **138**, prepared as shown in [Equation \(54\)](#), proved to be an efficient condensing agent for the formation of amides and esters [<1999TL5327>](#).



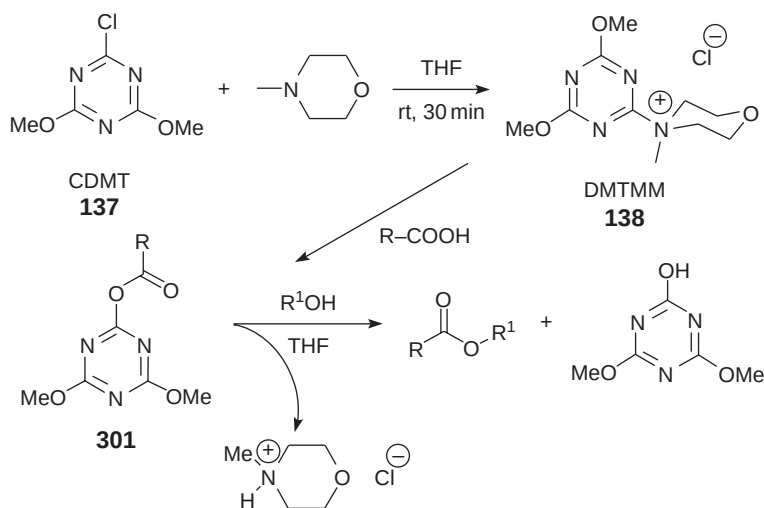
(54)

DMTMM **138** decomposes completely within 3 h at room temperature if suspended in CH_2Cl_2 , by demethylation at the morpholinium nitrogen (Equation 55). The compound is stable in diethyl ether, ethyl acetate, or tetrahydrofuran (THF), but decomposes slowly in DMSO or MeCN. Moreover, neither demethylation nor solvolysis occurred when DMTMM was dissolved in water or MeOH; thus, reaction can be conducted in nonanhydrous solvents. No allergic properties of DMTMM were observed <1999T13159>.



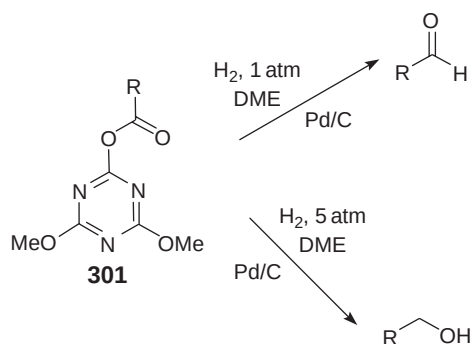
(55)

Generally, reactions conducted with DMTMM **138** instead of CDMT **137** require longer times and occur with lower conversions than those performed with CDMT/NMM. However, the reactions can be forced by prolonging the reaction times <1999T13159>. Condensation of carboxylic acids and amines using DMTMM proceeded in THF to give the corresponding amides in good yields <1999T13159>. The corresponding esters can be obtained by esterification of carboxylic acids with DMTMM in methanol, ethanol, isopropanol, and *t*-butyl alcohol in the presence of 1 equiv of free NMM (Scheme 63). The quantity of the alcohol can be reduced to a stoichiometric amount by carrying out the reaction in THF <1999S1255>.



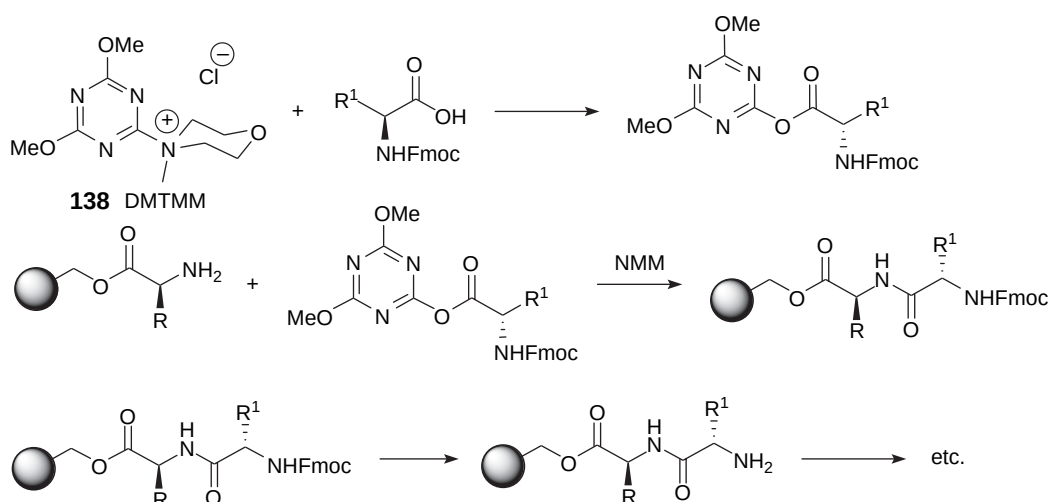
Scheme 63

The activated ester **301** from DMTMM can be formed also with N-protected amino acids in dimethoxyethane (DME). A solution of this ester can be treated directly with H_2 (1 atm pressure) at room temperature in the presence of 10% Pd/C catalyst to give the corresponding aldehyde, which is recovered practically pure by evaporation of the solvent (Scheme 64) <1999JOC8962>.



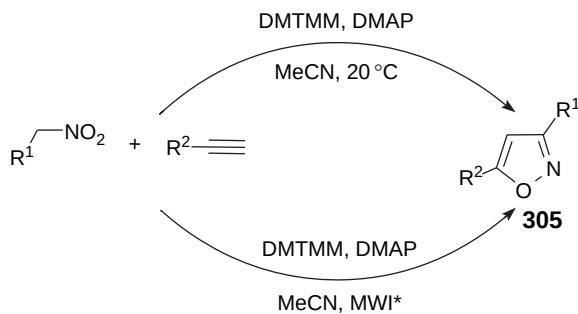
Scheme 64

The salt **138**, formed from 2-chloro-4,6-di-methoxy[1,3,5]triazine and *N*-methylmorpholine (DMTMM), is also an effective coupling agent for solid-phase peptide synthesis that can be used as economical alternative to PyBop (Scheme 65) <2000SL275>.



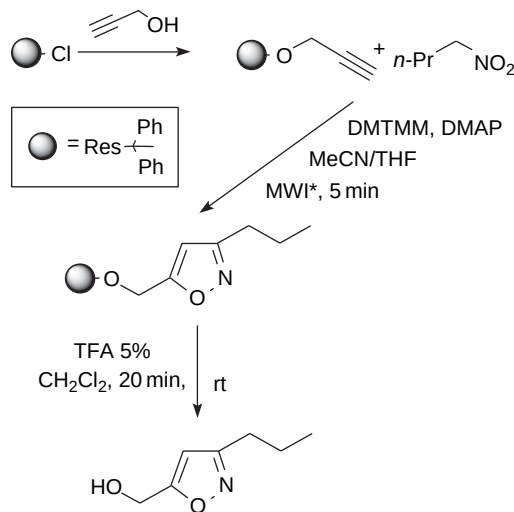
Scheme 65

The reagent DMTMM has been used also for the generation of nitrile oxides *in situ* from nitroalkanes under very mild conditions using microwave irradiation. The reaction requires the presence of 4-dimethylaminopyridine (DMAP) as catalyst (Scheme 66).



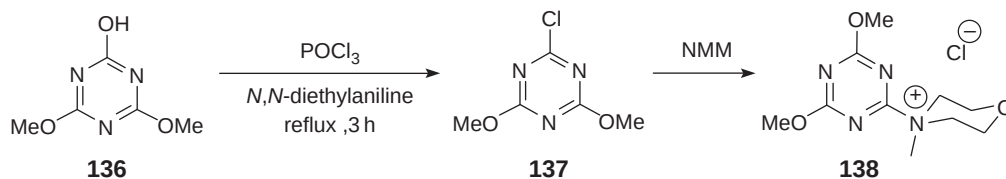
Scheme 66

The reaction has been tested for the synthesis of chiral α -aminoacids containing the isoxazole moiety (cf., **305**; (Scheme 66) <1998TL9241>, and this procedure can be applied conveniently to synthesis on a polymeric support (Scheme 67) <2003T5437>.



Scheme 67

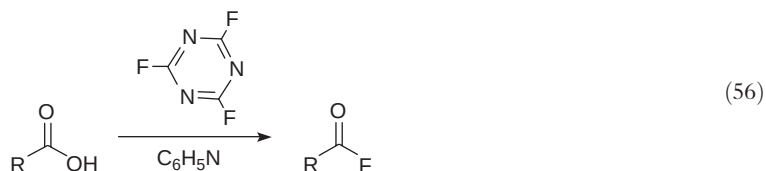
In all these methodologies, the co-product along with the formation of the desired product is 2-hydroxy-4,6-dimethoxy[1,3,5]triazine **136** (HO-DMT). This product can be recycled by treatment with POCl_3 to give CDMT, which is further converted to DMTMM (Scheme 68) <2002TL3323>.



Scheme 68

9.03.12.4 2,4,6-Trifluoro-1,3,5-triazine

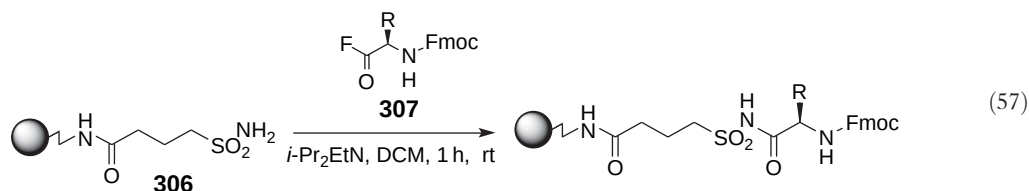
2,4,6-Trifluoro-1,3,5-triazine (cyanuric fluoride) is a colorless liquid, which is used mainly in dye manufacturing. Cyanuric fluoride is a mild reagent that is suitable for the preparation of acyl fluorides even when unsaturated double bonds, hydroxyl groups, or aromatic rings are found in the molecule. Carboxylic acids were converted into the corresponding acyl fluorides by treatment with cyanuric fluoride in the presence of pyridine (Equation 56).



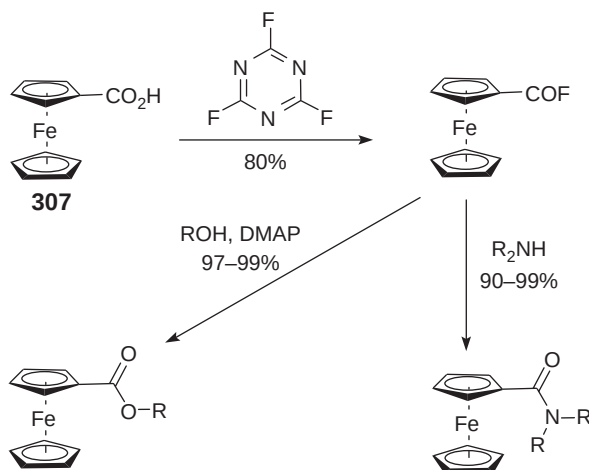
Carboxylic acids are converted into alcohols by chemoselective reduction of their corresponding fluorides with sodium borohydride and dropwise addition of methanol. The method is general and mild and displays a high level of functional group compatibility. N-Protected amino and peptide alcohols, bearing various protecting groups, are prepared in the same way from their corresponding amino acids and peptides without racemization <1996JOC6994>.

Merrifield's standard methods of stepwise solid-phase synthesis could not be applied previously to the synthesis of important naturally occurring peptides because of difficulties arising from the pronounced steric hindrance, and the lack of any general method for the loading of C-terminal amino alcohols to resin supports. It was shown recently that the adoption of 9-fluorenylmethoxycarbonyl (Fmoc) amino acid fluorides as coupling reagents makes possible the facile, general assembly of such peptides <1995JOC405>.

Fmoc-protected amino acid fluorides **307** were found to be excellent reagents for the acylation of sulfonamide safety-catch linkers (SCLs) **306** suitable for the subsequent preparation of peptide C-terminal thioesters (Equation 57). This generally applicable approach enables high loadings on different types of resins using short reaction times with low levels of racemization <2002OL1187>.

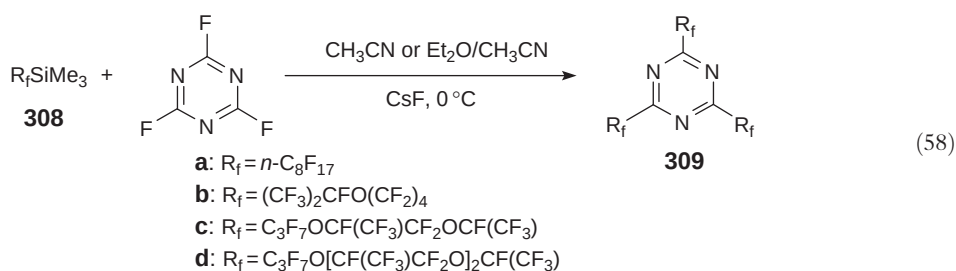


A commonly used intermediate in the synthesis of ferrocene-based catalysts is chlorocarbonylferrocene. Formation of this acid chloride from the corresponding acid is capricious and can often result in low yields. To circumvent these difficulties, recently, Rotello and co-workers have investigated the use of the corresponding acid fluoride as a synthetic intermediate (Scheme 69) <1999JOC3745>.

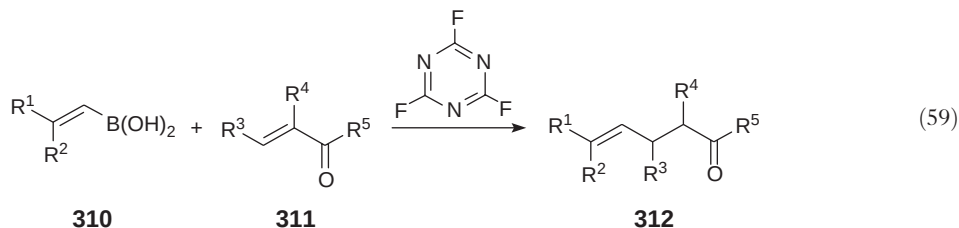


Scheme 69

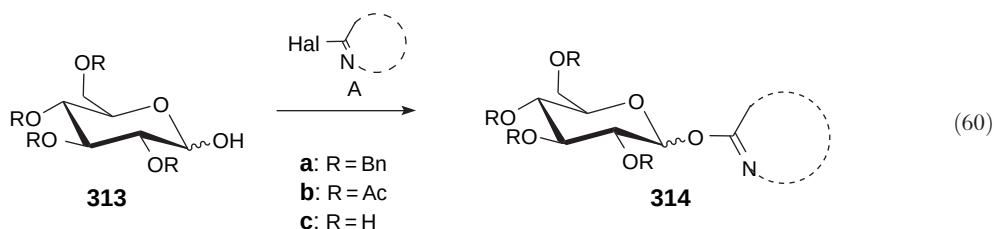
Two new, single-step processes were provided by Chen *et al.* for the preparation of 2,4,6-tris(perfluoroalkyl) **309a** and **309b** and -(perfluoroalkylether) 1,3,5-triazines **309c** and **309d**. One method involves the nucleophilic substitution of cyanuric fluoride with (perfluoroalkyl) **308a** and **308b** and (perfluoroalkylether) trimethylsilanes **308c** and **308d** in the presence of cesium fluoride (Equation 58) <1998JFC217>.



Hara *et al.* found that, in the presence of cyanuric fluoride, alkenylboronic acids **310** reacted with α,β -unsaturated ketones **311** through 1,4-addition to give γ,δ -unsaturated ketones **312**, selectively. The reaction proceeded under mild conditions, and a variety of functional groups could be introduced into the products (Equation 59) <1996SL993>.

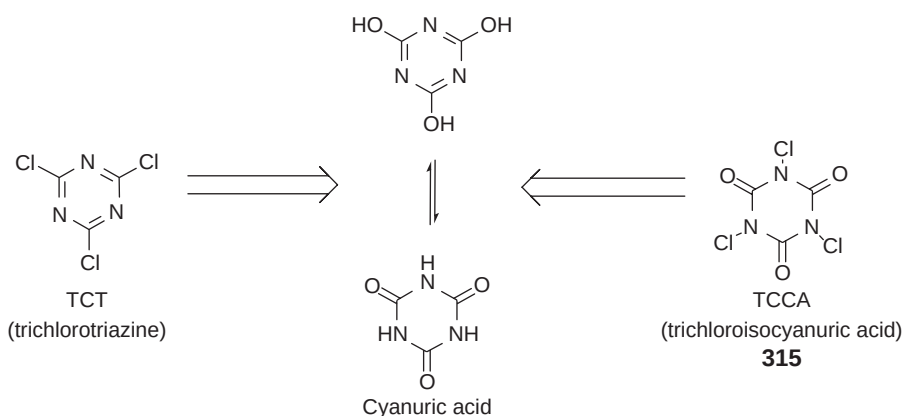


Direct anomeric O-arylation and hetarylation of 2,3,4,6-tetra-*O*-benzyl-D-glucose **313a**, 2,3,4,6-tetra-*O*-acetyl-D-glucose **313b**, and even of glucose **313c** itself, with electron-deficient aromatic and heteroaromatic compounds, has been shown recently to be quite efficient, leading directly to aryl and hetaryl glucopyranosides **314** (Equation 60) <1998EJO1353>.



9.03.12.5 1,3,5-Trichloro-1,3,5-triazinane-2,4,6-trione as a Reagent in Organic Synthesis

Over the past years, there has been some confusion about the correct structure of some derivatives of 1,3,5-triazine: in particular, the structure of 1,3,5-trichloro-2,4,6-triazinetriene or trichloroisocyanuric acid, TCCA **315**. TCCA has been confused with CC, that is, the acid chloride of cyanuric acid (Scheme 70).



Scheme 70

As seen from the structure, TCCA belongs to the large group of *N*-chloroimides and amides that are used as bleaching agents, disinfectants, and bactericides owing to their function as chlorinating agents and oxidants. Their properties are similar to those of *N*-chloroamines, which however are more unstable. A few of them are commonly

TCCA **315** was reported first in 1902 by Chattaway and Wadmore and is prepared by chlorination of CYA **1** with chlorine gas (Equation 61). It is readily soluble in organic solvents <1902JCS191>.



Chemical reaction scheme (62) showing the conversion of a 1,2,4-triazole derivative (316) to a 1,2,4-triazole derivative (317) using N,N'-dichloro-1,3,5-triazine-2,4,6-tricarboximide.

Structure 316: A 1,2,4-triazole ring with substituents R^1 and R^2 .

Structure 317: A 1,2,4-triazole ring with substituent R^2 .

Reaction conditions: CH_2Cl_2 , rt or solid phase, rt.

Reaction (62):

$$\text{316} \xrightarrow[\text{solid phase, rt}]{\text{CH}_2\text{Cl}_2, \text{rt}} \text{317}$$
$$R^1 = H, Na; R^2 = \text{alkyl, aryl}$$

318 $\xrightarrow[\text{wet SiO}_2, \text{NaNO}_2]{\text{TCCA}}$ 319

X = F (98%)
 X = CH₃ (85%)

(63)

$$\begin{array}{c}
 \text{R}^1 \text{---} \text{X} \\
 \diagup \quad \diagdown \\
 \text{C} \\
 \diagdown \quad \diagup \\
 \text{R}^2 \text{---} \text{X}
 \end{array}
 + \text{HS---} \left(\text{---} \right)_n \xrightarrow[\text{CHCl}_3, \text{rt}]{\text{1(cat.), } n=1, 2} \begin{array}{c} \text{R}^1 \text{---} \text{S---} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{R}^2 \text{---} \text{S---} \left(\text{---} \right)_n \end{array}$$

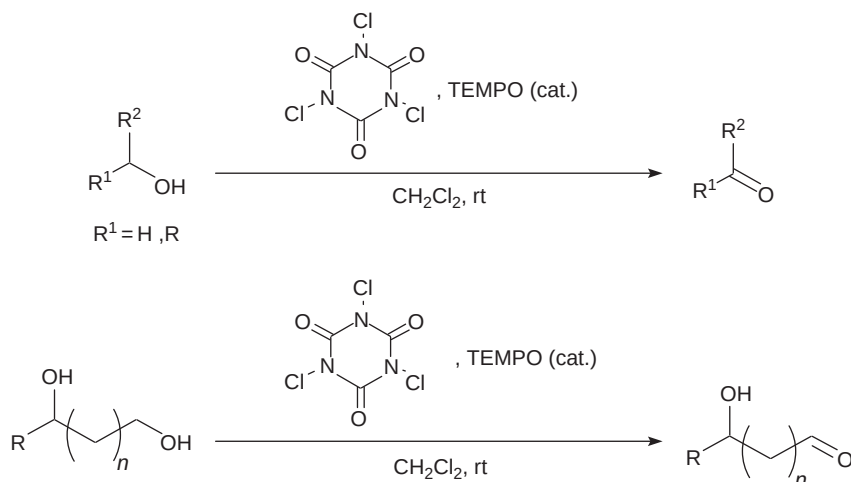
(64)

$\text{R}^1 = \text{aryl, alkyl, cinnamyl, ferrocenyl}; \text{R}^2 = \text{H, alkyl}; \text{X} = \text{-OMe, -OEt, XX = O, -O(CH}_2\text{)}_3\text{O-, -O(CH}_2\text{)}_2\text{S-, -(OCH}_2\text{)}_2\text{C(CH}_2\text{O)}_2\text{-}$

315

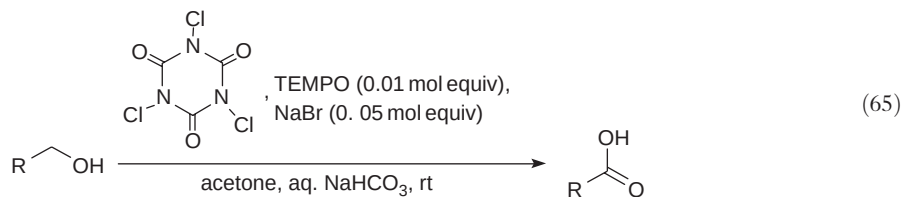
Primary alcohols are oxidized to acids using stoichiometric TCCA and catalytic RuCl_3 in the presence of $n\text{-Bu}_4\text{NBr}$ and K_2CO_3 in $\text{MeCN}/\text{H}_2\text{O}$. Secondary alcohols are oxidized to ketones in the same manner using $\text{MeCN}/\text{H}_2\text{O}$ or $\text{EtOAc}/\text{H}_2\text{O}$. The effects of pH, solvent, and base were also studied <2004OPD931>.

Efficient oxidation of primary alcohols and α -amino alcohols to the corresponding aldehydes and β -amino aldehydes can be carried out at room temperature in methylene chloride, using TCCA in the presence of catalytic 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO): aliphatic, benzylic, allylic, and α -amino alcohols are rapidly oxidized without overoxidation to carboxylic acids (Scheme 71). Secondary carbinols are slowly oxidized such that the reaction is highly chemoselective <2001OL3041>.

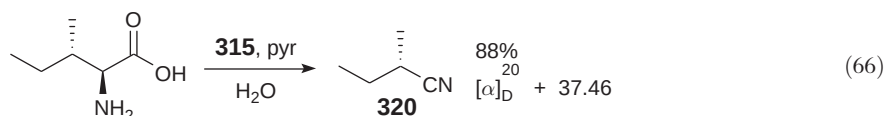


Scheme 71

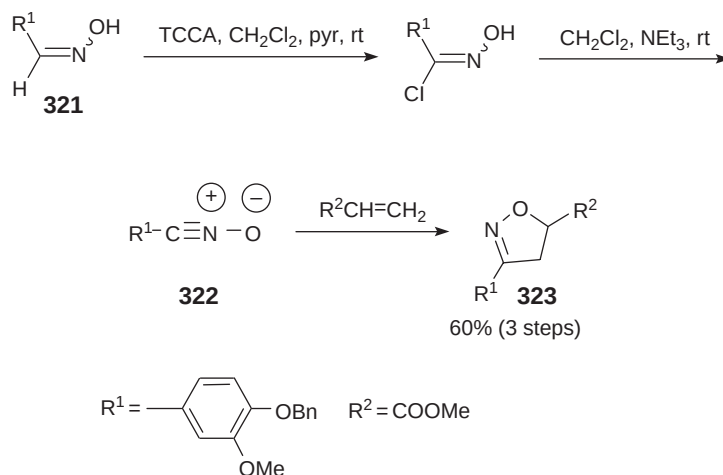
Recently, Giacomelli and co-workers have reported an efficient oxidation of primary alcohols to carboxylic acids through a TEMPO-catalyzed procedure. The procedure is based on the addition of 2 molar equiv of TCCA to an acetone solution of the alcohol followed by catalytic amounts (0.1 equiv) of TEMPO, NaBr, and then 1 equiv of aq. NaHCO_3 (Equation 65). This system operates at room temperature, the oxidation of the primary alcoholic group being practically quantitative. Secondary alcohols are oxidized to ketones. The mild conditions of this procedure and the total absence of any transition metal make this reaction suitable for safe laboratory use <2003JOC4999>.



Amino acids are cleanly and efficiently converted into nitriles by means of a decarboxylation reaction carried out with TCCA in water or methanol in the presence of pyridine. Using TCCA, (*S*)-(+)-2-methylbutyronitrile **320** is obtained with the highest optical purity (Equation 66) <2004SC3449>.

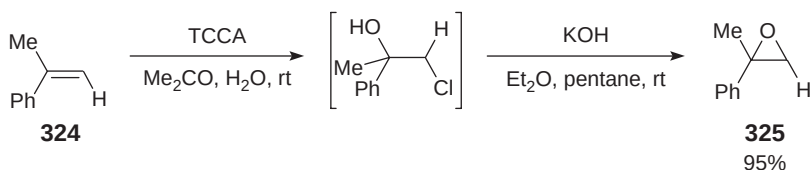


Aldoximes derived from an *o*-protected vanillin **321**, when treated with TCCA in the presence of olefins as dipolarophiles, afford nitrile oxides **322**. Subsequent 1,3-dipolar cycloaddition generates the corresponding isoxazolines **323** (Scheme 72) <2001SC3075>.



Scheme 72

The epoxide **325** can be produced under mild conditions by reaction of alkene **324** with TCCA in aqueous acetone followed by treatment of the resulting chlorohydrin with aqueous KOH in Et₂O/pentane (Scheme 73) <2002JBS700>.

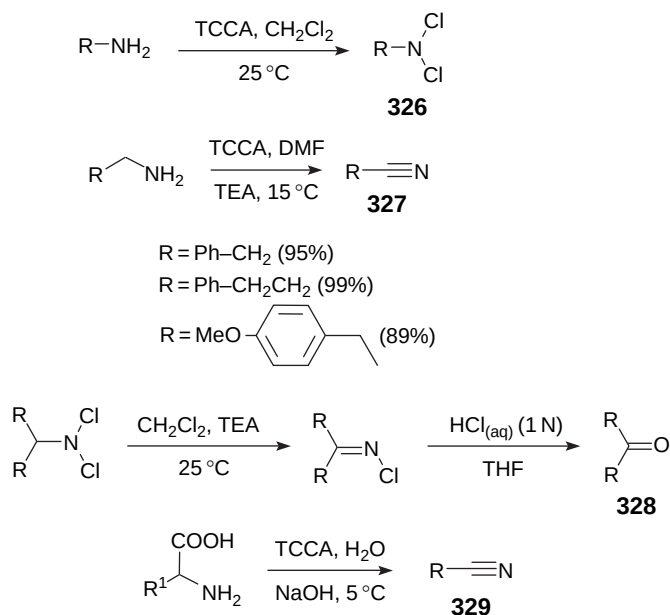


Scheme 73

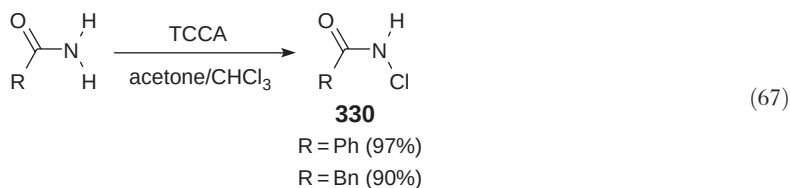
Kaushik and co-workers have made use of TCCA as an effective reagent for the rapid conversion of dialkyl phosphites to their corresponding dialkyl chlorophosphates under mild conditions. The authors have confirmed that TCCA detoxifies completely sulfur mustard, a potential chemical warfare agent <2005TL5293>.

De Luca and Giacomelli studied the possibility of using TCCA instead of *N*-chlorosuccinimide (NCS) in chlorination reactions of amines, owing to its lower cost and higher stability. The reaction between amines or α -aminoacids with TCCA was studied under various conditions: *N,N*-dichloroamines **326**, nitriles **327**, and ketones **328** could be obtained from appropriately substituted primary amines, while free amino acids underwent oxidative decarboxylation to the corresponding nitriles **329** with one less carbon atom (Scheme 74) <2004SL2180>.

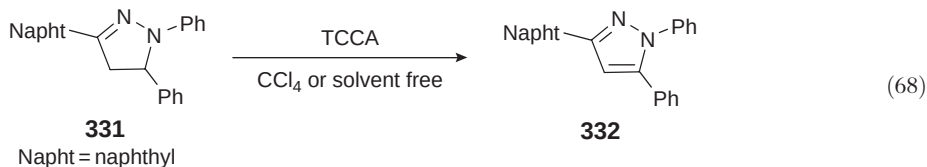
Amides, lactams, and carbamates of α -amino acids can be transformed easily into the corresponding *N*-chlorinated compounds **330** through reaction with TCCA, under mild reaction conditions (Equation 67) <2005SL223>.



Scheme 74

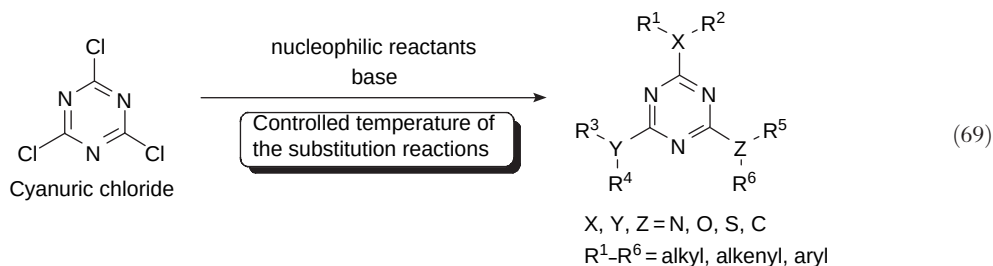


TCCA was used also as an effective oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazoline **331** to the corresponding pyrazole **332** under both heterogeneous and solvent-free conditions (Equation 68). The 1,3,5-trisubstituted pyrazole was obtained by simple filtration and evaporation of the solvent <2004TL2181>.

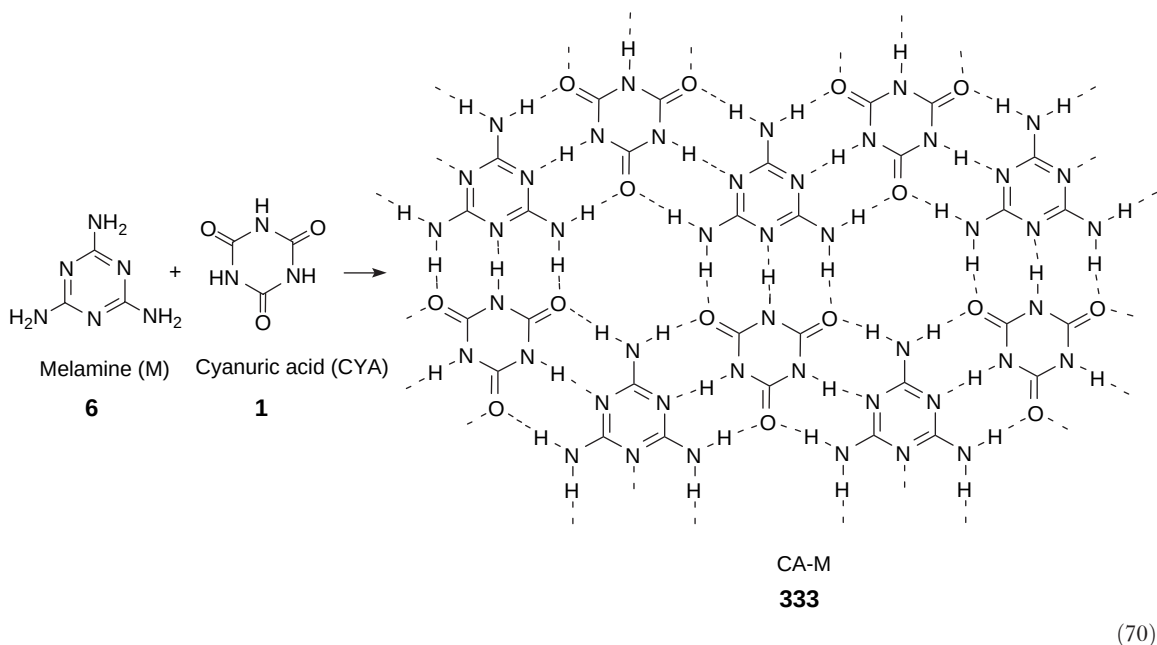


9.03.12.6 1,3,5-Triazines in Supramolecular Chemistry

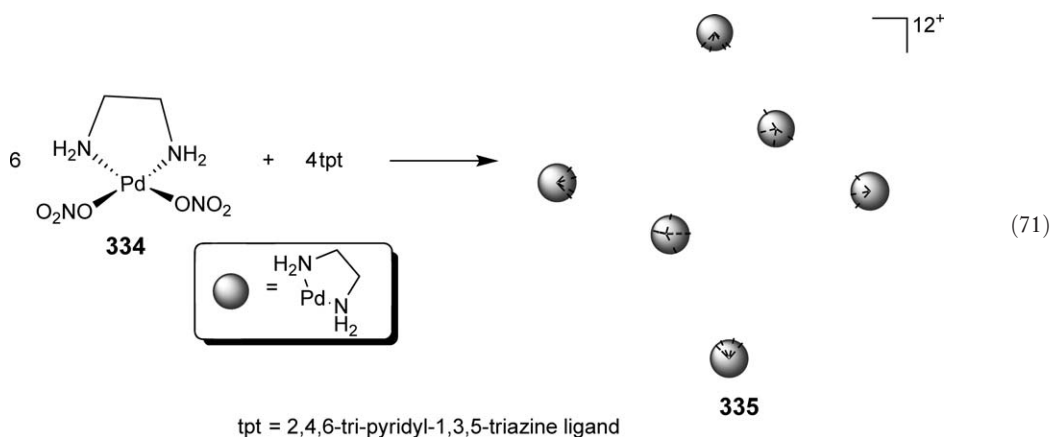
Supramolecular chemistry is one of the topical fields of contemporary chemistry and was defined first in 1978 by Jean-Marie Lehn as the “chemistry of molecular assemblies and of the intermolecular bond” <B-1995MI1>. Supramolecular chemistry is a vast interdisciplinary field of research and technology, where noncovalent bonding may be a common ground. Crystal structure prediction has progressed tremendously, and the challenge for the contemporary supramolecular chemist is now to produce custom-made functional (and multifunctional) materials involving intermolecular interactions <2001CRV1629>. Since the early 1990s, 1,3,5-triazine derivatives have shown their potential as building blocks for the preparation of such materials (Equation 69) <1996CC1313, 1992JA5473>.



Recently, in a very interesting review, Gametz and Reedijk described a selection of outstanding examples of supramolecular networks involving the 1,3,5-triazine unit [<2006EJI29>](#). In particular, they have illustrated the ability of melamine derivatives [333](#) to generate H-bond networks, as applied elegantly by several research groups to produce host–guest or porous materials ([Equation 70](#)).



The straightforward synthetic routes to generate sophisticated star-shaped polydentate N-ligands [334](#) have allowed the preparation of molecular cages [335](#) with applications in catalysis or separation, coordination polymers with magnetic properties or host–guest cavities, and anion-hosting materials ([Equation 71](#)).



The judicious combinations of H-bonding and coordinative interactions through the use of well-designed 1,3,5-triazine building blocks such as **336** have generated functional materials with applications in mass spectrometric labeling and in sensing (**Figure 29**).

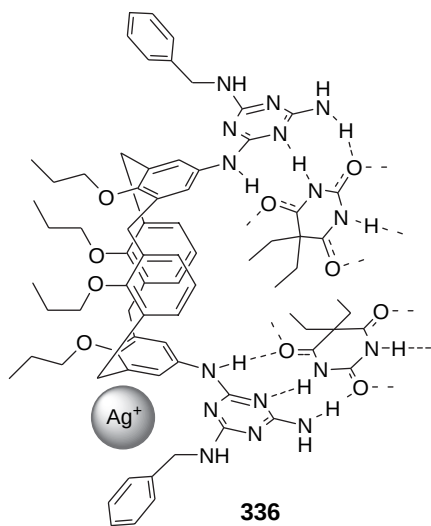


Figure 29

The controlled preparation of hybrid inorganic–organic materials has improved remarkably since the late 1990s, and the important challenge of the contemporary supramolecular chemist is now to control the functionalization of such solids. This includes the capacity to design intricate ligands which will act both as structural and functional building blocks for the preparation of custom-made materials possessing one or more specific properties, which can certainly be envisaged starting from the inexpensive, readily available 2,4,6-trichloro-1,3,5-triazine.

9.03.12.7 Agricultural Chemicals

Triazine herbicides are the most commonly used herbicides to control weeds during the production of corn, sorghum, and sugarcane in the US. These herbicides all have a similar structure and the most common triazine herbicides are shown in **Figure 30**.

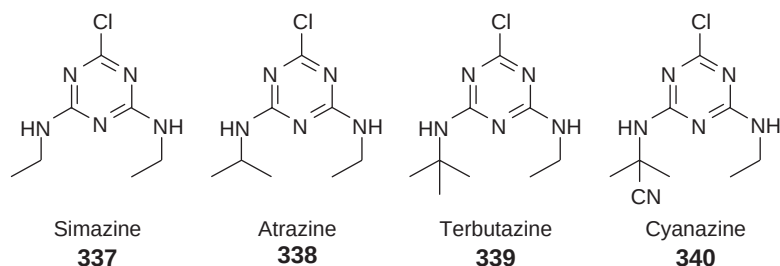
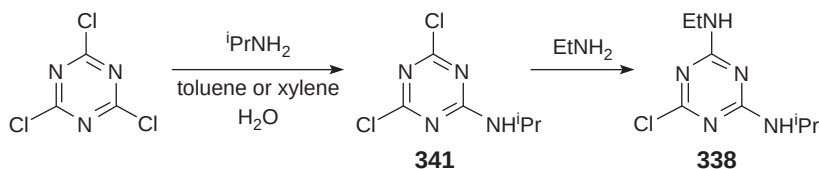


Figure 30

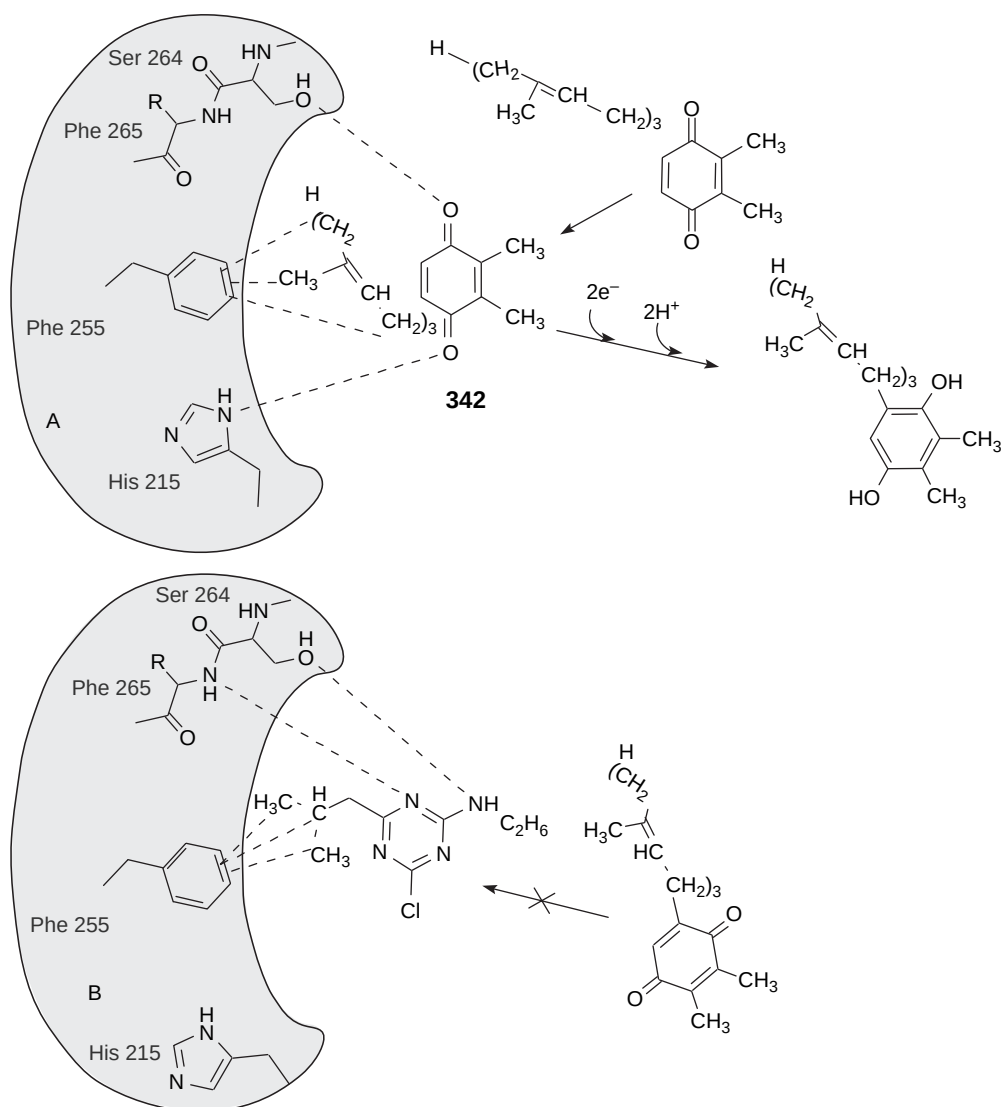
Atrazine **338** is synthesized by the reaction of CC and isopropylamine in xylene or toluene, in the presence of water. This reaction leads to an intermediate **341** that is converted further under the same reaction conditions with ethylamine. In the final step of the reaction, sodium hydroxide is added and separation of the product **338** is performed (**Scheme 75**) <2003OPD1071>.

The activity of atrazine within the plant is not fully understood; however, the general idea postulated in the late 1960s seems to be prevalent. It is thought that the atrazine molecules enter into the chlorophyll of the plant, disrupting photosynthesis in broadleaf weeds <1997JMB883>. Without an ability to perform photosynthesis, the weeds die, and crop production increases.



Scheme 75

Although atrazine herbicides and some of the metabolites are potent poisons of the photosynthetic machinery of many plants, the target crops (corn, sorghum, and sugarcane) are resistant to the herbicide and its metabolites, but the weeds problematic to these crops are destroyed. This selectivity is not found in other currently available herbicides. The molecular basis for plant death results from the triazine herbicide being able to effectively mimic an essential small molecule, plastoquinone, and displace it from its binding site in the photosynthetic apparatus. Plastoquinone **342** is a critical component in the electron-transport process involved in photosynthesis. Scheme 76 below shows plastoquinone **342** in its binding site ready to accept electrons (A) and the binding site blocked with atrazine preventing binding of plastoquinone (B) (Scheme 76) <1991WSC458>.



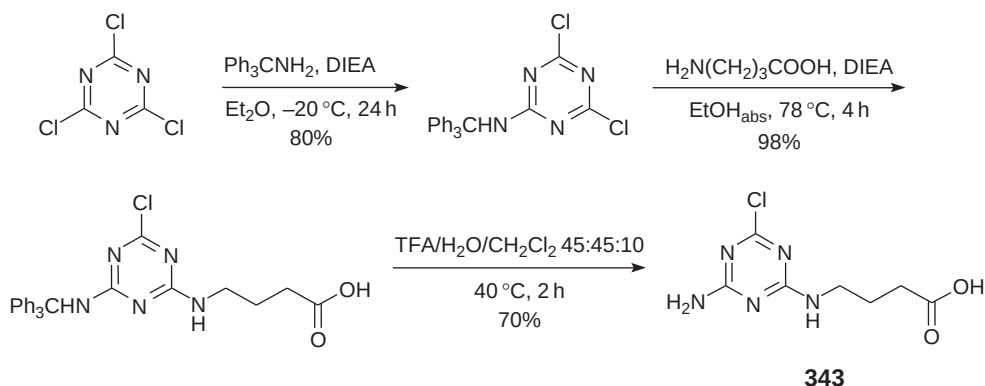
Scheme 76

Unfortunately, these herbicides are detected commonly in ground- and drinking water, and, accordingly, these molecules have been banned in Europe because their use has been linked to cancer and endocrine gland disruption in humans.

Chen and co-workers have reported a novel, simple, economical, and environmentally friendly, tunable immunosorbent-based immunoassay for sensitive and selective determination of atrazine <2003ABI251>. Hammock and co-workers have developed an antibody for simazine and atrazine that exhibits low cross-reactivity to propazine relative to most atrazine antibodies evaluated heretofore <1996JFA2210>.

The analysis of highly polar molecules in water samples at the trace level is often limited by the efficiency of the extraction procedures. Due to their high solubility in water, these molecules are frequently not sufficiently retained in the stationary phases of the chromatographic or solid-phase extraction supports. Immunochemical techniques present an advantage to allow direct measurements in aqueous media. Therefore, it is necessary to develop screening methods to efficiently monitor contamination by these triazine degradation products.

The development of an indirect, competitive enzyme-linked immunosorbent assay (ELISA) for dealkylated hydroxytriazines was reported by Marco and co-workers. The assay uses polyclonal antibodies raised against *N*-(4-amino-6-hydroxy-[1,3,5]triazin-2-yl)-4-aminobutanoic acid **343** (hapten) conjugated to keyhole limpet hemocyanin by the active ester method (Scheme 77). The immunizing hapten was synthesized by first introducing the amino group to the triazine ring in a protected form in order to increase its solubility in organic media. The resulting assay uses a homologous competitor hapten coupled to conalbumin by the mixed anhydride method. Under the optimized conditions, this ELISA is specific for dealkylated hydroxytriazines, reaching suitable limits of detection <2003JFA156>.

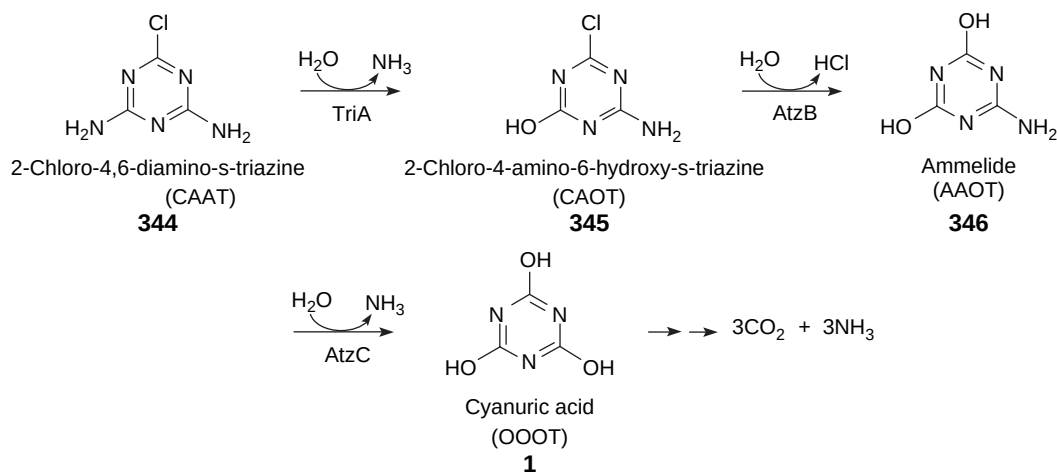


Scheme 77

In a study by Wackett, melamine deaminase (TriA), which is 98% identical to Atrazine chlorohydrolase (AtzA), catalyzed deamination of CAAT **344** to produce 2-chloro-4-amino-6-hydroxy-*s*-triazine **345** (CAOT). CAOT underwent dechlorination via hydroxyatrazine ethylaminohydrolase (AtzB) to yield ammelide **346**. This represents a newly discovered dechlorination reaction for AtzB. Ammelide was hydrolyzed subsequently by *N*-isopropylammelide isopropylaminohydrolase to produce CYA **1**, a compound metabolized by a variety of soil bacteria (Scheme 78) <2002AEM4672>.

9.03.12.8 Pharmaceuticals

Plasma (PM) lipoprotein profiles play an important role in the development of atherosclerosis, a major cause for cardiovascular mortality. In 1996, Xia *et al.* disclosed, by random screening and structure–activity relationship (SAR) development, a new class of cholesteryl ester transfer protein (CETP) inhibitors, namely, the 2,4,6-trisubstituted 1,3,5-triazine derivatives represented by structure **347** (Figure 31). In a subsequent SAR development, they have replaced the hydrazone group in **347** with a variety of isosteric substituents. These compounds exhibit low PM inhibition of CETP *in vitro* and may have potential use in treating cardiovascular diseases caused by low high-density lipoprotein (HDL) levels <1996BML919>.



Scheme 78

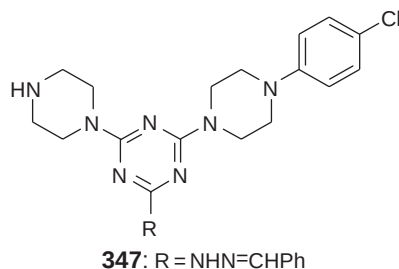


Figure 31

The resistance of tumor cells to cytotoxic drugs is a major problem in cancer chemotherapy. By systematic screening, it was found that almitrine **348**, a triazinylpiperazine currently used for respiratory insufficiency, moderately sensitized the highly resistant cell line DC-3F/AD to actinomycin D. This starting point led to the synthesis of a series of analogs in order to select more potent modulator agents and provided S9788 **349**, which is currently in Phase I clinical trials (Figure 32) <1996JME4099>.

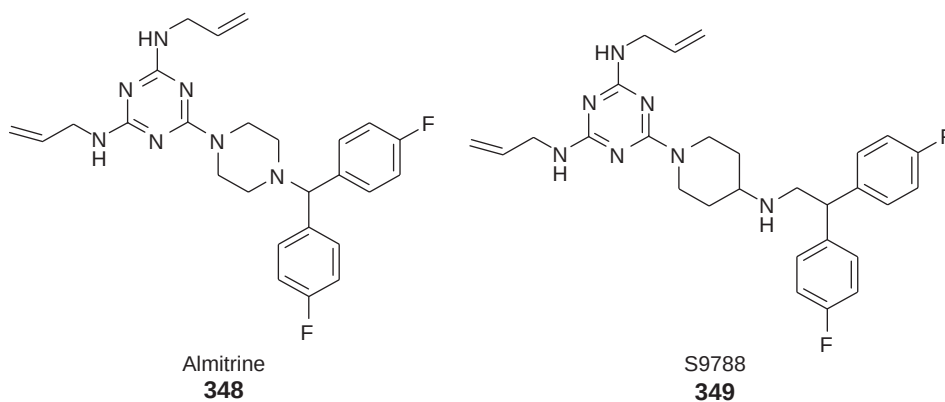
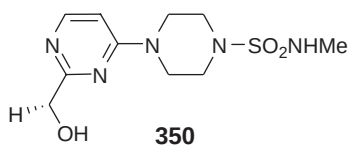
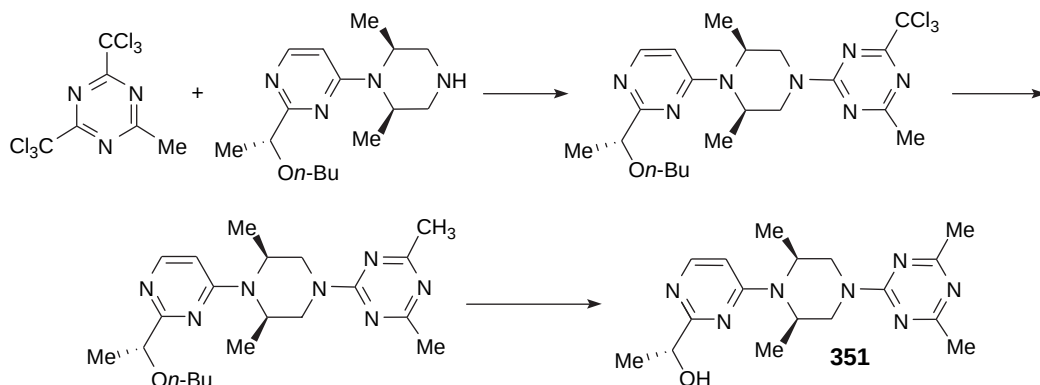


Figure 32

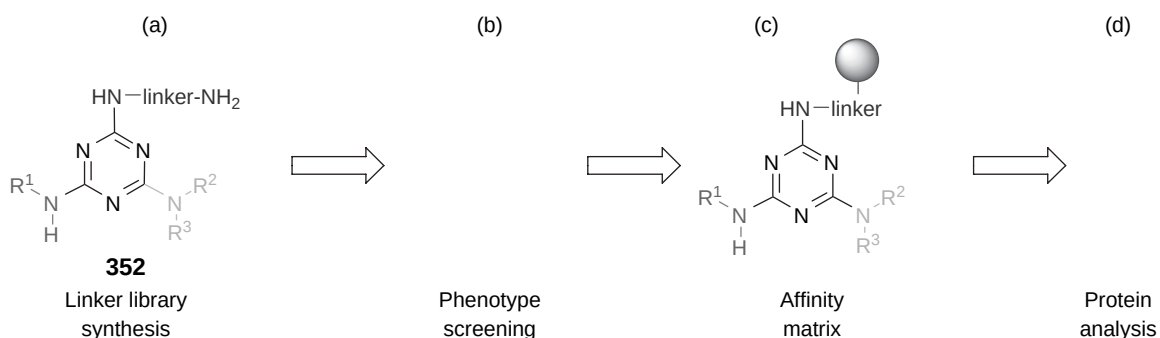
Sorbitol dehydrogenase inhibitor (SDI) **350** was evaluated in normal and diabetic rats for its effects on nerve conduction velocity (NCV) (Figure 33). A surrogate for the pyrimidine side chain with the potential to lower pK_a , which had not been fully exploited, was an *s*-triazine.

**Figure 33**

Recently, Mylari *et al.* have prepared, according to [Scheme 79](#), a novel sorbitol dehydrogenase inhibitor **351** that shows very high oral potency ($50 \mu\text{g kg}^{-1}$) in normalizing elevated fructose levels in the sciatic nerve of chronically diabetic rats and sustained duration of action ($>24 \text{ h}$) [\[2002JME4398\]](#).

**Scheme 79**

Chemical genetics is an emerging field that offers powerful tools to search for novel drug candidates and their targets. The design of a tagged library was based on a triazine scaffold **352** due to its ease of manipulation and structural similarity to purine and pyrimidine, which have already been demonstrated to be active in various biological systems ([Scheme 80](#)). In addition, the triazine scaffold has threefold symmetry, and the positional modification is much more flexible than that in the purines or pyrimidines.

**Scheme 80**

The current study elucidated the first novel small-molecule inhibitors for several ribosomal accessory proteins or their complex as the target, which are important for the early brain/eye development before gastrulation. Among the 1536 triazines tested, one library compound **353** was found to generate significant phenotype changes on zebrafish brain and eyes at $50 \mu\text{M}$ ([Figure 34\(b\)](#)).

To identify target proteins, Chang and co-workers have immobilized **353** on activated agarose beads (Affi gel 10) to afford **359** (1-Affi) ([Figure 35](#)). After loading of **353**, the remaining active sites of the agarose bead were blocked by ethanolamine [\[2003JA11804\]](#).

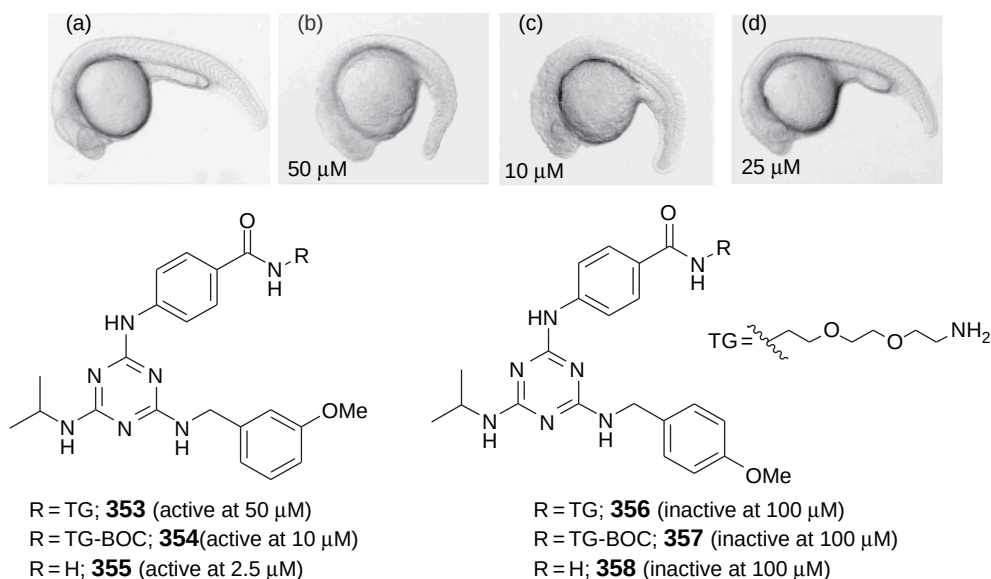


Figure 34

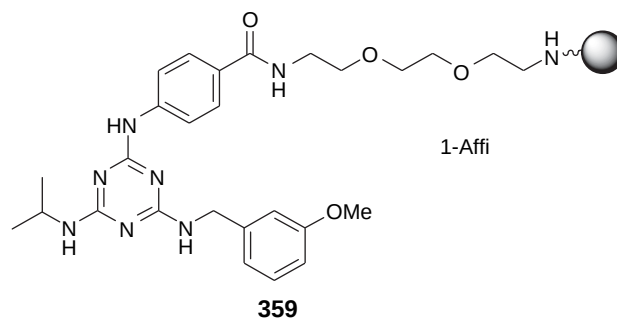


Figure 35

Random screening provided no suitable lead structures in a search for novel inhibitors of the bacterial enzyme DNA gyrase. Therefore, an alternative approach had to be developed by Boehringer and co-workers [\[2000JME2664\]](#). Relying on the detailed 3-D structural information of the targeted ATP binding site, their approach combines as key techniques (1) an *in silico* screening for potential low molecular weight inhibitors, (2) a biased high-throughput DNA gyrase screen, (3) validation of the screening hits by biophysical methods, and (4) a 3-D guided optimization process.

A fundamental process in biology is the proliferation of cells mediated by the cell cycle. On the basis of previous studies, Kuo *et al.* identified the pyrazino-pyridine compound **360** as a potent vascular endothelial growth factor inhibitor and the pyrimidino-pyridine species **361** as a moderately potent cyclin-dependent kinase (CDK) inhibitor (Figure 36). A proposed combination of CGP-60474 and compound **361** led to the discovery of the [1,3,5]triazino-pyridines **362** as a new series of potent CDK inhibitors [\[2005JME4535\]](#).

Palladium-catalyzed C-C bond-formation reactions, particularly the Negishi coupling reaction, were used to assemble various triazine-heteroaryl analogs, effectively. Among them, compound **363**, prepared by two different methods, displayed high inhibitory potency at CDK1 (IC₅₀ 0.021 μM), CDK2, and CDK5 and submicromolar potency at CDK4, CDK6, and CDK7 (Figure 37).

CC has been used as a scaffold for the synthesis of potential agents for BNCT, viz. **364** and **365**, containing a carborane cluster, a sugar moiety as hydrophilic arm, and an amino acid for the conjugation with bioactive molecules (Figure 38). Such compounds open the possibility for the generation of remarkable diversity employing a combinatorial approach. It is in fact possible to introduce various oligosaccharidic structures as well as to use this class of derivatives for the synthesis of biologically relevant peptides [\[2004SL1007\]](#).

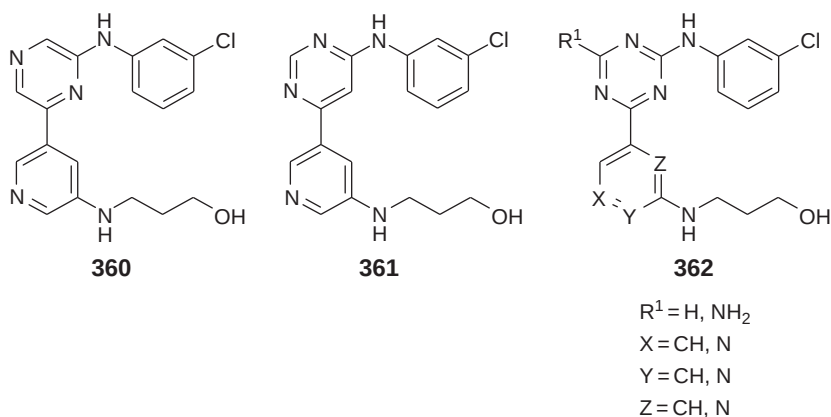


Figure 36

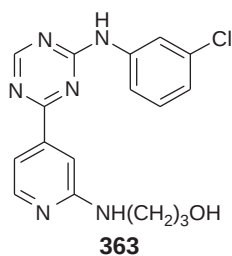


Figure 37

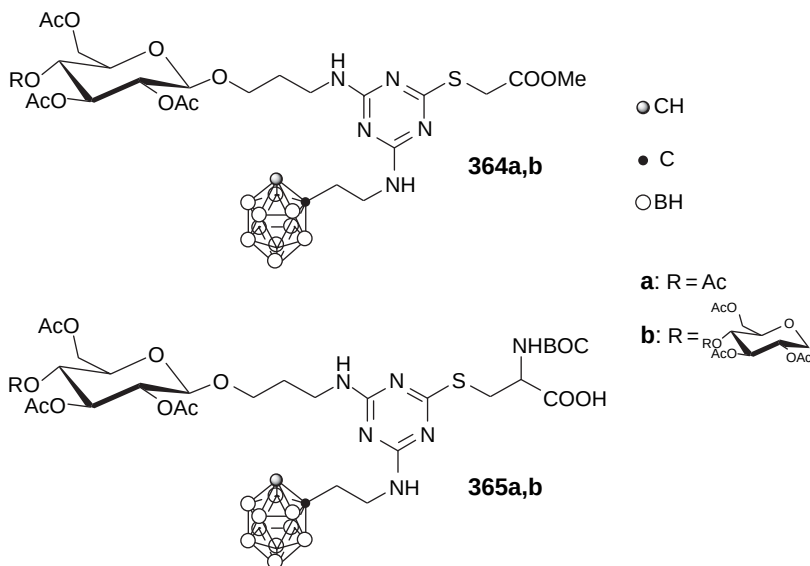
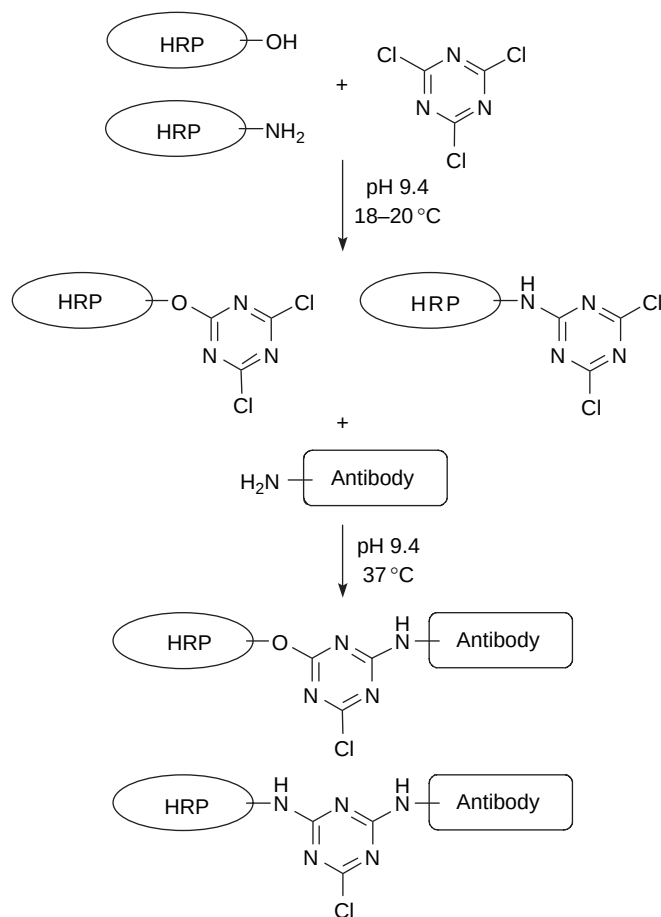


Figure 38

Inosine monophosphate dehydrogenase (IMPDH) is an enzyme in the *de novo* synthetic pathway of guanosine nucleotides. Pitts *et al.* have identified several series of novel triazine inhibitors of the enzyme IMPDH II. These compounds demonstrate that the urea or diamide isosteres can be replaced effectively by heterocycles <2002BML2137>.

Horseradish peroxidase (HRP) is a plant glycohemoprotein found in relatively large amounts in the roots of horseradish. HRP is a popular enzyme for commercial, as well as in-house labeling of antibodies and antigens for the development of ELISA and immunohistochemical staining methods. Very recently, Abuknesha *et al.* have described an efficient and mild method for the labeling of IgG with HRP using CC (2,4,6-trichloro-1,3,5-triazine) as a bridging molecule (**Scheme 81**) <2005JIM211>.



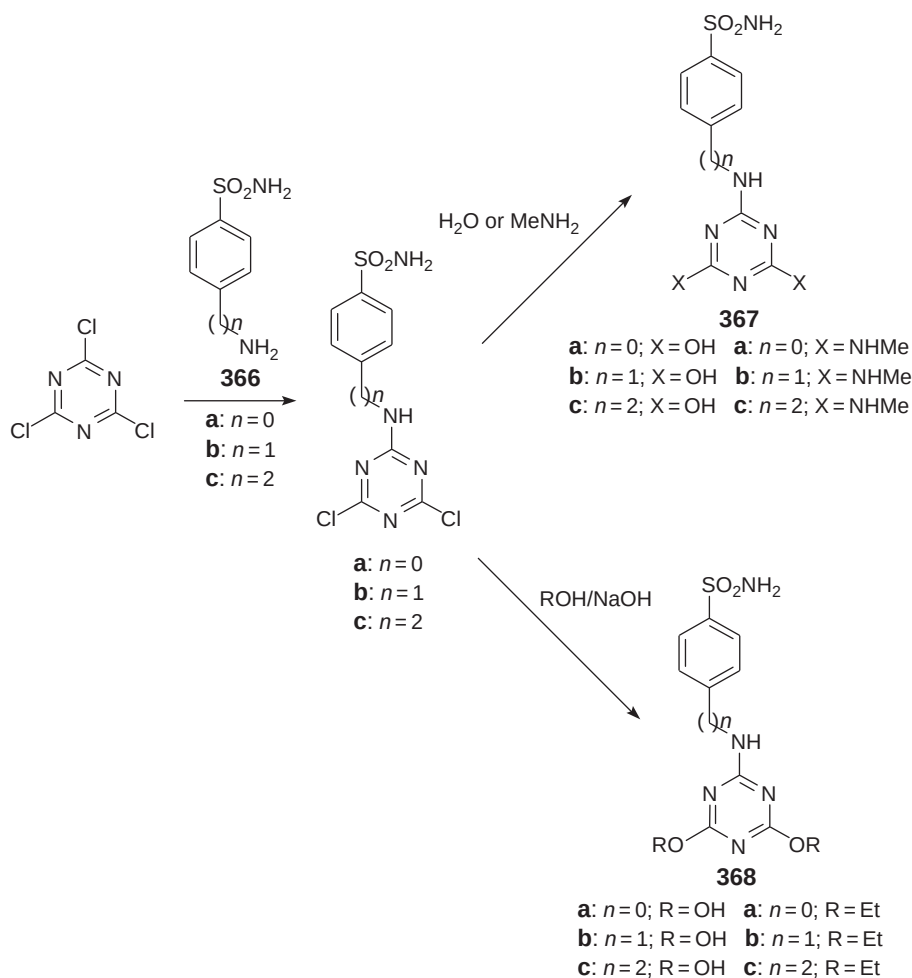
Scheme 81

Triazinyl-containing sulfonamides **367** and **368**, obtained from cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and amino-benzenesulfonamides **366**, followed by treatment with water, MeNH₂, or ROH, act as highly effective inhibitors of the zinc-containing enzyme, carbonic anhydrase (CA, EC 4.2.1.1) (**Scheme 82**) <2005BML3102>.

1,3,5-Triazine derivatives containing various amino groups at position 2, 4, or 6, such as tretamine, furazil, and dioxadet, have been known as anticancer drugs. Structural modifications consisting of the replacement of an ethyleneimino moiety with either dialkylamino, alkoxy, alkylaryl, or hydroxy groups led to discovery of novel chemotherapeutic agents.

The *in vitro* antitumor activity of the 2-[4-amino-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]-2[[4-(dimethylamino)phenyl]imino]acetonitrile **369** has been tested (**Figure 39**). It shows remarkable activity against melanoma MALME-3 M cell line (GI₅₀ = 3.3 × 10⁻⁸ M, TGI = 1.1 × 10⁻⁶ M) and is a leading candidate for further development <2006EJM219>.

The P2 transporter is a nucleoside transporter, which is unique to the protozoan parasite *Trypanosoma brucei*, the causative organism of human African trypanosomiasis. The transporter has been shown to bind some structural motifs not recognized by other transporters.



Scheme 82

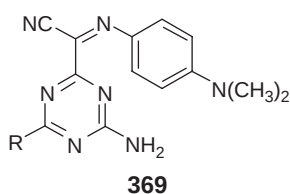
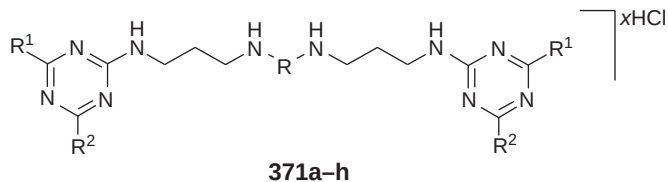
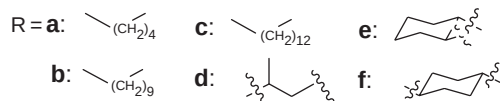
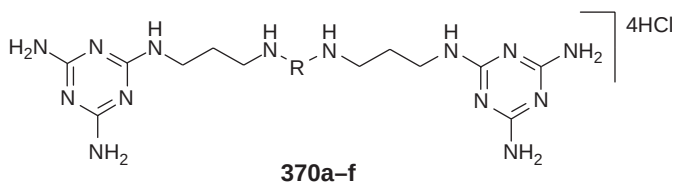


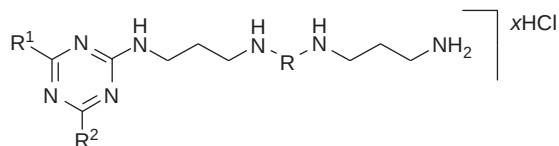
Figure 39

Gilbert and co-workers have reported the design and synthesis of triazine-substituted polyamines as drugs against *T. brucei* spp., the causative agent for African sleeping sickness. Four different types of test compounds **370a–f**, **371a–h**, **372a–e**, and **373a–f** were prepared using a five-step synthesis consisting of Michael addition, BOC-protection, hydrogenation, arylation, and BOC-deprotection (Figure 40) <2001JME3444>.

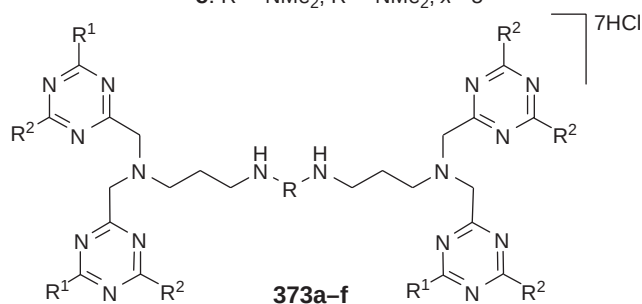
SAR studies of 1,3,5-triazine-2,4,6-triones as human gonadotropin-releasing hormone receptor antagonists resulted in potent compounds. Guo *et al.* have prepared a series of novel 1,3,5-triazine-2,4,6-triones **374** as potent antagonists of the hGnRH receptor (Figure 41). A SAR study at the left-hand side demonstrated that branched primary amines, such as the substituted 2-aminoethyl or 3-aminopropyl groups, were a key feature for high binding affinity. A SAR study around the bottom of the 1,3,5-triazine-2,4,6-trione core in **374** led to the discovery of analogs with better binding affinities than the 2,6-difluorobenzyl compounds <2005BML3685>.



- a:** $R^1 = NH_2; R^2 = NHMe; x = 4$ **e:** $R^1 = NH_2; R^2 = NHMe; x = 5$
b: $R^1 = NH_2; R^2 = NMe_2; x = 5$ **f:** $R^1 = NH_2; R^2 = NMe_2; x = 5$
c: $R^1 = NHMe; R^2 = NHMe; x = 4$ **g:** $R^1 = NHMe; R^2 = NHMe; x = 5$
d: $R^1 = NMe_2; R^2 = NMe_2; x = 5$ **h:** $R^1 = NMe_2; R^2 = NMe_2; x = 5$



- R = (CH2)9** **a:** $R^1 = NHMe; R^2 = NHMe; x = 5$
R = (CH2)12 **b:** $R^1 = NH_2; R^2 = NMe_2; x = 4$
c: $R^1 = NH_2; R^2 = NMe_2; x = 4$
d: $R^1 = NHMe; R^2 = NHMe; x = 5$
e: $R^1 = NMe_2; R^2 = NMe_2; x = 5$



- R = (CH2)9** **a:** $R^1 = NH_2; R^2 = NH_2$
b: $R^1 = NH_2; R^2 = NMe_2$
c: $R^1 = NHMe; R^2 = NHMe$
R = (CH2)12 **d:** $R^1 = NH_2; R^2 = NMe_2$
e: $R^1 = NH_2; R^2 = NMe_2$
f: $R^1 = NHMe; R^2 = NHMe$

Figure 40

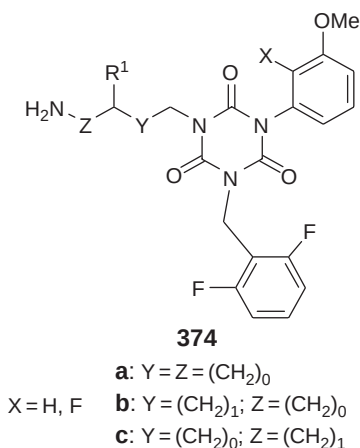


Figure 41

9.03.12.9 Miscellaneous Applications

Among a wide variety of structurally modified nucleic acids synthesized over the past decade, peptide nucleic acids (PNAs) such as **375a–l** have come to the fore because they recognize the complementary nucleic acids through Watson–Crick base pairing and exhibit strand invasion (Figure 42). Employing nonnatural nucleobase ligands in place of natural nucleobases would help in understanding the recognition process in terms of various factors contributing to the complementation events, such as hydrogen bonding and inter-nucleobase stacking.

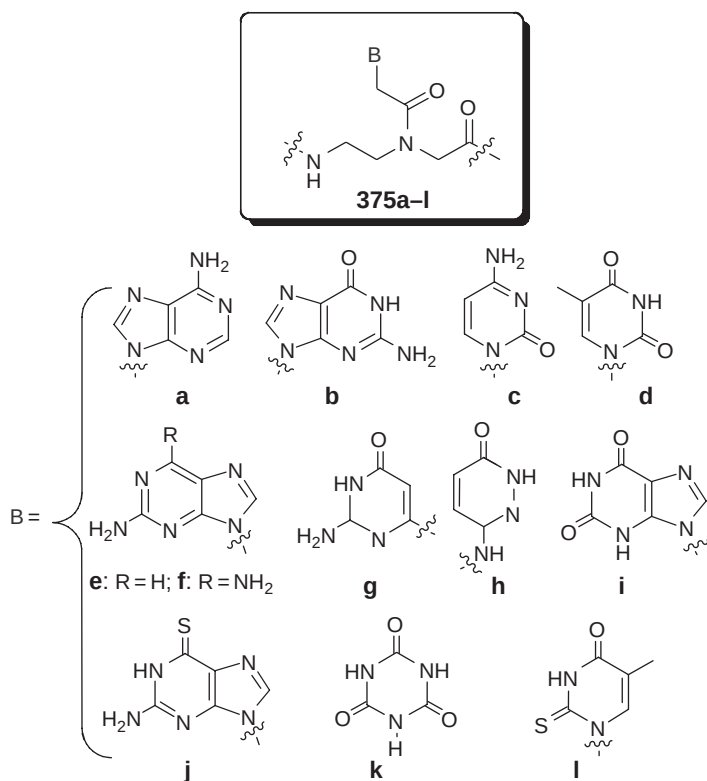


Figure 42

Ganesh and co-workers have presented a method for the synthesis of cyanuryl-PNA monomer **376** that is useful in the preparation of new PNA analogs. Moreover, the crystal structure of **376** shows molecular tapes arising from continuous intermolecular dimeric hydrogen bonding, with successive tapes held by single hydrogen bonds in the backbone (Figure 43) <2000OL2825>.

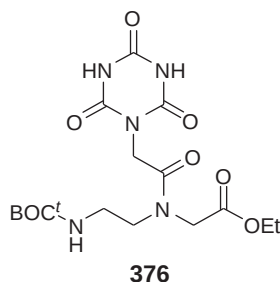


Figure 43

The double quantum filtering correlation spectroscopy (DQF-COSY) assignment, and observance of diagnostic cross-peaks between R-CH₂ of the 2-aminoethyl and the CH₂ adjacent to the cyanuryl residue, in the nuclear Overhauser enhancement spectroscopy (NOESY) ¹H NMR of **376** indicated the major rotamer to be the *trans*-isomer, identical to that of the crystal structure (Figure 44).

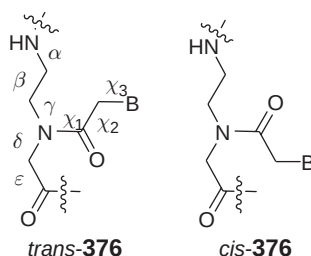


Figure 44

Currently, RDX is among the most widely used explosives. Many military installations have soils, sediments, surface water, and groundwater contaminated with RDX. To aid in the evaluation of the potential toxicity of *N*-nitroso derivatives of RDX, Pan *et al.* have described a pressurized liquid extraction (PLE) followed by liquid chromatography–electrospray ionization–mass spectrometry (LC–ESI–MS) method for determination of RDX and its *N*-nitroso derivatives: hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine (MNX), hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine (DNX), and hexahydro-1,3,5-trinitroso-1,3,5-triazine (TNX) in soils (Figure 45) <2006JCH1107>.

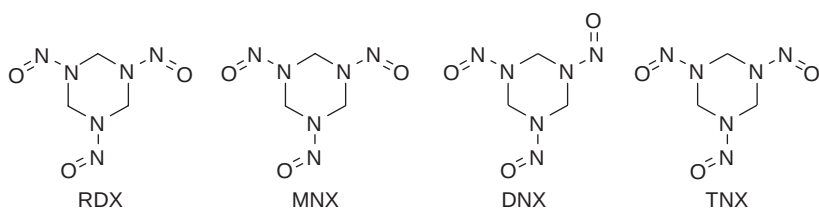


Figure 45

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Biographical Sketch



Professor Giampaolo Giacomelli was born in 1942 in Livorno. He received his degree in chemistry at the University of Pisa, 1967, and his Ph.D. at Pisa, Scuola Normale Superiore, with Prof. P. Pino in 1971. He continued his academic career as a scientist at the Chemical and Industrial Department in Pisa in 1972, and then as associated professor of organic chemistry at the University of Pisa from 1980. In 1986, he moved to the University of Sassari as full professor of organic chemistry. He is a member of the Società Chimica Italiana and American Chemical Society. After a first period of work on asymmetric organic syntheses assisted by organometallics, starting from 1985 he became interested in catalytic asymmetric synthesis and in the synthesis of biologically active organic molecules, mainly in the field of amino acids and peptidomimetics containing heterocyclic unities. His current research focuses on the design and implementation of practical synthetic methodology for the synthesis of heterocycles, such as polymer-supported organic reactions, combinatorial chemistry, and in the development of reactions under mild conditions. He is author (or co-author) of more than 150 papers in international journals and of several communications at international congresses.



Dr. Andrea Porcheddu was born in 1970 at Sassari (Italy). He studied chemistry at the University of Sassari, and got his 'Laurea' degree in chemistry in 1995 with first-class honors. His diploma thesis dealt with the synthesis of piperazic acid derivatives as CPP analogs, work carried out under the direction of Dr. Massimo Falorni. He then undertook doctoral research, designing novel strategies to use cyanuric chloride (TCT) in friendly organic processes, under the supervision of Prof. Maurizio Taddei at the University of Sassari and was awarded his Ph.D. in 1999. After an additional period of research (one year) as a postdoctoral fellow in the group of Dr. Charles Mioskowski at Louis Pasteur University in Strasbourg (France), he moved back to Sassari and joined the research group of Prof. Giacomelli. He currently has a position as research assistant and lectureship at the University of Sassari. His field of interests is mainly focused on solid-phase synthesis of heterocyclic compounds and combinatorial chemistry, new methodologies for friendly reactions, and the synthesis of modified peptide nucleic acids (PNAs) and their application in antisense therapy. He has over 40 scientific publications in refereed international journals.

9.04

1,2,3-Oxadiazines and 1,2,3-Thiadiazines

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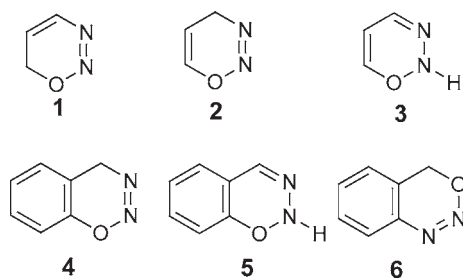
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9.04.1 Introduction

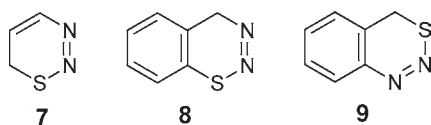
1,2,3-Oxadiazines and 1,2,3-thiadiazines were covered previously in CHEC(1984) and CHEC-II(1996) <1984CHEC(3)1039, 1996CHEC-II(6)637>. This chapter is intended to update the previous work, concentrating on major new preparations, reactions, and concepts. At the beginning of each main section, a sentence or short paragraph explaining the major advances since the publication of the earlier chapters has been provided.

The heterocyclic systems in this chapter are dealt with in the order, oxadiazines and their benzo derivatives, followed by thiadiazines and their benzo derivatives in which sulfur is divalent, then thiadiazines in which sulfur exhibits a valency of four.

The 1,2,3-oxadiazines **1** and their isomeric 4*H*- **2** and 2*H*- **3** derivatives still remain elusive ring systems. However, the nitrogen radical of the tetrahydro derivative of system **1** was investigated using *ab initio* calculations (see Section 9.04.2) <1999JA6367>. There is no report yet of fully conjugated 1-oxonia derivatives nor, to date, have the 4*H*- **4** and 2*H*-1,2,3-benzoxadiazines **5** been prepared. However, analogs of the benzoxadiazine system **6** have been studied for their antimicrobial activities (see Section 9.04.12) <1995BCF503>. The use of a derivative of the benzoxadiazine system **6** as the base for nucleotide analogs is also reported (see Section 9.04.12) <1996USP5541307>. However, the earlier claims to the preparation of 1,2,3-oxadiazines, mentioned in the first and second editions <1984CHEC(3)1039, 1996CHEC-II(6)637>, still remain unsubstantiated.



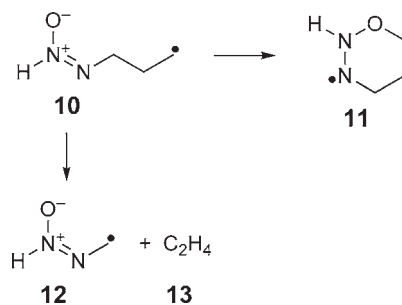
While the 1,2,3-thiadiazines **7** and the 2*H*- and 4*H*-1,2,3-benzothiadiazine systems **8** are still uncommon, their 1-oxide and 1,1-dioxides are prepared by oxidation reactions (see Sections 9.04.9 and 9.04.10) <2000SUL109, 1995USP5464831, 1996USP5510347, 1999JHC1081, 1998H143, 1997JIC314>. Similarly the 4*H*-3,1,2-benzothiadiazines **9** are still unknown. A cyclin-dependent kinase 4 (CDK4) inhibition study of a 1,1-dioxide derivative of benzothiadiazine system **8** <1999MI4279> and the synthesis and carbonic anhydrase inhibition studies of thienothiadiazines, <1995USP5464831> and <1996USP5510347>, are also reported (see Sections 9.04.10 and 9.04.12). Additionally, the antibacterial activity of a 1,1-dioxide derivative of benzothiadiazine system **8** has been studied (see Section 9.04.12) <1999WO9967240>.



9.04.2 Theoretical Methods

9.04.2.1 *Ab Initio* Calculations

Similar to the previous edition <1996CHEC-II(6)637>, theoretical calculations on 1,2,3-oxadiazines and 1,2,3-thiadiazines are scarce. However, an *ab initio* calculation was carried out using the Becke3LYP/6-31G* level to evaluate the possible intermediates for the transformation of **10** to **11**. While the calculations yielded no low energy transition structure for the cyclization of **10** to **11** (Scheme 1), the lowest energy transition state was found to be 44.3 kcal mol⁻¹ above **10** and, accordingly, the authors concluded that **10** fragments directly to **12** and **13** (ethylene). Transition structures were first optimized at the UHF/6-31G* level with the requirement that each must have one imaginary frequency corresponding to the reaction coordinate <1999JA6367>.



Scheme 1

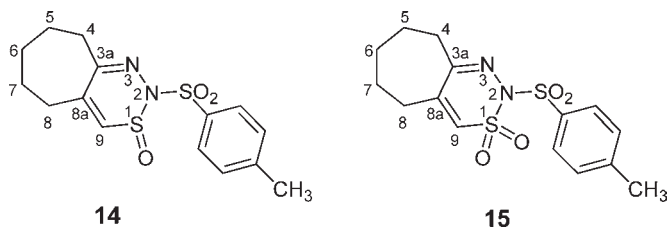
9.04.3 Experimental Structural Methods

9.04.3.1 Spectroscopic Studies

9.04.3.1.1 IR and NMR spectra

Infrared (IR) spectroscopy has been used to confirm the structure of the 1,2,3-thiadiazine-1-oxide **14**. The sulfinyl function showed an IR absorption (KBr) at 1106 cm⁻¹ <2000SUL109>. The ¹³C nuclear magnetic resonance (NMR) spectrum of compound **14** in CDCl₃ showed the characteristic peaks at 155.5 ppm for C-3a and 127.7 ppm for C-9.

The proton NMR spectrum of compound **14** indicated H-9 at 7.04 ppm <2000SUL109>. The IR spectrum (KBr) of compound **15** showed two sets of bands for the cyclic and exocyclic SO₂ groups at 1368, 1338, 1200, and 1117 cm⁻¹, while its proton NMR spectrum in acetone-*d*₆ showed the characteristic peak for H-9 at 7.18 ppm as a singlet. In the ¹³C NMR spectrum in acetone-*d*₆, peaks at 154.0, 146.9 and 127.3 ppm were assigned to C-3a, C-8a, and C-9, respectively. The IR, ¹H, and ¹³C NMR spectra of compounds **14** and **15** where the phenyl group has no substituent and where it is substituted as 3-NO₂ are also given in the same article <2000SUL109>. Similar IR and NMR spectral properties are also reported for compound **16** (shown later) and its 1,1-dioxide form <1999JHC1081>.

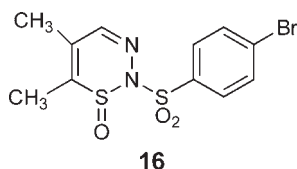


9.04.3.1.2 Mass spectra

The mass spectrum of compound **14** showed the molecular ion peak at 338, the M⁺-SO peak at 290, and multiple fragment ion peaks <2000SUL109>. Similarly, the mass spectrum of compound **16** showed the molecular ion peak at 354, the M⁺-SO₂ peak at 290, and multiple fragment ion peaks <2000SUL109>. The mass spectra of compounds **14** and **15** where the phenyl group has no substituent and where it is substituted as 3-NO₂ showing the molecular ion peaks at 340 and 385, respectively, are also described in the same article <2000SUL109>.

9.04.3.2 X-Ray Crystallography

During 1995–2006, no crystal structure of the oxadiazines was reported. However, a crystal structure was published for the 1,2,3-thiadiazine-1-oxide **14** <2000SUL109>. It was crystallized by slow evaporation of an ethanol solution. There is electron delocalization within the heterocyclic ring as evidenced from the bond lengths of the heterocycle. Furthermore, the exocyclic sulfonylimino group also participates in the delocalization. The X-ray crystal structure of another 1,2,3-thiadiazine-1-oxide, viz. **16**, was reported also without any discussion on the geometric and conformational features of the compound <1999JHC1081>.



9.04.4 Thermodynamic Aspects

Apart from the X-ray crystal structure and the *ab initio* calculation discussed previously, no thermodynamic discussions appear in the literature regarding the structure, stability, and tautomeric nature of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems and their 1-oxide and 1,1-dioxides.

9.04.5 Reactivity of Fully Conjugated Rings

Since CHEC-II(1996) <1994CHEC-II(6)637>, there have been no developments in the chemistry concerning the reactivity of fully conjugated rings of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems. However, it is worth mentioning that, as discussed in CHEC-II(1996) <1996CHEC-II(6)637>, the cycloaddition reaction of a cross-conjugated thione with diethyl azodicarboxylate (DEAD) in a diene-transmissive Diels–Alder reaction has been shown to give 3,4-dihydro-2*H*-1,2,3-thiadiazole. The 3,4-dihydro-2*H*-1,2,3-thiadiazoles upon prolonged heating with DEAD have been also shown to undergo cycloaddition reactions to give pyridazino[3,4-*e*]-1,2,3-thiadiazine derivatives in good yields.

9.04.6 Reactivity of Nonconjugated Rings

Similar to the reactivity of the fully conjugated rings, there have been no developments in the chemistry related to the reactivity of nonconjugated rings of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems since CHEC-II(1996) <1996CHEC-II(6)637>.

9.04.7 Reactivity of Substituents Attached to the Ring Carbon Atoms

Since CHEC-II(1996) <1996CHEC-II(6)637>, there have been no developments in the chemistry concerning the reactivity of substituents attached to the ring carbon atoms of the 1,2,3-oxadiazine and 1,2,3-thiadiazine systems.

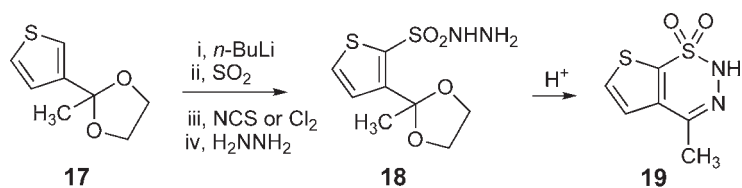
9.04.8 Reactivity of Substituents Attached to the Ring Nitrogen and Sulfur Atoms

Since CHEC-II(1996) <1996CHEC-II(6)637>, the only type of reaction of the ring sulfur atom observed involves oxidation to a 1-oxide or 1,1-dioxide (see Section 9.04.9) <1999JHC1081, 2000SUL109>. One of the few reactions of the ring nitrogen atom involves methylation of the 1,2,3-benzoxadiazine-1,1-dioxides using dimethylsulfate under alkaline conditions to preferentially alkylate the 4-amino group (see Section 9.04.10) <1997JIC314>. Another reaction of the ring nitrogen atom involves acetylation of the 1,2,3-benzoxadiazine-1,1-dioxides using acetic anhydride and pyridine, resulting in a preferential acetylation of the 4-amino group (see Section 9.04.10) <1997JIC314>.

9.04.9 Ring Synthesis from Acyclic Compounds

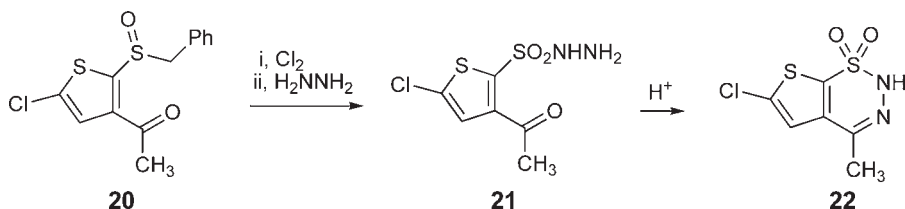
9.04.9.1 Condensation Reactions

Similar to the examples discussed in CHEC-II(1996) <1996CHEC-II(6)637>, condensation reactions remain the primary methods for the synthesis of benzothiazines. 1,2,3-Benzothiazine-1,1-dioxides were synthesized successfully via intramolecular condensation of a thiophene sulfonic acid hydrazide with a carbonyl group in moderate to high yields (Schemes 2 and 3) <1995USP5464831>. The products **19** and **22** were characterized using mass spectrometry and proton NMR spectroscopy. These compounds are important in the treatment of glaucoma (see Section 9.04.12).



R = methyl, 2-methylpropyl, 4-(morpholinyl)ethyl

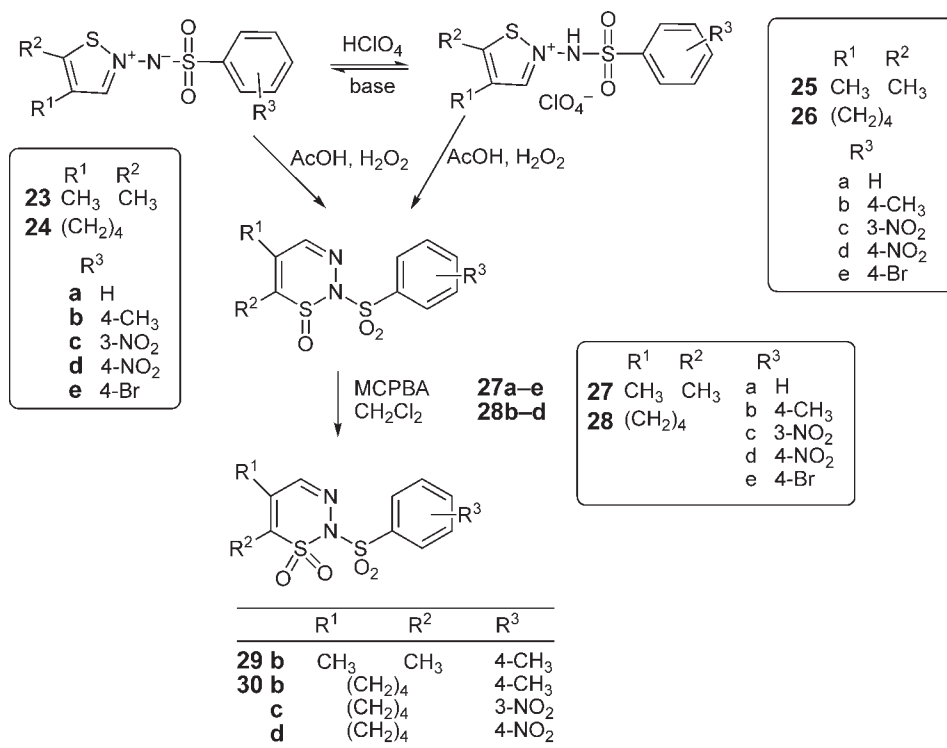
Scheme 2



R = methyl, 2-methylpropyl, 4-(morpholinyl)ethyl

Scheme 3

Several 1,2,3-thiadiazine 1-oxides were prepared in moderate yields by oxidation of 2-benzenesulfonylaminothiazolium salts and the corresponding imines with hydrogen peroxide at 0° C (Scheme 4) <1999JHC1081>. The X-ray crystal structure of the 1,2,3-thiadiazine 1-oxide **27e**, where R¹ = R² = CH₃ and R³ = 4-Br, has also been reported. The structures of the products were confirmed by IR and ¹H and ¹³C NMR spectroscopy. Conversion of the 1,2,3-thiadiazine 1-oxides to the more common 1,2,3-thiadiazine 1,1-dioxides was achieved by treatment with *meta*-chloroperbenzoic acid (Scheme 4).

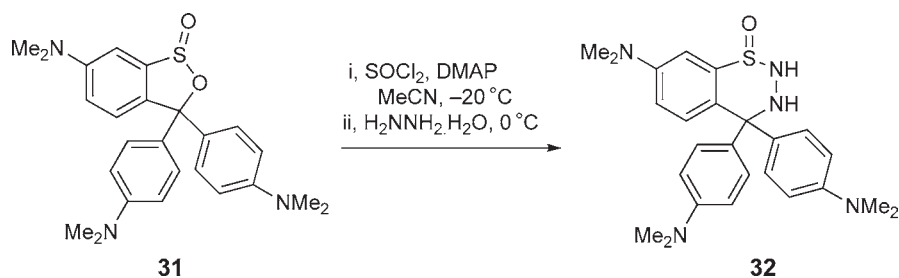


Scheme 4

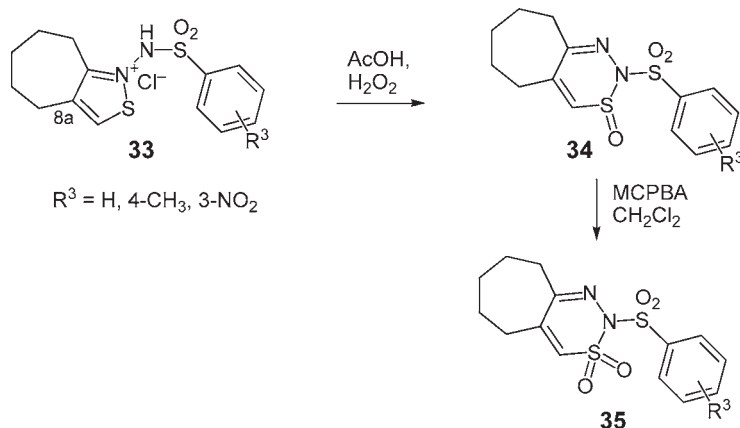
9.04.10 Ring Synthesis by Transformations of Another Ring

In 1995–2006, synthesis of benzothiazines by transformation of another ring was also another common approach, similar to the previous review in CHEC-II(1996) <1996CHEC-II(6)637>. The dihydrogenated benzodiazine *S*-oxide **32** was synthesized successfully by a two step reaction. Compound **32** was obtained in 81% yield by treatment of **31** with 4-dimethylaminopyridine (DMAP) and thionyl chloride in acetonitrile, followed by treatment with 10 equiv of hydrazine monohydrate (Scheme 5) <1998H(49)143>. The structure of compound **32** was confirmed by ¹H and ¹³C NMR spectroscopy and microanalysis. In addition, the potential use of compound **32** as a color former for carbonless imaging was tested.

1,2,3-thiadiazine 1-oxides **34** were prepared as the sole products of a hydrogen peroxide (30% in acetic acid) oxidation of **33** at room temperature (Scheme 6) <2000SUL109>. The products of the hydrogen peroxide oxidation, viz. **34**, were converted effortlessly into the corresponding 1,2,3-thiadiazine 1,1-dioxides **35** by treatment with *meta*-chloroperbenzoic acid. The mechanism of the oxidative ring enlargement presumably starts with nucleophilic attack of hydrogen peroxide on the C-8a atom in the isothiazolium hydrochloride starting material. The 1,2,3-thiadiazine 1-oxides and 1,1-dioxides were characterized IR and ¹H and ¹³C NMR spectroscopy (see Section 9.04.3.1.1). The crystal structure of the 1,2,3-thiadiazine 1-oxide where the substituent on the phenyl group is 4-CH₃ has also been reported (see Section 9.04.3.2).

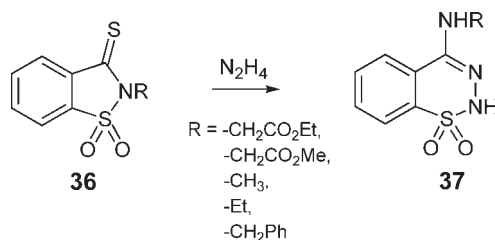


Scheme 5

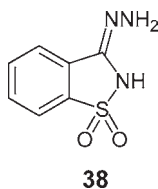


Scheme 6

Several 1,2,3-benzoxadiazine-1,1-dioxides **37** have been synthesized successfully also by the reaction of 2-substituted-3-thiosaccharins **36** with hydrazine hydrate (Scheme 7) <1997JIC314>. However, this reaction does not give the expected 1,2,3-benzoxadiazine-1,1-dioxide when $\text{R} = \text{H}$; instead, compound **38** is obtained. The possible mechanism for this result has not been investigated. Methylation of the 4-amino-1,2,3-benzoxadiazine-1,1-dioxides **37** using dimethyl sulfate under alkaline conditions preferentially alkylates the 4-amino group. Similarly, acetylation of the 4-amino-1,2,3-benzoxadiazine-1,1-dioxides using acetic anhydride and pyridine results in a preferential acetylation of the 4-amino group. The 1,2,3-benzoxadiazine-1,1-dioxides, as well as their methyl and acyl derivatives, were characterized using elemental analysis, and with IR and proton NMR spectroscopy.



Scheme 7

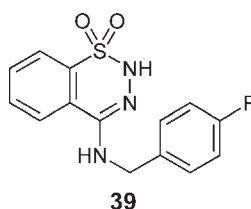


9.04.11 General Synthetic Methods

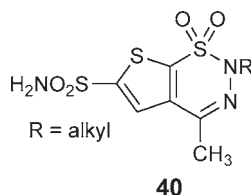
There are no new developments regarding the synthesis of 1,2,3-oxadiazines and their benzooxadiazine analogs since CHEC-II(1996) <1996CHEC-II(6)637>. Similarly, no new syntheses of 1,2,3-thiadiazines or benzothiadiazines were reported during 1995–2006. The main approaches for the synthesis of benzothiadiazine-1-oxide and -1,1-dioxides have been through condensation reactions (see Section 9.04.9) and ring synthesis via transformation of another ring (see Section 9.04.10).

9.04.12 Important Compounds and Applications

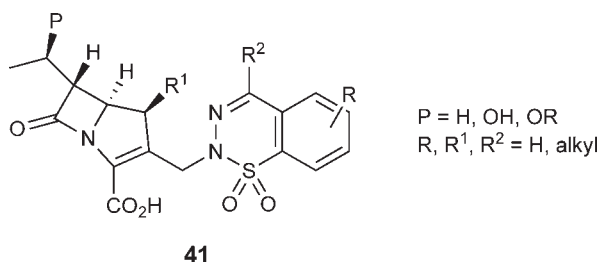
The cyclin-dependent kinase 4 (CDK4) inhibitory activity of the benzothiadiazine 1,1-dioxide derivative **39** was investigated. Compound **39** was found to be a potent inhibitor of CDK4/D1 with an IC_{50} of 0.33 μ M, while it weakly inhibits CDK2/A and CDK2/E with an IC_{50} >100 μ M <1999MI4279>.

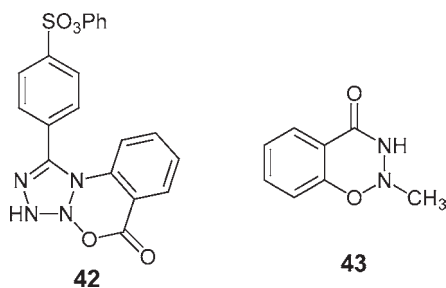


N-Alkyl and sulfonamide derivatives of the 1,2,3-benzothiadiazine-1,1-dioxides **40**, whose synthesis is shown in Schemes 1 and 2, are inhibitors of carbonic anhydrase <1995USP5464831, 1996USP5510347>. These compounds are used as a treatment for chronic primary angle glaucoma that is associated with a sustained increase in the intraocular pressure of the diseased eye. Topical administration of carbonic anhydrase inhibitors can be used to control intraocular pressure with a reduced risk of side effects such as nausea, dyspepsia, fatigue, and metabolic acidosis.



The antibacterial activity of several benzothiadiazine-1,1-dioxide derivatives **41** has been studied <1999WO9967240>. These derivatives are useful against Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS). Similarly, the antibacterial activity of the benzoxadiazine system **42** is worth mentioning <1995BCF503>. Another benzoxadiazine, viz. **43**, was used in the preparation of oligonucleotide analogs <1996USP5541307>.





Finally, the 1,2,3-benzoxadiazine-1,1-dioxides and their methylated and acetylated derivatives shown in [Scheme 6](#) have been investigated for their pharmacological effects. The compounds were administered intraperitoneally to adult healthy albino rats (100–200 g) of either sex in the form of a suspension using Tween-80 as the suspending agent at the dose range 10–100 mg kg⁻¹. Several of the compounds were found to be muscle relaxers with sedation in concentrations as low as 50 mg kg⁻¹ [\[1997JIC314\]](#).

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Biographical Sketch



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9.05

1,2,4-Oxadiazines and 1,2,4-Thiadiazines

P. Norris

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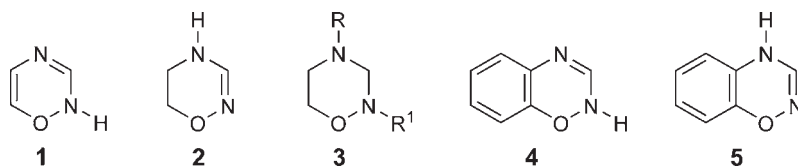
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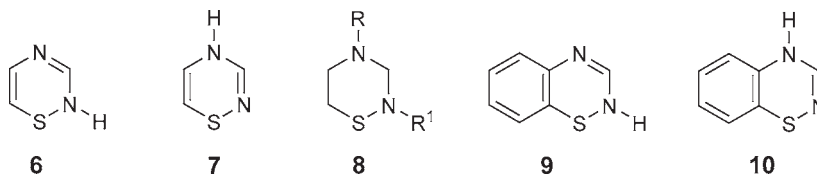
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9.05.1 Introduction

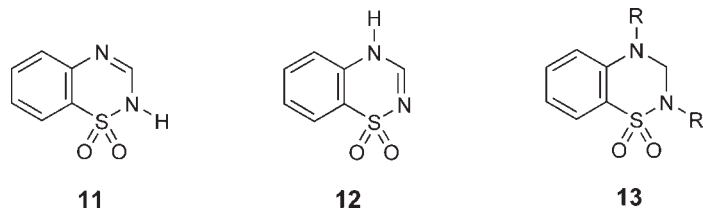
2*H*-1-Oxa-2,4-diazines **1**, as well as the 4*H*- and 6*H*-isomers, are uncommon; the 5,6-dihydro- **2** and fully saturated tetrahydro-1-oxa-2,4-diazine **3** derivatives are more widespread. Both the 2*H*- **4** and the 4*H*- **5** isomers of benzo-1-oxa-2,4-diazines have been reported.



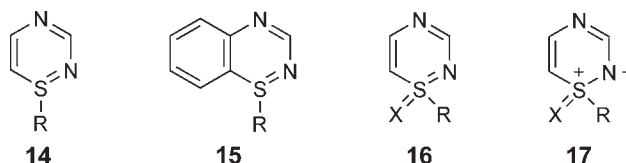
Examples of 2*H*- **6** and 4*H*-1-thia-2,4-diazines **7** are essentially unknown in the literature; however, the related tetrahydro- **8**, 2*H*-benzo- **9**, and 4*H*-benzo-1-thia-2,4-diazine **10** systems have been synthesized.



2*H*-Benzo-1-thia-2,4-diazine 1,1-dioxides **11** and the corresponding 4*H*-isomer **12** are much more common than the compounds containing divalent sulfur, as are the closely related 2,3-dihydro derivatives **13**.

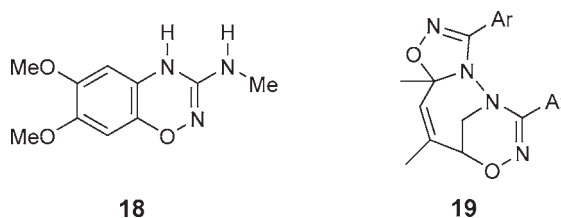


1-Thia-2,4-diazine compounds in which the ring sulfur atom participates in four covalent bonds (cf. **14**) are called 1 λ^4 -thia-2,4-diazines; similarly for the benzo analogs **15** <1984CHEC(1)32>. Cyclic sulfoximides (**16**: X=O) and sulfimides (**16**: X=NH) are drawn as the conjugated form **16** as opposed to the dipolar representation **17**. None of the compounds described in this chapter are considered to be fully conjugated within the 1-oxa- or 1-thia-2,4-diazine ring (see Section 9.05.5).

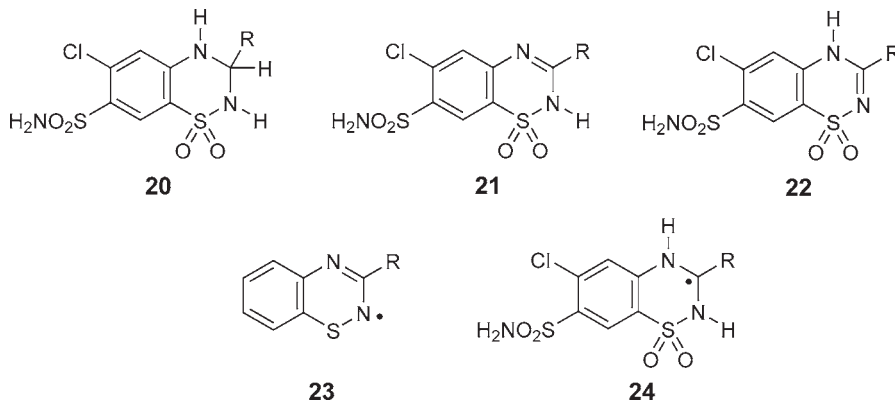


9.05.2 Theoretical Methods

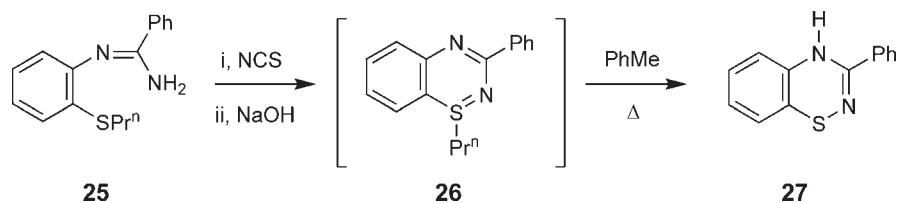
Theoretical methods applied to 1-oxa-2,4-diazines are limited. AM1 semi-empirical calculations have been carried out on the 4*H*-benzo-1-oxa-2,4-diazine **18**, which was proposed as a potential transition state analog and hapten for raising antibodies to catalyze isoxazole ring-opening reactions <1996JA6462>. Bond angles and bond lengths obtained from density functional theory (DFT) calculations on 1-oxa-2,4-diazine **19** (Ar = mesityl), the product of a 1,3-dipolar cycloaddition between a 1,2-diazepine and a nitrile oxide, are in close agreement with values obtained from the X-ray crystal structure <2002JST183> (see Section 9.05.3.1.5).



DFT methods have been applied to a series of substituted benzo-1-thia-2,4-diazine 1,1-dioxide diuretics including hydrochlorothiazide (**20**: R = H), althozide (**20**: R = CH₂SCH₂CH=CH₂), and trichloromethiazide (**20**: R = CHCl₂), as well as related oxidized analogs chlorothiazide (**21**: R = H) and benzthiazide (**21**: R = CH₂SCH₂Ph). The minimized structure for the dihydro compound (**20**: R = H) shows the heterocycle ring to be nonplanar <2003IJQ339>, which agrees with the X-ray structure reported earlier <1972AXB2340>. For chlorothiazide (**21**: R = H) and its analogs, the 4*H* tautomer **22** was concluded to be favored over the 2*H* form **21**. Each of the substituents (i.e., R) analyzed stabilizes the heterocyclic ring; however, an earlier conclusion from X-ray diffraction, that a mesomer with a formal negative charge at C-7 plays a significant role in the overall structure of hydrochlorothiazide (**20**: R = H), was not supported. Related DFT studies have investigated the dynamics of the NH₂ group of thiazides <2004JST211>, as well as the C-6 Cl atom <2002AMR193>, in the solid state. Comparisons of the results from DFT studies with spectroscopic data obtained from ¹³C magic angle spinning nuclear magnetic resonance (NMR) <2003JST211>, nuclear quadrupole resonance (NQR), and electron spin resonance (ESR) <2003MRC395, 2004CPL324, 2005JGM329> appear in Sections 9.05.3.1.2 and 9.05.3.1.3. These techniques have been used to probe how the electronic structure of the thiazide diuretics correlates with their biological activities <2005JGM329>. Detailed comparisons of results from *ab initio* (UB3LYP/6-31G*) and DFT calculations have led to an understanding of the molecular geometries of the thiadiazinyl radical **23** <2001PCA7615, 2001PCA7626>. DFT calculations and their correlation with experimental data, primarily ESR spectra, have been carried out on related radicals <2004JOC7525> (see Section 9.05.3.1.3). Similarly, DFT methods have been applied to the thiazide-derived radicals **24** <2004CPL324, 2005JGM329>.



The E_i mechanism, considered to be operating in the conversion of benzamidine **25**, via sulfinilimine **26**, into the 4*H*-benzo-1-thia-2,4-diazine **27** (Scheme 1) has been investigated using DFT methods <2004JOC2551>. The elimination is more facile than for the analogous sulfoximine, and the concomitant tautomerism to the 4*H*-isomer **27** is believed to contribute to the overall exothermicity of the process.



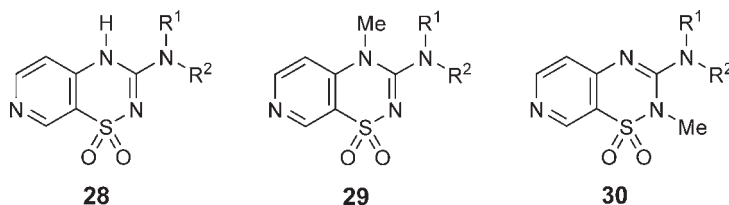
Scheme 1

9.05.3 Experimental Structural Methods

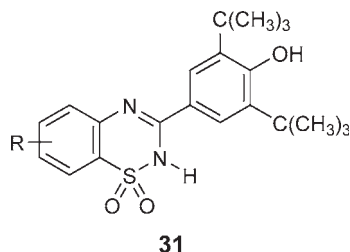
9.05.3.1 Spectroscopic Studies

9.05.3.1.1 Ultraviolet and infrared spectra

Ethanollic solutions of pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides (**28**: R¹, R² = H, alkyl) have ultraviolet (UV) absorbances in the 247–250 nm range, which are similar to the values (252–257 nm) observed for the 4-methylated derivatives **29** (R¹, R² = H, alkyl), thus suggesting that the former exist primarily as the 4*H*-tautomer in solution. The 2-methylated analogs **30** exhibit absorbances in the 271–278 nm range and a second absorption maximum at 290–303 nm. This additional absorption is seen in **28** but not in **29**, which suggests the presence of a small amount of the 2*H*-tautomer of **29** in solution <1999T5419>. X-Ray crystal structures of a number of these compounds support the tautomeric assignments (see Section 9.05.3.1.5).



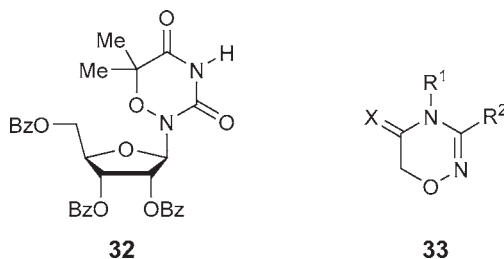
The 3-substituted benzo-1-thia-2,4-diazine 1,1-dioxides **31** have been prepared and their abilities to act as radical scavengers studied by UV spectroscopy. That these compounds exist as the 2*H*-tautomers is supported by absorbances in the 294–326 nm range <1996T12587> (see also Section 9.05.3.1.3 for ESR studies on radicals derived from **31**). The UV spectra of persistent benzo-1-thia-2,4-diazinyl radicals such as **57** (see Section 9.05.3.1.5) show additional absorbances above 500 nm as compared to their precursors <2004JOC7525>.



Infrared (IR) and Raman spectra of various thiazide diuretics have been compared with results from DFT and ³⁵Cl NQR studies <2002AMR193> (see Section 9.05.2 and Section 9.05.3.1.2).

9.05.3.1.2 NMR spectra

Most of the compounds produced in Sections 9.05.6–9.05.11 have been characterized thoroughly by ^1H and ^{13}C NMR spectroscopy. Low-temperature one-dimensional (1-D) and 2-D NMR studies show that the uridine-related 1-oxa-2,4-diazine **32** associates through H-bonding between the C-3 carbonyl oxygen and the N-4 proton of adjacent molecules <1998CEJ621>. The ^{13}C NMR spectra of 1-oxa-2,4-diazine-6(5*H*)-ones and thiones (**33**: X = O or S, respectively) have been recorded, with particular attention being paid to the chemical shifts for C-3; for X = O ($\text{R}^1 = \text{Me}$, Ph; $\text{R}^2 = \text{H}$, Me, Ph), the C-3 signal appears at 141.6–150.0 ppm, while for X = S ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Me}$, Ph), C-3 shows at 131.2–138.3 ppm <1998MRC878>.



Using solid-state ^1H NMR at different temperatures, the dynamics of the NH_2 group in various thiazide diuretics has been investigated and the results related to DFT studies <2004JST211>. Application of ^{35}Cl NQR spectroscopy to the molecular dynamics of these compounds provided evidence for their relative rigidities <2002AMR193>, and the same technique has been used to study the electron-withdrawing abilities of the different C-3 substituents <2003MRC395>. Chemical shifts and chemical anisotropy measurements from solid-state ^{13}C magic angle spinning experiments on hydrochlorothiazide, althiazide, and trichloromethiazide (**20**: $\text{R} = \text{H}$, $\text{CH}_2\text{SCH}_2\text{CH}=\text{CH}_2$, CHCl_2 , respectively) reveal the relative electron-withdrawing abilities of the C-3 substituents to be $\text{CHCl}_2 > \text{CH}_2\text{SCH}_2\text{CH}=\text{CH}_2 > \text{H}$ <2003JST211>. General overall observations have been made relating spectroscopic data (NMR, NQR, and ESR) and DFT results <2004CPL324>, and these correlations analyzed in terms of the electronic structure of the thiazide diuretics and their biological activities <2005JGM329>.

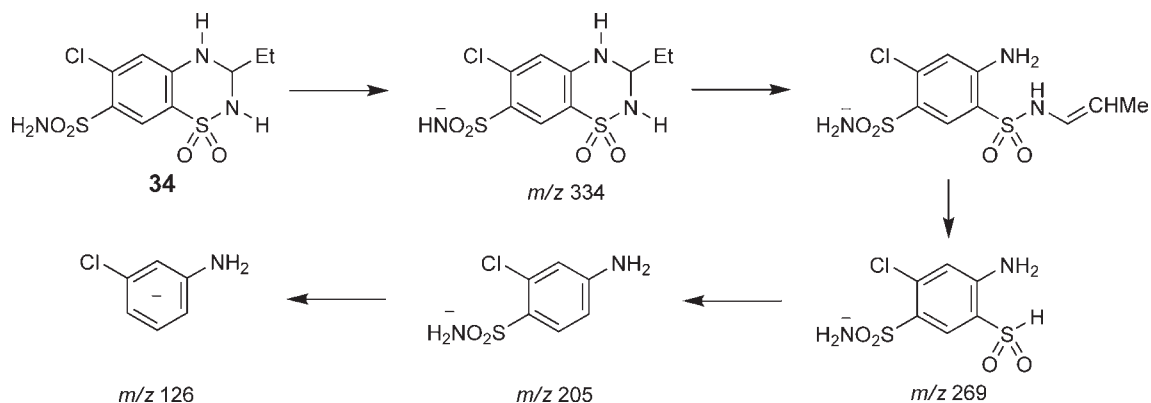
The ^{13}C NMR spectra of the pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides **28–30** have been analyzed with the signal for C-3 appearing in the 150.9–157.1 range in each case. A difference in the ^{13}C chemical shifts for C-4a in the pyrido ring has been used to support the identity of the major tautomer of unmethylated **28** as gathered from UV data. The signals for C-4a in **28** are shielded (142.3 ppm) to a similar degree as those in the 4-methylated derivatives **29** (144.7–146.2 ppm) when compared to C-4a in the 2-methylated isomers **30** (150.6–151.2 ppm) <1999T5419>.

9.05.3.1.3 ESR spectra

ESR, along with NMR and NQR, has been used to study the electronic structures of thiazide diuretics **20** and **21** <2004CPL324, 2005JGM329>. In related work, γ -irradiation of a number of these diuretics resulted in radicals, the ESR spectra of which proved the radicals to be formed mostly by H abstraction from C-3 of the 1-thia-2,4-diazinyl rings <2004AMR345>. A bis(1-thia-2,4-diazinyl) radical, which was stable enough to be studied by X-ray diffraction (see **56**, Section 9.05.3.1.5), gave an X-band ESR spectrum that was consistent with extensive delocalization <2005CC1218>. The ESR spectra of a series of similarly persistent 1-thia-2,4-diazinyl radicals related to **57** (see Section 9.05.3.1.5) have been recorded and vary from being unresolved quintets to more complicated spectra when coupling with F is possible <2004JOC7525>. The antioxidant potential of radicals derived from phenols **31** (see Section 9.05.3.1.1) has been studied by ESR spectroscopy <1996T12587>.

9.05.3.1.4 Mass spectra

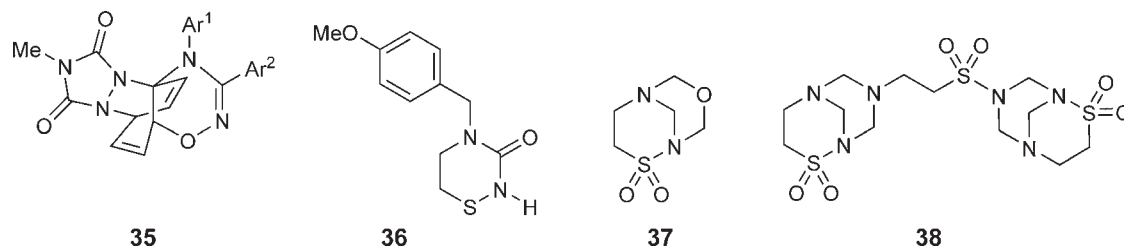
Mass spectrometry has been used to characterize many of the compounds that are detailed in Sections 9.05.6–9.05.11; 1-oxa-2,4-diazines, 1-thia-2,4-diazines, and the common 1-thia-2,4-diazine 1,1-dioxides all typically exhibit a molecular ion in their electron ionization (EI) mass spectra. Two closely related studies on the thiazide diuretics using electrospray ionization (ESI) and collision-induced dissociation (CID) have revealed detailed fragmentation patterns for these compounds and their isotopically labeled analogs <2002JMP940, 2002ANC3802>. For example, the C-3 ethyl derivative **34** gives ($\text{M}-\text{H}$), which fragments via stepwise cleavage of the 1-thia-2,4-diazinyl 1,1-dioxide ring, ultimately to the *m*-chloroaniline species (Scheme 2) <2002ANC3802>.



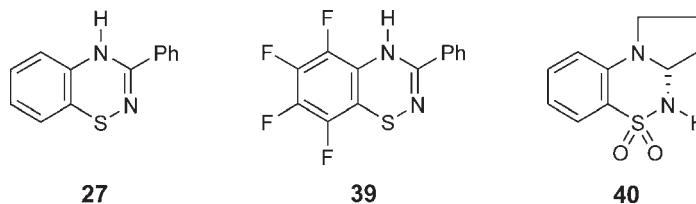
Scheme 2

9.05.3.1.5 X-Ray crystallography

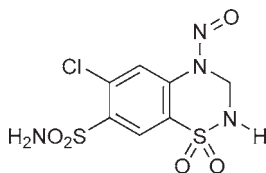
The 1-oxa-2,4-diazine **19** (see Section 9.05.2) crystallizes in a triclinic form and the X-ray crystal structure reveals the tricyclic nature of this compound <1996AXC736>, which results from cycloaddition between a nitrile oxide and a 1,2-diazepine (see Section 9.05.2) <2002JST183>. Cycloaddition between a triazolinedione and a [4,9 α]-dihydrocyclohepta-1-oxa-2,4-diazine (viz. **266**; see Section 9.05.10) affords the crystalline adduct **35**, the triclinic unit cell of which is centrosymmetric containing two enantiomeric molecules that are linked by hydrogen bonds between two molecules of water and the N-2 atoms of each 1-oxa-2,4-diazine ring <2002EJO569>. Ring enlargement of a 3-alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxide yields the triclinic 5,6-dihydro-2*H*-1-thia-2,4-diazin-3(4*H*)-one **36** (see Section 9.05.10 for ring synthesis), a rare example of the divalent 1-thia system <1997SL316>. Treatment of the antibiotic Taurolidine (see Section 9.05.12) with excess formaldehyde leads to derivatives **37** and **38**, crystals of both of which are monoclinic, and the X-ray crystal structures of which show that the 1-thia-2,4-diazine 1,1-dioxide rings adopt distorted chair conformations <1999AXC232>.



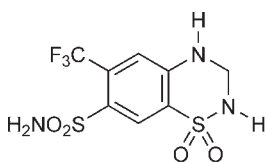
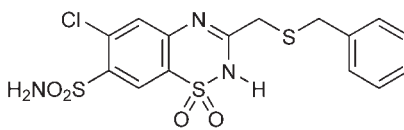
3-Phenyl benzo-1-thia-2,4-diazine **27** (see Section 9.05.2 for its formation) crystallizes in a monoclinic form as does the tetrafluorobenzo analog **39**, the former belonging to the $P2_1/c$ space group, the latter to $C_{2/c}$ <2004JOC2551>. The X-ray structures of both show them to be the 4*H*-tautomers and reveal puckering within the heterocyclic rings through the S(1)–N(4) axis. An X-ray structure of the C(3)–N(4)-fused benzo-1-thia-2,4-diazine 1,1-dioxide **40** proves this selective α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor modulator to have the (*S*)-configuration at C-3 <1996BML3003> (see Section 9.05.6.2.4 for stereoselective synthetic approaches to **40**).



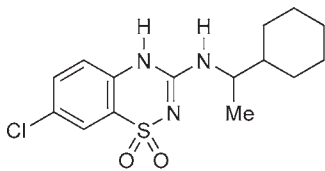
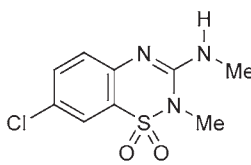
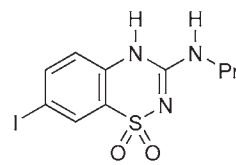
A monoclinic crystalline 1:1 solvate of hydrochlorothiazide (**20**: R = H) with aniline belongs to the $P2_1/n$ space group <2005AXE2520>, whereas the related 1:1 solvate with 1,4-dioxane is triclinic and belongs to the $P1$ group <2005AXE2573>. Both crystal structures reveal extensive H-bonding between molecules in the crystal lattice. The 4-nitroso derivative **41** of hydrochlorothiazide (**20**: R = H) forms crystalline monoclinic and triclinic complexes with 18-crown-6 and *cis-anti-cis*-dicyclohexyl-18-crown-6, respectively, the former being in the $P2_1/c$ space group, the latter being in $P1$ <2005T6596>.

**41**

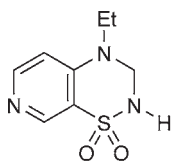
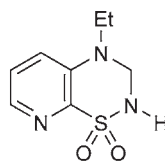
Crystals of the diuretic and hypertensive agent hydroflumethiazide **42** belong to the $P2_1$ space group and the crystal structure shows the envelope, that is, puckered, conformation about the heterocyclic ring (2004XSAO139). Benzthiazide **43** and its monohydrate have been studied as potential synthons for crystal engineering <2003MI487>. The anhydrous form of **43** produces monoclinic crystals in the $P2_1/a$ space group while crystals of the hydrate of **43** are also monoclinic and belong to the $P2_1$ group. The crystal structure of the anhydrate form of **43** shows significant intramolecular interaction, through π -stacking, between the benzylic phenyl ring and the benzo group of the benzo-1-thia-2,4-diazine system, whereas the hydrated form crystallizes in an elongated conformation with more extensive intermolecular hydrogen-bonding interactions.

**42****43**

Single crystal diffraction studies on the orthorhombic crystals of both enantiomers of C-3 amino-substituted benzo-1-thia-2,4-diazine 1,1-dioxide **44**, belonging to the $P2_1$ space group, established the configuration of each antipode and confirmed both as being the 4*H*-tautomers <1999AXC1945>. Methylation at N-2 traps 3-aminomethyl derivative **45** in the 2*H*-isomeric form, and its monoclinic crystals, which belong to the $P2_1/a$ space group, exhibit extensive intermolecular hydrogen bonding between the N–H of the C-3 aminomethyl group and the SO_2 group of other molecules <2001AXE652>. The C-3 amino-substituted 7-iodo-benzo-1-thia-2,4-diazine 1,1-dioxide **46** crystallizes in a monoclinic form in the $P2_1/n$ space group, the crystal structure of which proves it to be the 4*H*-tautomer <1999AXC1152>.

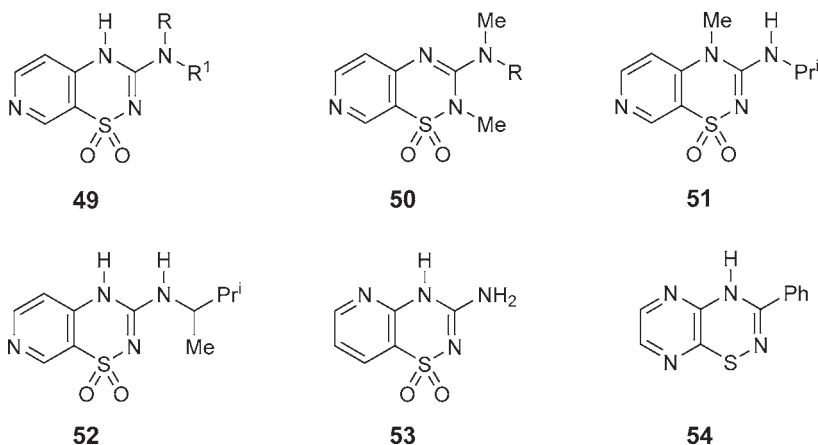
**44****45****46**

The structures of the 2,3-dihydro-4*H*-pyrido analogs **47** and **48**, both of which give monoclinic crystals in the $P2_1/n$ space group, show little difference in the conformations of the two 1-thia-2,4-diazine rings, suggesting that the more significant biological activity of **48** is mainly due to the position of the nitrogen in the pyrido ring <1999AXC461>.

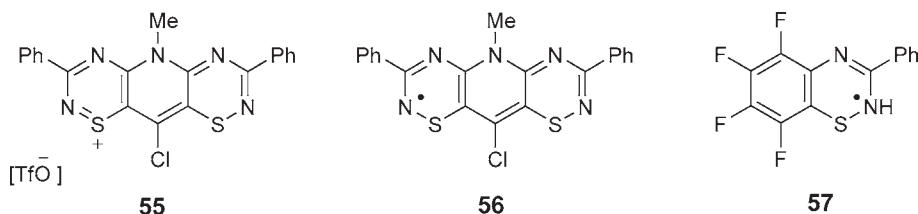
**47****48**

The X-ray crystal structures of a series of 3-alkylamino-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides (**49**: $R = R^1 = H$; $R = H$, $R^1 = Me$; $R = Me$, $R^1 = H$; $R = R^1 = Me$) and the related N-2-methylated compounds **50** ($R = H$, Me) clearly establish the former as the 4*H*-tautomer and the latter as the 2*H*-tautomer in the solid state <1999T5419>. The related 3-isopropylamino-substituted 1,1-dioxide **51** is trapped as the 4*H*-isomer, which is indicated by X-ray analysis of monoclinic crystals that belong to the $P2_1/c$ space group <1996AXC1741>. The solid-state structure of racemic analog

52 reveals that the N–H bonds at N-4 and in the exocyclic C-3 amino group are aligned in an essentially parallel fashion in the crystal lattice <2001AXE1050>. 3-Amino-4*H*-pyrido[2,3-*e*]-1-thia-2,4-diazine 1,1-dioxide **53**, which yields orthorhombic crystals, is firmly identified as being the 4*H* form from its X-ray crystal structure <2001AXE602>. The triclinic crystals of pyrazino derivative **54**, which crystallize in the P1 space group, show intermolecular interaction between molecules via the N-4 proton and N-7 of the pyrazino ring on adjacent molecules <2004JOC2551>.

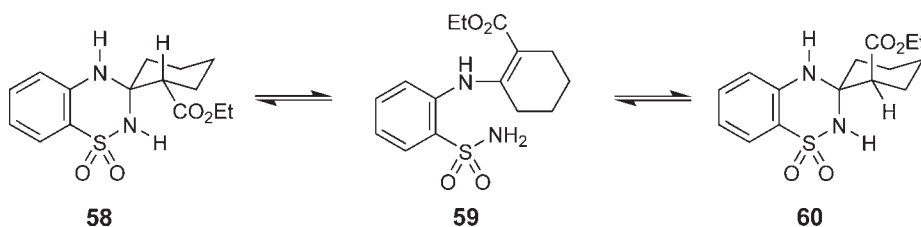


The 1-thia- λ^4 -2,4-diazine **55** produces orthorhombic crystals in the Pbc_a space group, and is reduced by dimethylferrocene to the thiadiazinyl radical **56** <2005CC1218> (see Section 9.05.6.3.4). The low-temperature crystal structure of **56**, which forms monoclinic needles in the P2₁/c space group, shows that it does not dimerize in the solid state and that the ring system is completely planar, including the phenyl groups at C-3 of each of the 1-thia-2,4-diazinyl rings. The related radical **57** crystallizes in monoclinic form in the C2/c space group, and its nearly planar structure has been compared with the parent system **39** <2004JOC7525>.



9.05.4 Thermodynamic Aspects

Evidence for the 2*H*- versus 4*H*-tautomeric preferences of various pyrido- and benzo-1-thia-2,4-diazine 1,1-oxides gathered from UV, NMR, and X-ray studies is discussed in Sections 9.05.3.1.1, 9.05.3.1.2, and 9.05.3.1.5, respectively. NMR also has been used to investigate the interconversion of stereoisomers **58** and **60**, which inferred a ring-chain tautomerism involving the ring-opened structure **59** (Scheme 3) <2005T7294>. Equatorial isomer **58** converts very slowly into **60** with a 1:1 mixture being formed after 1.5 months. The concentration of **59** was too low to measure by NMR.

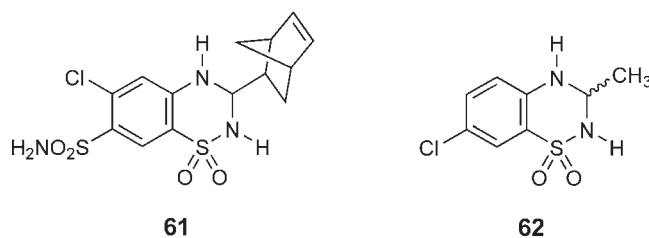


Scheme 3

Several studies of the interactions of hydrochlorothiazide (**20**; R=H) and its nitrosation product **41** (Section 9.05.3.1.5) with macrocyclic receptors have been carried out. The former produces a 1:1 inclusion complex with β -cyclodextrin <1996SPJ23>, while the latter gives different crystalline complexes with 18-crown-6 and *cis-anti-cis*-dicyclohexyl-18-crown-6, the structures of which have been analyzed in detail by X-ray diffraction <2005T6596> (see Section 9.05.3.1.5).

Application of a high-throughput method for the estimation of pK_a values to hydrochlorothiazide (**20**; R=H) gives values of 9.16 and 9.56, respectively, for the 2-NH and C-7 sulfonamide dissociations <2003ANC883>. Potentiometric measurements were carried out on trichlormethiazide (**20**; R=CHCl₂) to give pK_a values for the two dissociations in the ranges 7.30–9.46 and 10.0–12.44 in 0–70% aqueous acetonitrile mixtures. Chlorthiazide (**21**; R=H) gave ranges of 6.70–8.25 and 9.50–11.27 in the same solvent mixtures <1998TAL817>.

High-performance liquid chromatography (HPLC) has been used to estimate the lipophilicity of various drugs including hydrochlorothiazide <2002JCH117>, and a detailed study has been made on the influence of ionic strength and pH on the chromatographic retention of trichlormethiazide on an octadecylsilica stationary phase <2001JCH85>. Pirkle-type stationary phases, which feature enantiopure amines as the chiral selector, allow for the separation of the racemates of various benzo-1-thia-2,4-diazine 1,1-oxide diuretics <2000JCH221, 2002JSS1284, 2002BCH437>. Similar separations are also possible using silica-bound glycopeptides such as vancomycin, norvancomycin, teicoplanin, and ristocetin A <2004JCH205, 2004CHR443, 1998CH434, 1996TAL1767>, as well as derivatives of β -cyclodextrin <2004CH592, 2002HCA3283, 1996CH325>, and cellulose-based stationary phases <2003JCH185, 2002JBB15, 1999JCH51>. The eutomer of the diuretic cyclothiazide **61** has been isolated using such a cellulose-derived material and toluene–acetone as the mobile phase <1996JCH29>. HPLC also has been used to study the epimerization of compounds such as 7-chloro-3-methyl-3,4-dihydro-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **62** <2001CH94>.



9.05.5 Reactivity of Fully Conjugated Rings

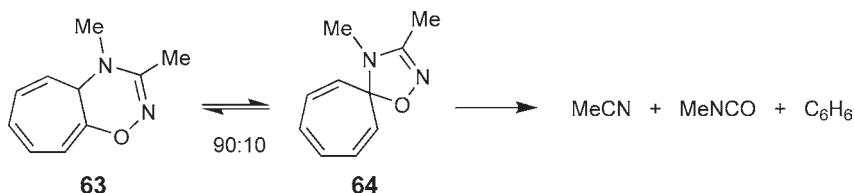
Although 1 λ^4 -thia-2,4-diazines (e.g., **16**, Section 9.05.1) are represented here as having fully conjugated heterocyclic rings, they, and the other heterocyclic systems detailed in this chapter, do not possess aromatic character within the heterocyclic ring. Since compounds such as **16** exist in the dipolar forms (e.g., **17**) <1975CSR189>, their reactivity is detailed in Section 9.05.6.

9.05.6 Reactivity of Nonconjugated Rings

9.05.6.1 1-Oxa-2,4-diazines and Benzo-1-oxa-2,4-diazines

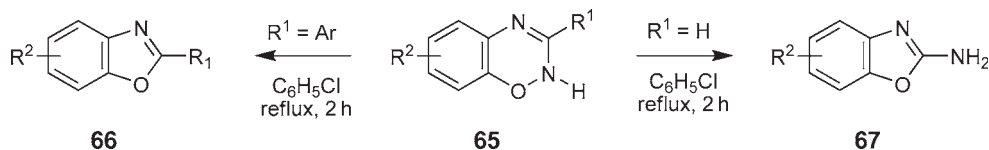
9.05.6.1.1 Thermal and photochemical unimolecular reactions

Studies detailing the thermal and photochemical reactions of these compounds are rare. The 1-oxa-2,4-diazine **63** is known, from ¹H NMR, to be in equilibrium with the spiro isomer **64**, with the former predominating. Heating this mixture above 40 °C results in decomposition to acetonitrile, methyl isocyanate, and benzene (Scheme 4) <1995H(40)619>. The formation of compounds such as **63** (and **64**) by cycloaddition of nitrile oxides to 8-azaheptafulvenes is discussed in Section 9.05.10.



Scheme 4

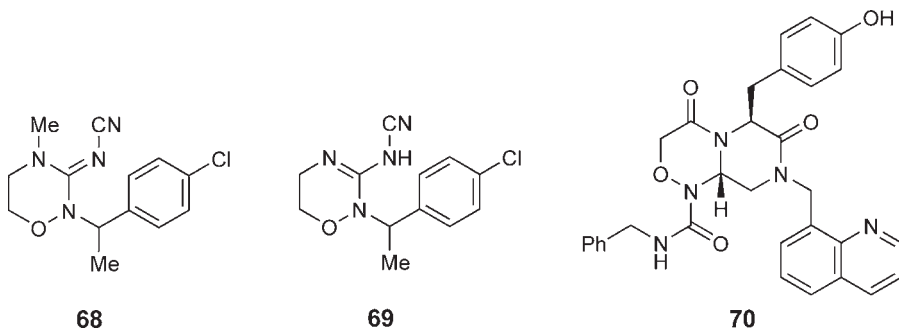
As described previously <1996CHEC-II(6)651>, the benzo-1-oxa-2,4-diazines **65** (R¹ = H, Ar; R² = 7-H, 7-Cl, or 7-NO₂) undergo thermal ring-opening processes resulting in the 1,3-benzoxazoles **66** or the 2-amino-1,3-benzoxazoles **67** depending upon the nature of R¹ (Scheme 5) <1975CC962, 1988JCP12169>.



Scheme 5

9.05.6.1.2 Electrophilic attack at nitrogen

Alkylation and acylation at nitrogen in 1-oxa-2,4-diazines, and the benzologs, has been discussed previously; in summary, regioselective alkylation is possible at N-4 of 4*H*-1-oxa-2,4-diazin-5(6*H*)-ones, and acylation at N-2 of 2*H*-benzo-1-oxa-2,4-diazines is slow <1996CHEC-II(6)651>. The N-2-alkylated 1-oxa-2,4-diazines **68** and **69** have been produced as potential pesticides <2005WO2005116032>; the N-2-acylated fused-ring derivative **70** has been claimed as a reverse-turn peptidomimetic with potential anticancer activity <2002WO2002096872>.



9.05.6.1.3 Electrophilic attack at oxygen

Acidic hydrolysis of 5-(ethoxycarbonylmethylene)-5,6-dihydro-4*H*-1-oxa-2,4-diazines results in cleavage of the N–O bond and the formation of amidoxime products <1996CHEC-II(6)652, 1982CPB3987>.

9.05.6.1.4 Electrophilic attack at carbon

3,4-Dihydro-2*H*-1-oxa-2,4-diazin-5(6*H*)-ones bearing an aryl substituent at C-3 are brominated at that position and the product undergoes elimination in the presence of base to afford the corresponding 4*H*-1-oxa-2,4-diazin-5(6*H*)-one <1996CHEC-II(6)652, 1989JHC129>.

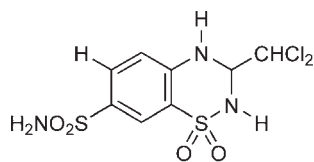
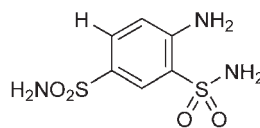
9.05.6.1.5 Reduction

Reductions of 1-oxa-2,4-diazine systems have been treated in detail previously [<1996CHEC-II\(6\)652>](#). Typically, catalytic reduction results in cleavage of the ring N–O bond.

9.05.6.2 1-Thia-2,4-diazines and Benzo-1-thia-2,4-diazines

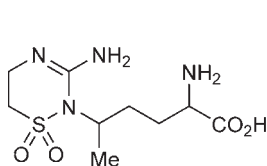
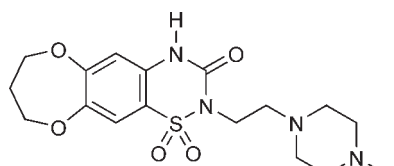
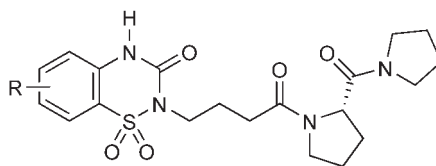
9.05.6.2.1 Thermal and photochemical unimolecular reactions

The major product of photochemical decomposition of trichlormethiazide (**20**: R = CHCl₂) was isolated and proven from spectroscopic data to be the 6-dechlorinated derivative **71** [<1996PHA774>](#). The closely related diuretic hydrochlorothiazide (**20**: R = H) undergoes a similar dechlorination when irradiated in methanol, along with ring cleavage, to produce the sulfonamide **72** [<2005ECL195>](#).

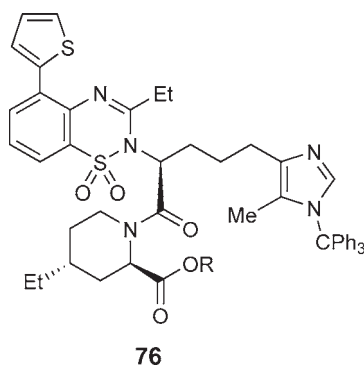
**71****72**

9.05.6.2.2 Electrophilic attack at nitrogen

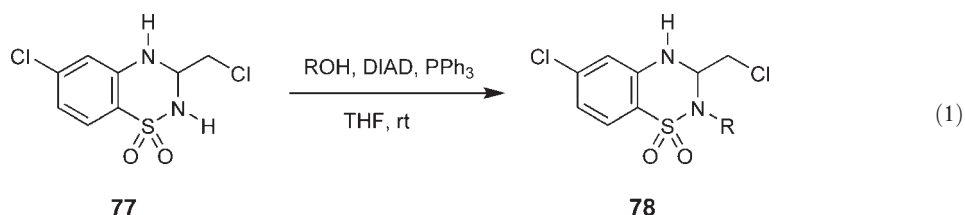
N-Alkylated derivatives of 1-thia-2,4-diazines and their benzo analogs display a broad spectrum of biological activities. The 2-substituted 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **73** has been used to block or remove toxic carbonyl and dicarbonyl materials in patients with diabetes-related conditions [<1997WO9717081, 1998WO9851260>](#). 2-Alkylated 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one **74** has been claimed for the treatment of micturition disturbance [<1997JPP09227380>](#), while the related 2-alkylated compounds **75** (R = Me, Cl, I, NO₂) have been produced as prolylendopeptidase inhibitors [<1997WO9707116>](#).

**73****74****75**

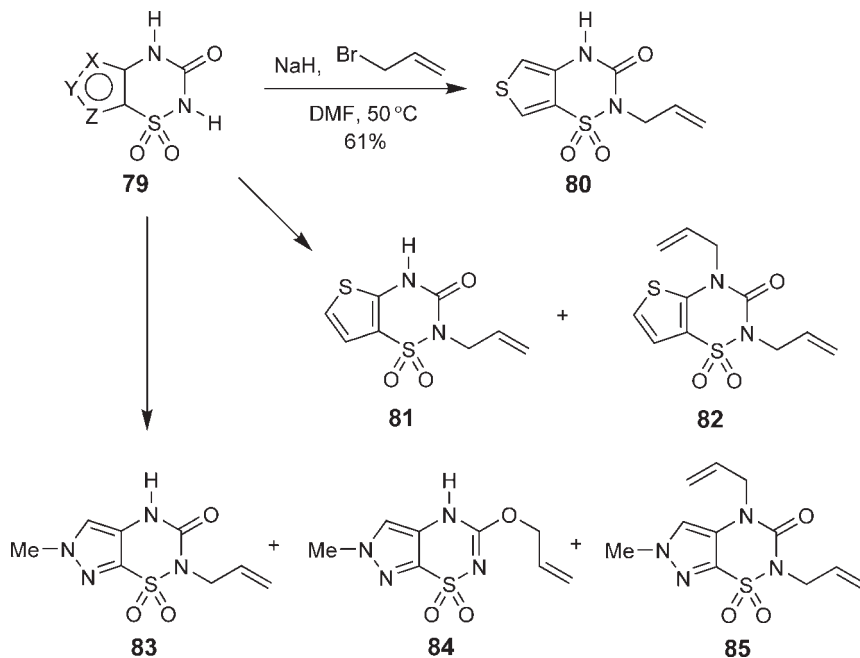
2-Substituted 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **76** (R = CH₂CMe₃, CH₂CH₂Ph) are representative of a series of compounds that possess interesting biological properties, for example, as thrombin inhibitors [<1999FRP2771094, 1998WO9842700, 1998WO9822443>](#).



Applying Mitsunobu conditions to the 2*H*-benzo-3,4-dihydro-1-thia-2,4-diazine 1,1-dioxide **77** results in alkylation at N-2 to afford **78** in 32–86% yield. Evidence for alkylation at N-2 and not N-4 was gained from a nuclear Overhauser effect (NOE) experiment, which showed interaction between the N-4 proton and H-5 of the benzo ring (Equation 1) <2005BMC1393>.



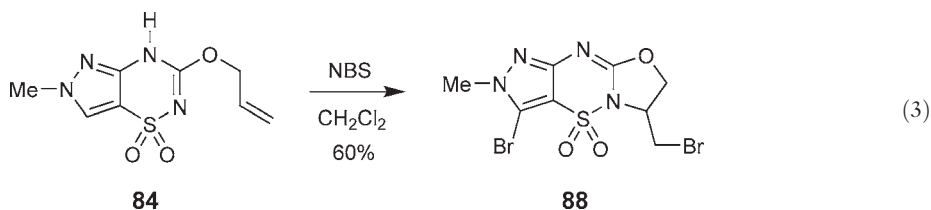
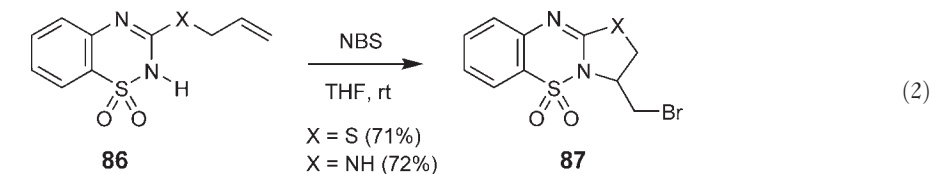
Alkylation of various heterocyclic analogs of 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **79** using NaH in dimethylformamide (DMF) at 50 °C results in different ratios of *N*-allyl products in each case <2005JHC755>. Beginning with the thieno[3,4-*e*] compound (**79**: X=CH, Y=S, Z=CH), only the N-2-allylated product **80** was isolated (Scheme 6). Under the same conditions, the thieno[2,3-*e*] analog (**79**: X=S, Y=CH, Z=CH) gave the N-2-allylated derivative **81** (68% yield), as well as the diallylated material **82** (7% yield). The pyrazolo precursor (**79**: X=N,



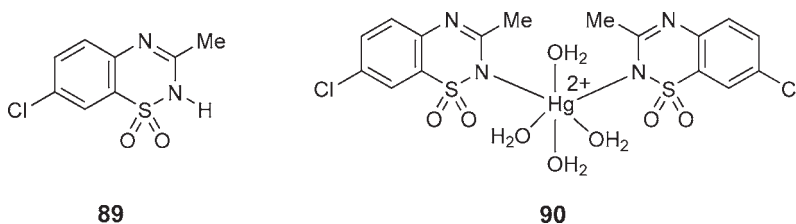
Scheme 6

Y = NMe, Z = CH) gave not only the N-2 allylated material **83** (42% yield) and the diallylated product **85** (7% yield) but also the O-3-monoallylated compound **84** (12% yield). Alkylation of the thieno[3,4-*e*] compound **79** (X = CH, Y = S, Z = CH) with 1,4-dibromobutane resulted in the N-2 alkylation product being isolated in 34% yield <2000EJM751>.

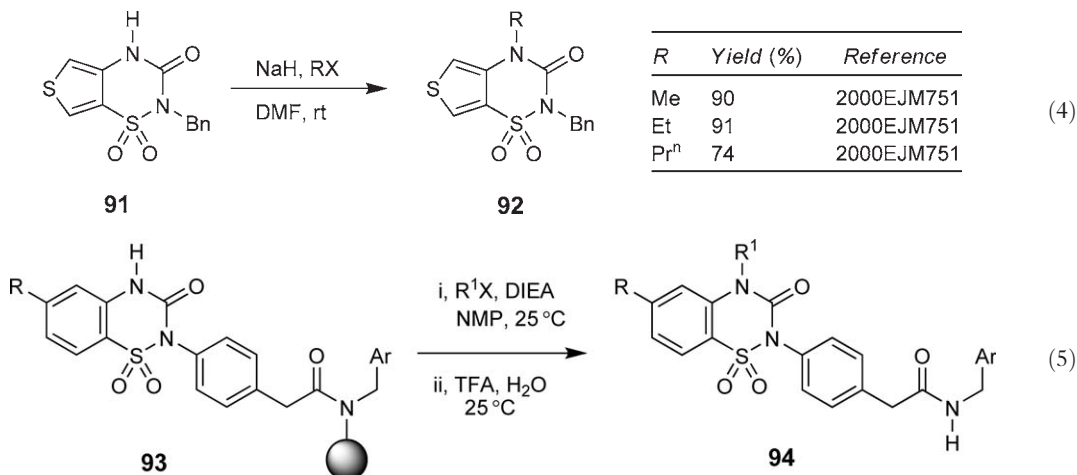
When a suitable electrophile is positioned at C-3 of 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides such as **86**, bromonium-induced intramolecular alkylation occurs at N-2 rather than N-4 to produce the cycles **87** (Equation 2) <1998JME3128>. Similarly, the pyrazolo 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxide analog **84** is considered to afford the linear tricyclic system **88** through N-2 alkylation despite evidence that the precursor **84** is mainly the 4*H*-tautomer in solution (Equation 3) <2005JHC755>.



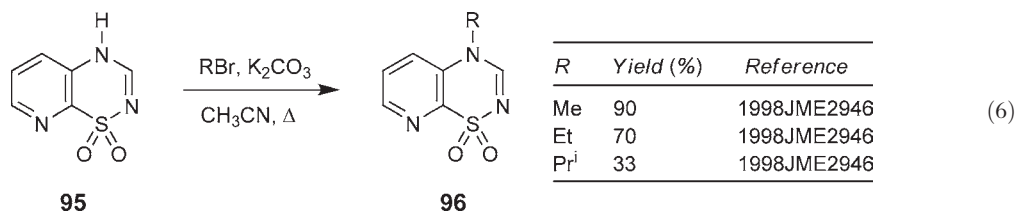
The diuretic 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide (diazoxide, **89**) produces N-2-metallated products such as **90**. Other metal ions used include CO^{2+} , Ni^{2+} , Fe^{3+} , and Al^{3+} <1996MBD25>.



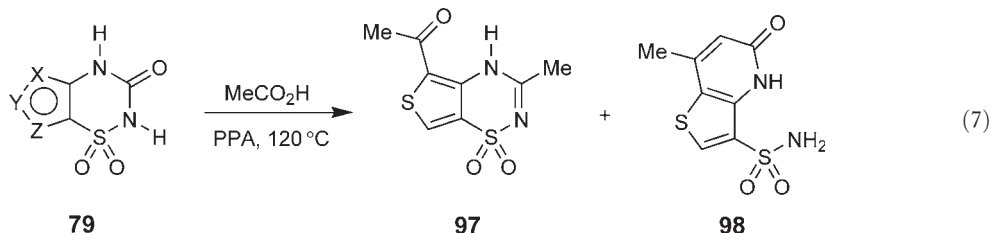
When N-2 is blocked, as in the 2*H*-thieno[3,4-*e*]-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **91**, alkylation occurs at N-4 to afford the dialkylated products **92** (Equation 4) <2000EJM751>. The polymer-supported 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **93** (R = H, CF₃, OMe) react similarly to give, after removal from the support, the N-4-alkylated derivatives **94** (R¹ = Me, CH₂Ar, CH₂CN, CH₂COAr) in 71–95% yields and 87% to >95% purity as judged by reverse-phase HPLC (Equation 5) <2003JCO73>. Synthesis of the benzo-1-thia-2,4-diazine 1,1-dioxide rings in precursors **93** is described in Section 9.05.9.2.3.



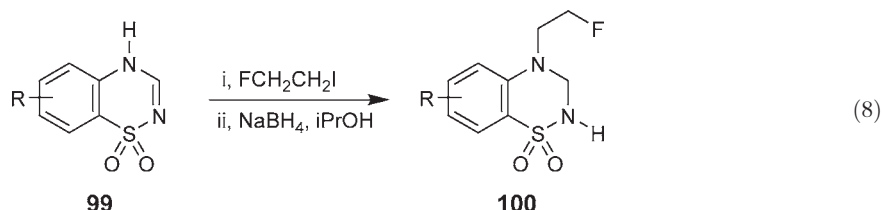
The pyrido analogs of 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides, that is, **95**, are alkylated at N-4 using an alkyl halide ($R = \text{Me, Et, Pr}^i$) with K_2CO_3 as base (Equation 6). The products, **96**, are useful as positive allosteric modulators of AMPA receptors <1998JME2946>.



Reaction of thieno[3,4-*e*] compound **79** ($X = Z = \text{CH, Y = S}$) with acetic acid and polyphosphoric acid resulted in two products: the C-3-methylated 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **97** (21% yield) and the thienopyridone **98** (33% yield). The latter is considered to be formed by initial acylation at N-4 of the benzo-1-thia-2,4-diazine ring followed by ring cleavage and intramolecular aldol cyclization (Equation 7) <2004JHC45>.



The 4-alkylated benzo-1-thia-2,4-diazine 1,1-dioxides **100** ($R = \text{H, Cl, NO}_2$), AMPA receptor modulators, were prepared from 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **99** by alkylation with 1-fluoro-2-iodoethane followed by reduction with NaBH_4 in Pr^iOH (Equation 8) <2005EPP1557412>.



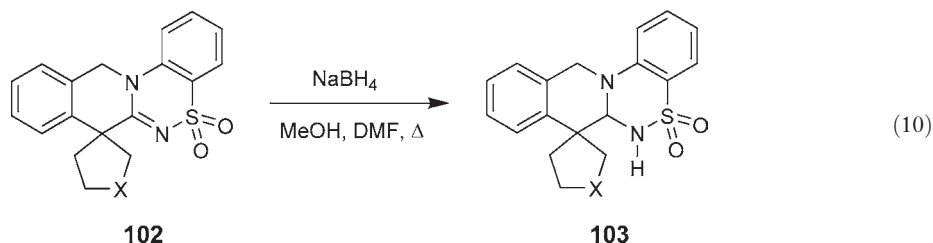
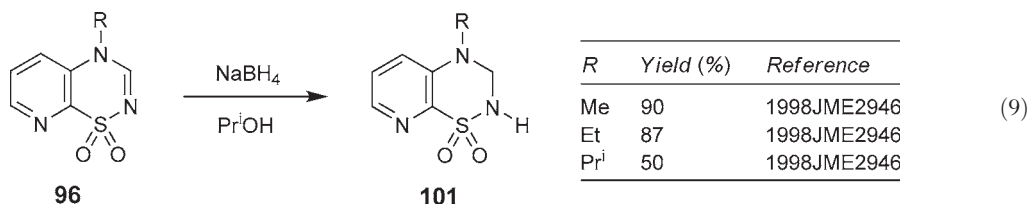
Various N-2- and N-4-monoalkylated, as well as N-2/N-4-dialkylated, 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides have been produced as potential aldose reductase inhibitors <1996KJM247>. Both N-2- and N-4-monoalkylated benzo-1-thia-2,4-diazines show activity as angiotensin antagonists <1998JCCS805>; 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides with Me or cyclopropyl groups at N-2 and the (2-methylbenzimidazole) group at C-4 are active against respiratory syncytial virus <2002USP2002099208, 2003WO2003053344>.

9.05.6.2.3 Electrophilic attack at carbon

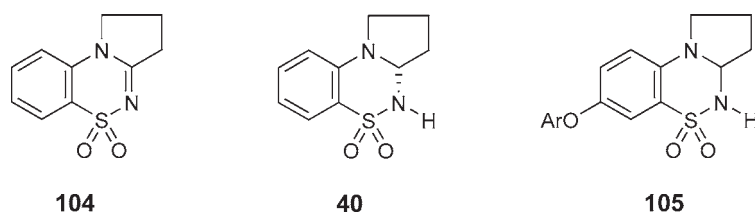
There are very few examples of ring carbon atoms in the 1-thia-2,4-diazine and benzo-1-thia-2,4-diazine systems reacting with electrophiles. As noted previously, a 2*H*-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxide has been shown to undergo substitution at C-6 when exposed to bromine in acetic acid at room temperature <1996CHEC-II(6)655, 1988S733>.

9.05.6.2.4 Reduction

The pyrido-4*H*-1-thia-2,4-diazine 1,1-dioxides **96** ($R = \text{Me, Et, Pr}^i$) are readily reduced, using sodium borohydride, as part of a route to the corresponding 4-alkylated derivatives **101** (Equation 9) <1998JME2946>. Similarly, the 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **102** ($X = \text{CH}_2, \text{CH}_2\text{O}$) produce **103** upon reduction (85% and 88% yield, respectively, for $X = \text{CH}_2$ and, CH_2O) (Equation 10) <2002CHE1130, 2000CHE1116>.



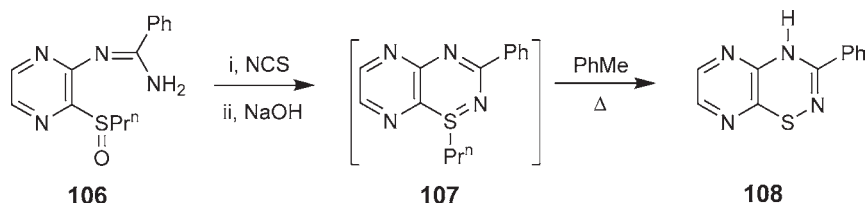
Pyrrolo-fused benzo-1-thia-2,4-diazine 1,1-dioxide **40** (see Section 9.05.3.1.5) is a selective AMPA receptor modulator, prepared in racemic form by reduction of the corresponding 4*H*-1-thia-2,4-diazine 1,1-dioxide **104**; the biologically significant *S*-enantiomer is isolated by chiral HPLC <1996EPP692484>. Asymmetric reduction of **104** to **40** using NaBH₄ or LiAlH₄ and a variety of chiral ligands gives ee's in the range 8–76% <1996BML3003>. Asymmetric catalytic hydrogenation of **104**, using [(*R*)-BINAPRuCl₂(*R,R*)-DPEN] (where DPEN = diphenylethylenediamine) at 60 °C, provides **40** in 97% yield with an ee of 87% <2003TA3431>. Related derivatives such as **105** have been produced in the search for more active AMPA receptor modulators <2004EPP1486503>.



9.05.6.3 1 λ^4 -Thia-2,4-diazines and Benzo-1 λ^4 -thia-2,4-diazines

9.05.6.3.1 Thermal and photochemical unimolecular reactions

Reaction of pyrazine-derived amidine **106** with *N*-chlorosuccinimide and then base is thought to generate the sulfilimine **107** (analogous to **26** in Section 9.05.2), which then undergoes elimination of propene to afford pyrazo-4*H*-1-thia-2,4-diazine **108** (Scheme 7) <2004JOC2551>. The intermediacy of **107** is supported by DFT calculations (see Section 9.05.2).



Scheme 7

9.05.6.3.2 Electrophilic attack at a ring heteroatom

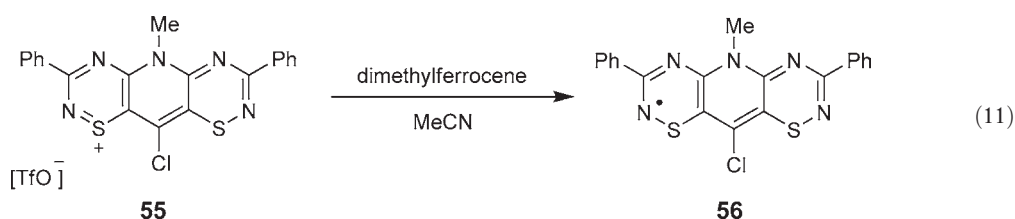
Acid-catalyzed hydrolysis of benzo-1 λ^4 -thia-2,4-diazines results in cleavage of the ring S–N bond and the isolation of an amidine sulfoxide product <1996CHEC-II(6)657>. The outcome of O- versus N-alkylation of the 1 λ^4 -thia-2,4-diazin-3(4*H*)-one 1-oxide system also has been detailed previously <1996CHEC-II(6)657>.

9.05.6.3.3 Electrophilic attack at carbon

Bromination of 1,5-diphenyl-1 λ^4 -thia-2,4-diazin-3(4*H*)-one 1-oxide occurs at the electron-rich C-6 position, whereas other electrophiles (e.g., NO₂⁺) react at the C-5 phenyl group <1996CHEC-II(6)657>.

9.05.6.3.4 Other reactions

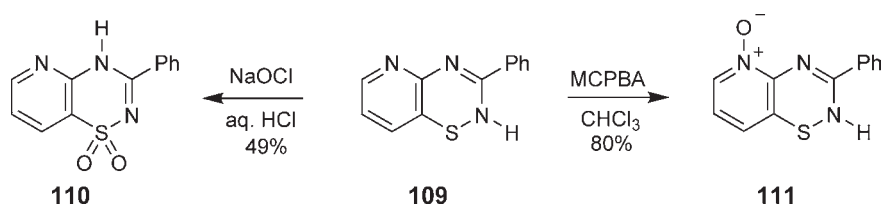
Reduction of the bis(1-thia-2,4-diazinyl) triflate salt **55** with dimethylferrocene in acetonitrile at room temperature affords the stable radical **56** (see Section 9.05.3.1.5 for the crystal structures of these compounds), which is of interest as a building block for radical-based conducting and magnetic materials (Equation 11) <2005CC1218>.



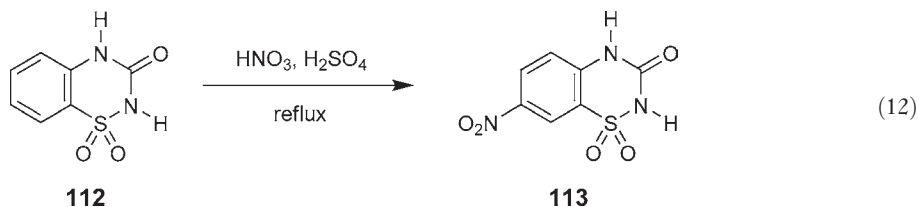
9.05.7 Reactivity of Substituents Attached to Ring Carbon Atoms

9.05.7.1 Unsubstituted Benzenoid Rings

Pyrido-1-thia-2,4-diazine **109** undergoes oxidation at different positions depending upon the oxidant used; NaOCl results in S-oxidation to afford the 1,1-dioxide **110**, whereas *m*-chloroperbenzoic acid (MCPBA) oxidation of **109** occurs at N-5 of the pyrido ring to produce *N*-oxide **111** (Scheme 8) <1998T13645>. Nitration of 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxide **112** affords the C-7 derivative **113** (Equation 12) <2002BMC1229>.

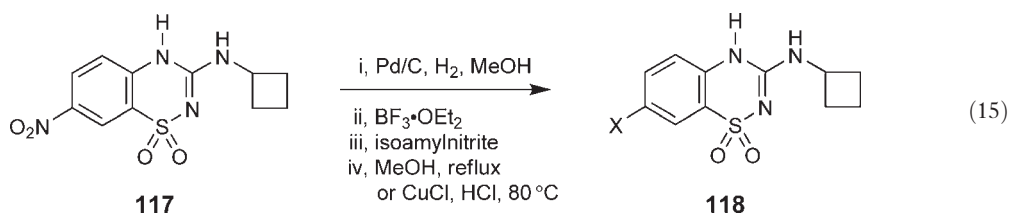
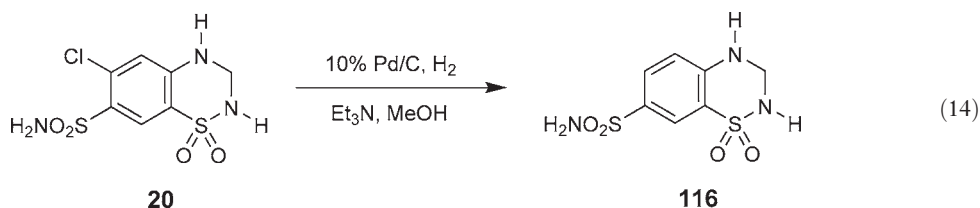
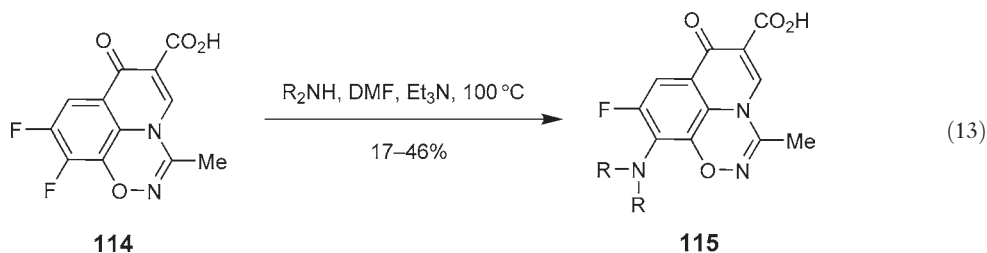


Scheme 8

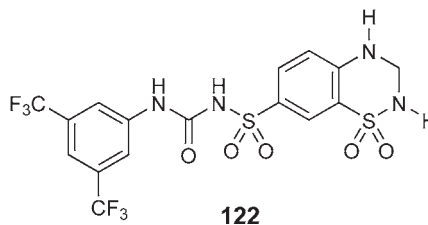
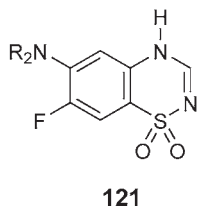
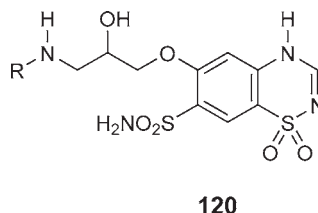
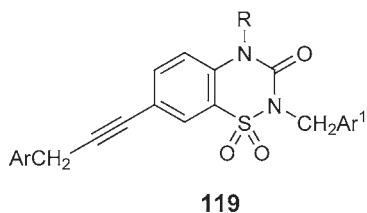


9.05.7.2 Substituted Benzenoid Rings

Treatment of benzo-1-oxa-2,4-diazine **114** with piperidine and piperazine derivatives causes displacement of the fluorine at C-8 resulting in 8-amino products **115** (Equation 13) <2000JHC297>. Hydrochlorothiazide (**20**; R = H) is reduced at C-6 by Pd on carbon to produce the dechlorinated derivative **116**, which is isolated in 85% yield after workup (Equation 14) <2002TL7247>. Reduction of the NO₂ group in 4*H*-benzo-1-oxa-2,4-diazine 1,1-dioxide **117** to the amine, followed by formation of the diazonium salt, allows for reduction to the parent benzo compound **118** (X = H) in 75% yield. Treatment with CuCl effects Sandmeyer-type chemistry to give **118** (X = Cl) in 74% yield (Equation 15) <2002BML2977>.

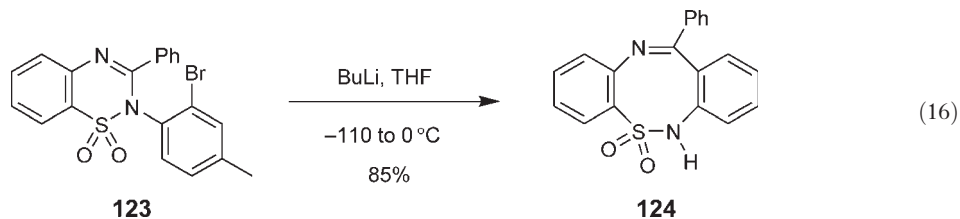


Palladium-catalyzed coupling of a 7-bromo-2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxide derivative with alkynes affords **119**, which have been claimed as metalloproteinase inhibitors <2003WO2003032999>. Alkylation of 6-hydroxy-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides with epichlorohydrin and then alkylamines results in the 6-[alkylamino(hydroxyl)propoxy] products **120** <1998IJH129>. Treatment of 6,7-difluoro derivatives of various 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides with amines produces the 6-amino-7-fluoro products **121** <1998RJO428>. The 7-sulfonamido-3,4-dihydro-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **122** has been synthesized as a potential imaging probe for diabetes <2003USP2003207823>.



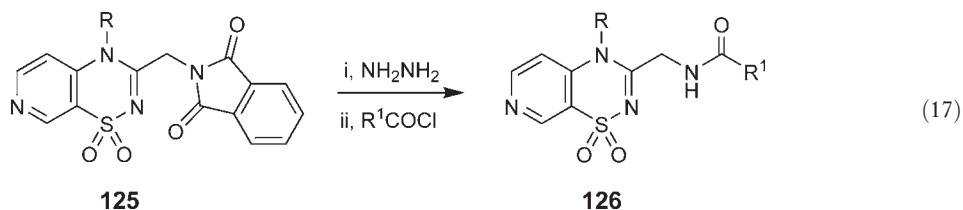
9.05.7.3 Aryl Groups

Reaction of 2-aryl-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **123** with BuLi results in the ring-expanded derivative **124** (Equation 16) <1996CHEC-II(6)658, 1983T2073>.

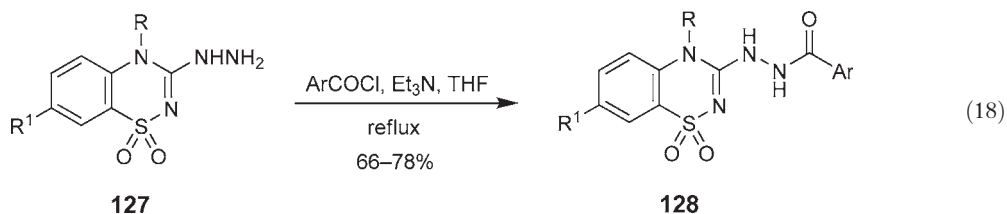


9.05.7.4 Amino and Other Nitrogen Groups

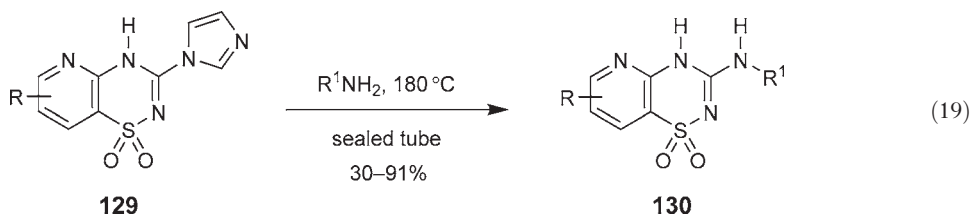
Phthalimidomethyl-substituted 4*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxide derivative **125** undergoes hydrazinolysis to produce the *C*-3-aminomethyl-substituted product, which is then acylated to yield the amido adducts **126** (R = H, Ph; R¹ = Ar, NHAr) as potential cholecystinin/gastric receptor ligands (Equation 17) <1997BSB781>. Similar acylation chemistry has been applied to the synthesis of related 5-(methanamides) of 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides (see Section 9.05.9.1.3) <2001CHE237>.



Acylation of 3-hydrazino-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **127** affords the adducts **128** (Equation 18), which were tested for their potential antibacterial properties <2006BMC650>. An alternative approach to compounds related to **128** is discussed in Section 9.05.7.7.

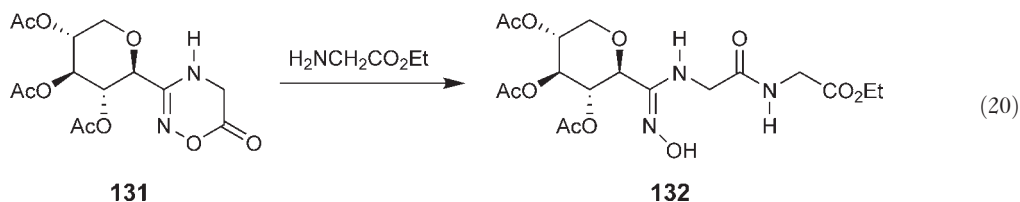


3-(1*H*-Imidazol-1-yl)-4*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides **129** (R = H, 7-Cl), the synthesis of relatives of which is considered in Section 9.05.9.2.3, undergo displacement reactions with amines to afford 3-alkylamino-4*H*-pyrido[2,3-*e*]-1-thia-2,4-diazine 1,1-dioxides **130** (R = H, 7-Cl; R¹ = alkyl, CH₂Ar) in (Equation 19) <2000JME1456>.

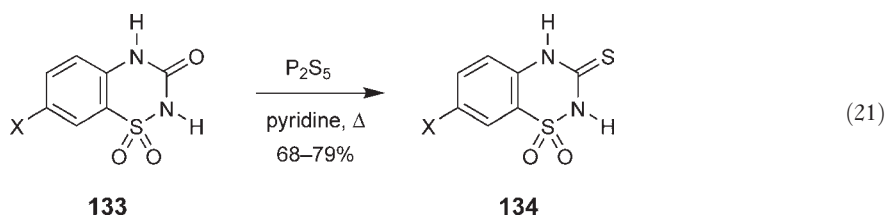


9.05.7.5 Hydroxy and Oxo Groups

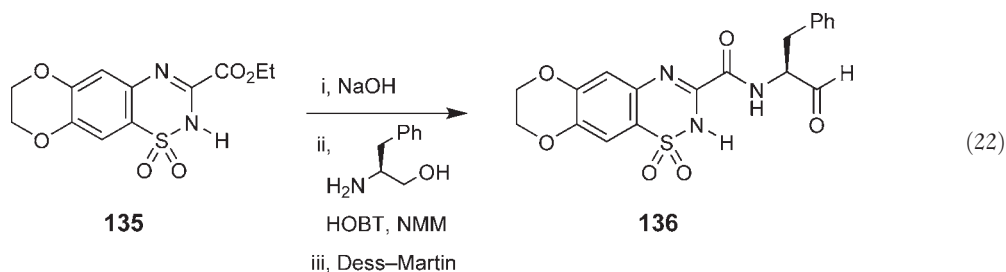
Pyranosyl 1-oxa-2,4-diazin-6(5*H*)-ones such as **131** have been isolated from reaction of the corresponding pyranosyl nitrile oxides with amino acid ethyl esters. Also, **131** has been proposed as an intermediate formed *en route* from the pyranosyl nitrile oxide to glycopeptide analogs. Once formed, **131** reacts with glycine ethyl ester at the C-6 carbonyl group to afford the ring-opened amidoxime **132** (Equation 20) <2004TL8913>. The synthesis of the precursor **131** is considered in Section 9.05.9.1.1.



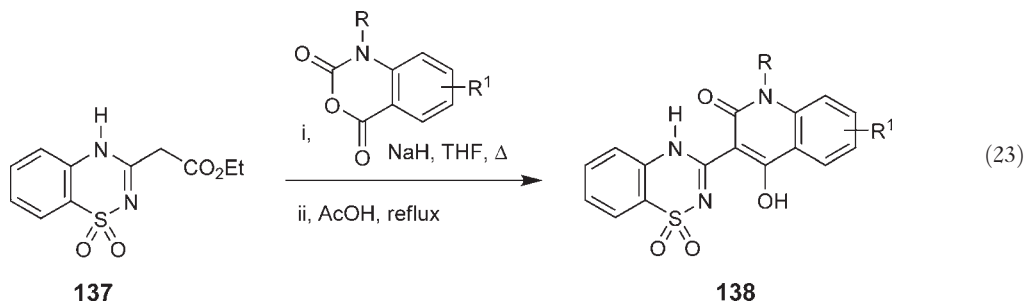
Reaction of 7-substituted 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **133** (X = F, Cl, Br, I) with phosphorus pentasulfide in pyridine produces the 3-thioxo compounds **134** (Equation 21) <2003JME3342>, which are used subsequently to make 3-alkylamino derivatives (see Section 9.05.7.6).



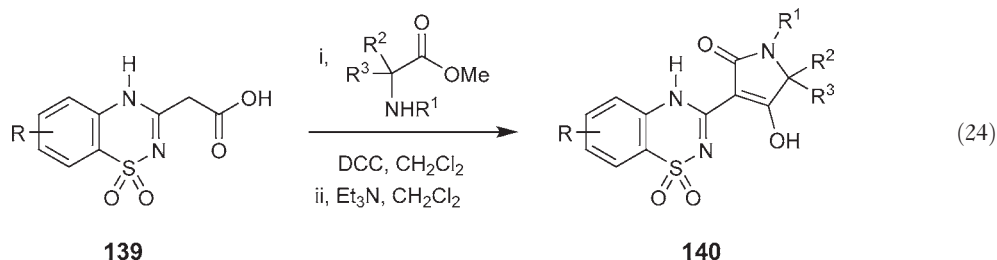
The C-3-carboxyethyl compound **135** undergoes a sequence of saponification, amide coupling, and finally selective oxidation to afford **136** in 96% overall yield (Equation 22) <2001JME3488>. The product was found to have activity as a calpain I protease inhibitor <1998WO9821186>. The synthesis of the thiadiazine ring in precursor **135** is considered in Section 9.05.9.1.3.



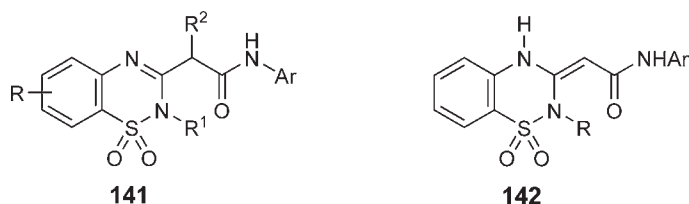
Ester **137** reacts with various benzoxazinediones in the presence of base to give, after boiling in AcOH, the C-3-substituted 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **138** (R = alkyl, CH₂Ar, etc.; R¹ = F, Cl, NO₂, etc.), which are potent inhibitors of hepatitis C virus RNA-dependent RNA polymerase (Equation 23) <2006JME971>. Compounds closely related to **138** have been claimed as novel anti-infectives <2004USP2004167123>.



Benzo-1-thia-2,4-diazine-substituted tetramic acids such as **139** result from a one-pot treatment of precursors **139** with amino acid methyl esters followed by base-induced cyclization (Equation 24) <2005OL5521>. The products **140**, and C-3-pyrimidinyl analogs <2003WO2003037262>, which are closely related to the 4-hydroxy-2(1*H*)-quinolones **138** (Equation 23), are also potent inhibitors of hepatitis C virus RNA-dependent RNA polymerase.

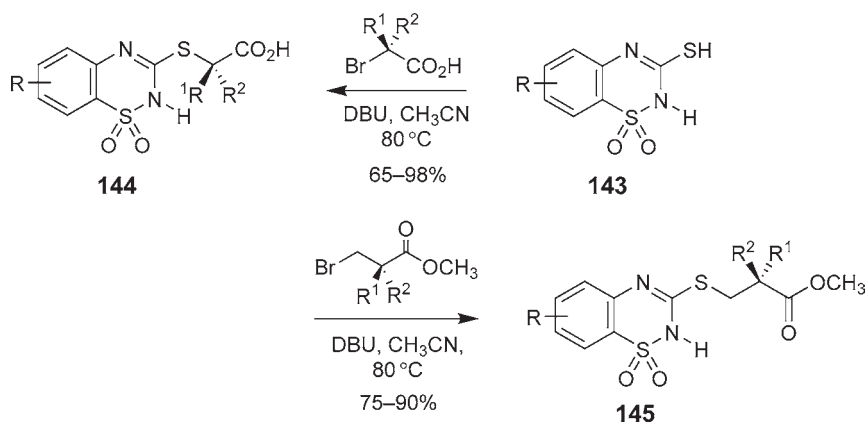


Amides **141** and **142**, of interest for their potential uses as dye intermediates for photographic applications, have been prepared from the corresponding carboxylic acid derivatives <2004JPP2004284979, 2006USP2006069252>.



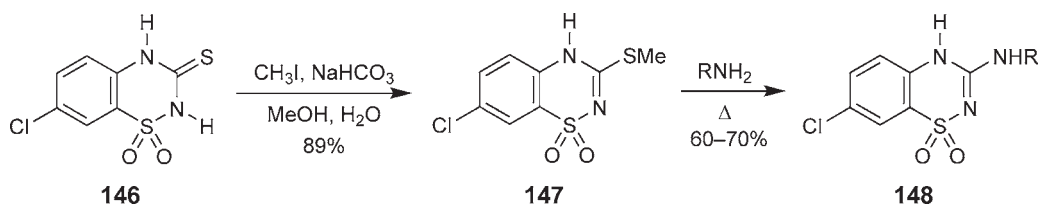
9.05.7.6 Sulfur-Linked Groups

Alkylation of 3-mercapto derivatives of 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides (**143**; R = H, CH₃, OCH₃, Cl) with optically pure α - and β -bromoesters (R¹ = H, CH₃; R² = H, CH₃) occurs exclusively at sulfur to provide **144** <1997TA2199> and **145** <1996TA2703>, respectively (Scheme 9). Both reactions occur mainly with Walden inversion and the ee of inverted products **144** was established by ¹H NMR using the chiral shift reagent Eu(hfc)₃ (Europium tris[3-(heptafluoropropylhydroxymethylene)-camphorate]) on the methyl esters of **144**. These compounds also display the SIDA phenomenon (i.e., self-induced diastereomeric anisochronism), which results in the enantiomers having different chemical shifts for the ester CH₃ and N-2 protons.



Scheme 9

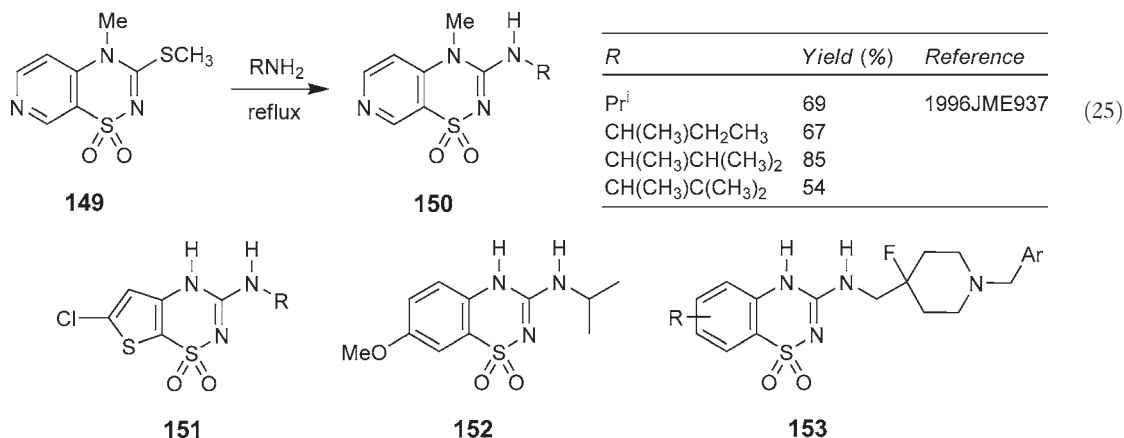
Reaction of 3-thioxo benzo-1-thia-2,4-diazine 1,1-dioxide **146** with CH₃I results in the S-alkylated 7-halo-3-methylsulfanyl-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **147**, which then serves as a substrate for displacement with amines to afford the 3-(alkylamino) derivatives **148** as potential K_{ATP} channel openers (Scheme 10) <2003JME3342, 2005JME4990>. Other halogenated substrates were studied and, notably, when bulky amines were employed in this



Scheme 10

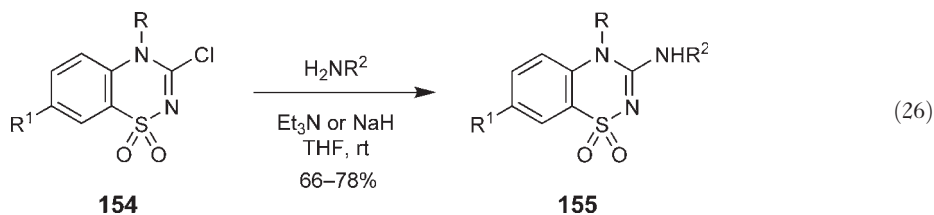
chemistry (e.g., Bu^tNH_2), displacement on **147** proved impractical and successful synthesis of the amine products required prior conversion of **147** to the sulfoxide analog <2003JME3342>. Alkylation of a 2-alkylated-3-thioxo benzo-1-thia-2,4-diazine 1,1-dioxide scaffold related to **146** with various alkyl halides and base yields the S-alkylated products in an automated flow-through synthesis of various heterocyclic thioethers <2004JCO584>.

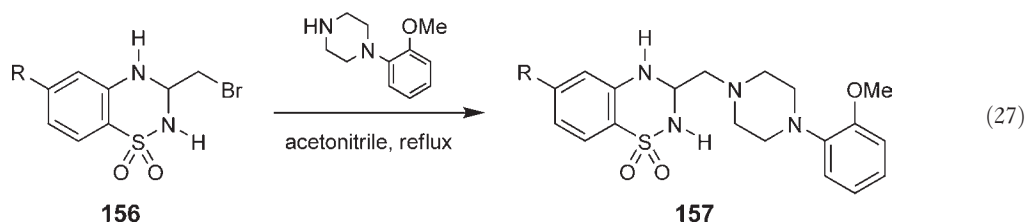
Refluxing 4-methyl-3-(methylthio)-4*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxide **149** with various amines affords the 3-(alkylamino) products **150** (Equation 25) (see Section 9.05.3.1.5 for X-ray structures of related compounds <1996JME937>, which have been claimed also as K_{ATP} channel openers <1997WO9726264>. The search for novel compounds with channel-opening activity has resulted in thieno[3,2-*e*] analogs **151** ($\text{R} = \text{alkyl}$) <1997WO9726265, 2000WO2000037474>, as well as 3-(isopropylamino)-7-methoxy 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **152** <2002DIA1896>. 3-(Alkylamino)-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **153** ($\text{R} = \text{H, Me}$) show activity as Cys-cysteine chemokine receptor-3 antagonists <2003WO2003087089, 2003WO2003091245>.



9.05.7.7 Halogen Atoms

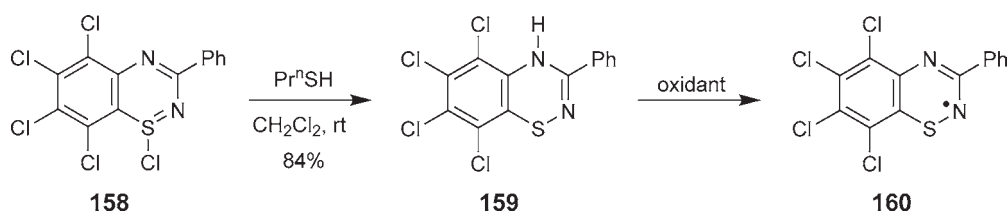
3-Chloro-4-substituted-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **154** ($\text{R} = \text{alkyl, Ph}$; $\text{R}^1 = \text{H, Cl}$) undergo substitution of the chloride in the presence of amines to provide the 3-(aminoalkyl) derivatives **155** ($\text{R}^2 = \text{COAr, NH}_2, \text{NHCOAr}$) (Equation 26) <2006BMC650>. Compounds related to **154** react similarly with aryl carboxamides in the presence of base to provide the C-3 *N*-amido analogs of **155** <2006BMC650>. The 3-(bromomethyl)-3,4-dihydro-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **156** ($\text{R} = \text{H, Me, Cl}$) react with piperidines to afford the substitution products **157** (Equation 27) as do the related 3-(bromomethyl)-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides <2005BML1185>. Similar displacements with piperazine nucleophiles on *N*-alkylated 2*H*-thieno[3,4-*e*]-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides have been reported <2000EJM751>.





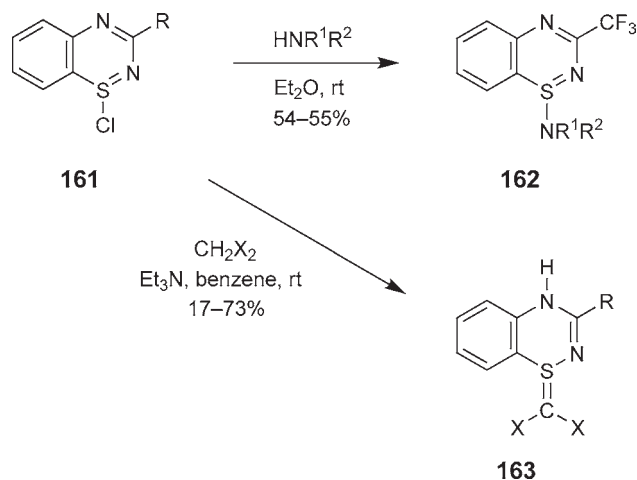
9.05.8 Reactivity of Substituents Attached to Ring Heteroatoms

The 1-chloro-benzo-1 λ^4 -thia-2,4-diazine **158** has been reduced to the benzo-4*H*-1-thia-2,4-diazine **159** using 1-propanethiol instead of the previously employed 4-chlorobenzenethiol (**Scheme 11**) <2004JOC7525>. Oxidation of **159**, for example with PbO₂ in the presence of K₂CO₃, or SO₂Cl₂ in pyridine, provided the stable radical **160** (see [Section 9.05.2](#) and [Section 9.05.3.1.5](#) for theoretical and X-ray analysis, respectively, on related compounds).



Scheme 11

1-Chloro-benzo-1 λ^4 -thia-2,4-diazine **161** (R = CF₃) affords 1-amino adducts **162** upon reaction with piperidine and cyclohexylamine (**Scheme 12**) <2002UKZ44>, while treatment of **161** (R = CCl₃, CF₃, Ph) with malonate-type nucleophiles produces ylides represented as **163** (X = CO₂R, CN) (**Scheme 12**) <2002UKZ80>.



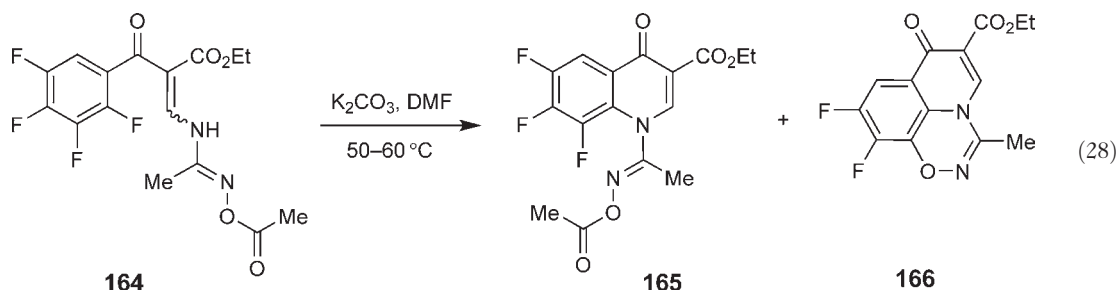
Scheme 12

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

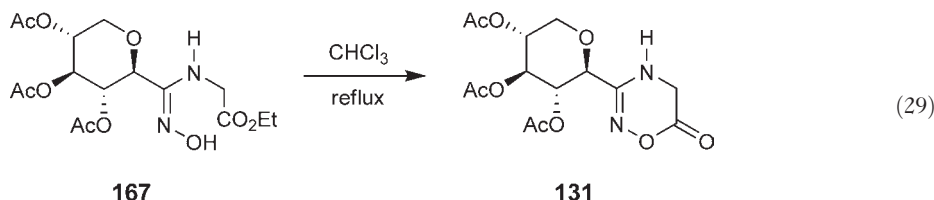
9.05.9.1 By Formation of One Bond

9.05.9.1.1 Between carbon and oxygen

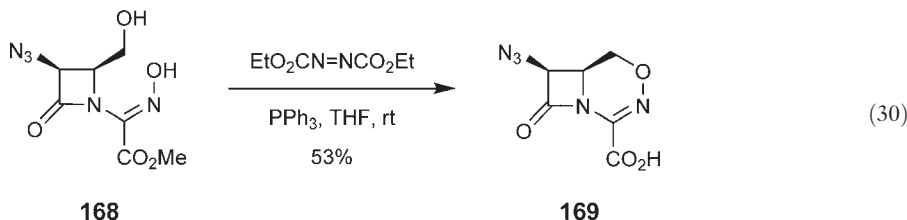
Reaction of **164** with K_2CO_3 induces nucleophilic aromatic substitution to yield, mainly, the pyridine **165** as well as the benzo-1-oxa-2,4-diazine **166** (~15% yield) (Equation 28) <2000JHC297>. Hydrolysis of the carboxy ester in **166** followed by exposure to various amines produces the C-8 amino derivatives, the syntheses of which are considered in Section 9.05.7.2.



Allowing amidoxime **167** to stir in $CHCl_3$ at room temperature for 2–3 days results in complete conversion to the 1-oxa-2,4-diazinone **131**, which is also formed when **167** is refluxed in the same solvent for 6 h (Equation 29) <2004TL8913>. Opening of the 1-oxa-2,4-diazine ring of **131** with amino acids is considered in Section 9.05.7.5.

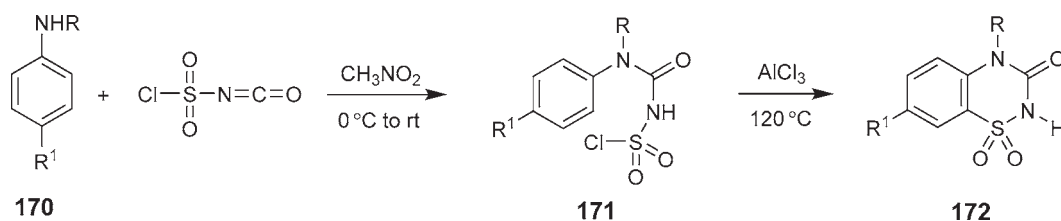


Application of typical Mitsunobu conditions to the oxime **168** provides 1-oxa-2,4-diazine-derived β -lactam **169** as the precursor to a novel cephalosporin-like antibacterial (Equation 30) <2003OBC2461>.



9.05.9.1.2 Between carbon and sulfur

Reacting 4-substituted aniline derivatives **170** with chlorosulfonyl isocyanate gives the N-acylated products **171** ($R = \text{Me}$, Et , Pr^i , Ph ; $R^1 = \text{H}$, Cl), which then cyclize to the 4-alkylated 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **172** in the presence of $AlCl_3$ (Scheme 13) <2006BMC650>. This reaction constitutes the use of [3+3] fragments and is

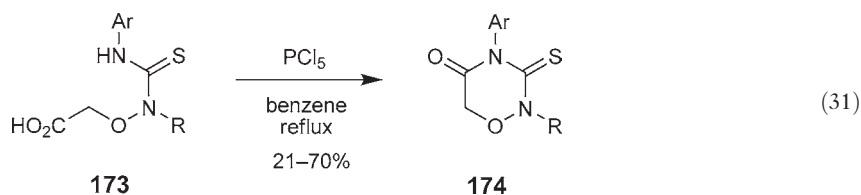


Scheme 13

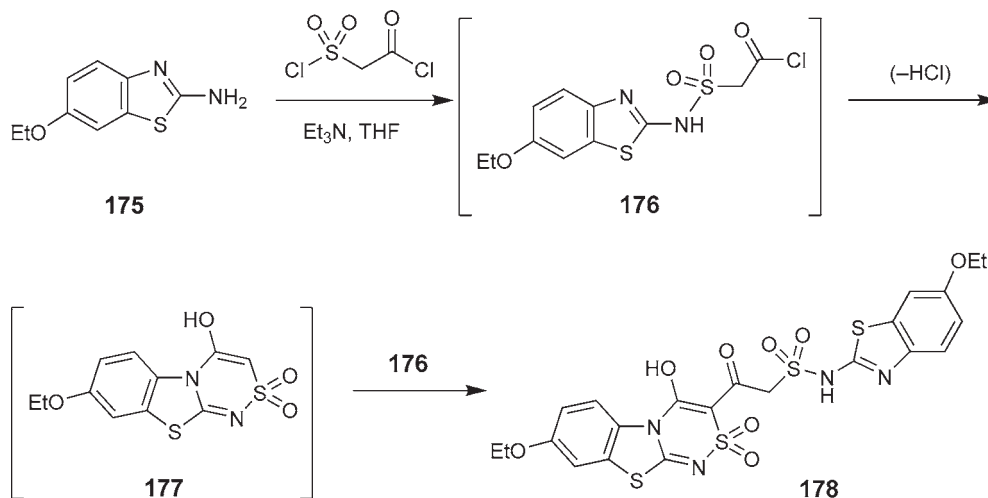
discussed further in that context in [Section 9.05.9.2.1](#). The products **172** serve as precursors to 3-(aminoalkyl) derivatives with potential antibacterial properties (see [Section 9.05.7.7](#)). The same chemistry affords 7-halo-2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides when 4-haloanilines are employed as starting materials [<2003JME3342>](#).

9.05.9.1.3 Between carbon and nitrogen

Thioureas **173** ($R = \text{Me, Et}$) react with PCl_5 in boiling benzene to furnish 1-oxa-2,4-diazines **174** (Equation 31), which were found to have serum high-density lipoprotein cholesterol-elevating activity [<2004JME681, 2002WO2002028845>](#).

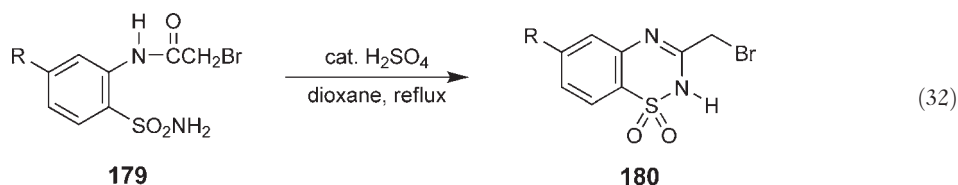


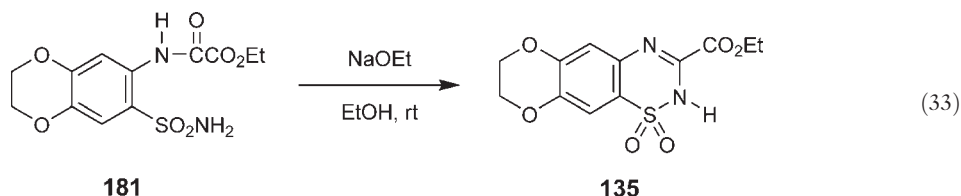
1-Thia-2,4-diazine **178**, of interest as a novel antagonist of the platelet adenosine diphosphate receptor (P2Y_{12}), is formed when 2 mol equiv of 6-ethoxy-2-aminobenzothiazole **175** is treated with 1 mol equiv of chlorosulfonylacetate in the presence of triethylamine ([Scheme 14](#)) [<2001BML1805>](#). It is thought that **175** reacts initially with the sulfonyl chloride to produce the sulfonamide derivative **176**, which then undergoes cyclization, with loss of HCl , to the 1-thia-2,4-diazine 1,1-dioxide ring system seen in **177**. Subsequent reaction of **177** with a second equivalent of acyl chloride **176** occurs at C-6 of the thiadiazine ring to produce **178** ([Scheme 14](#)).



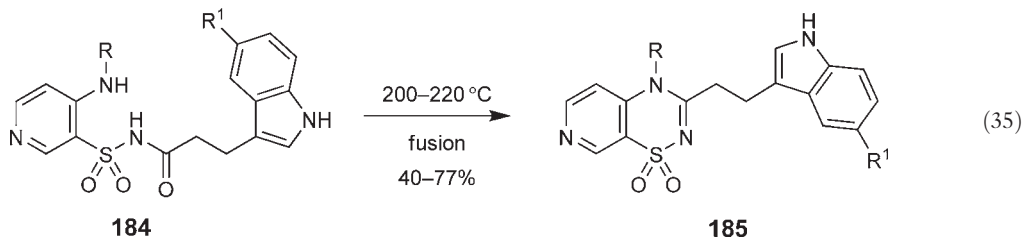
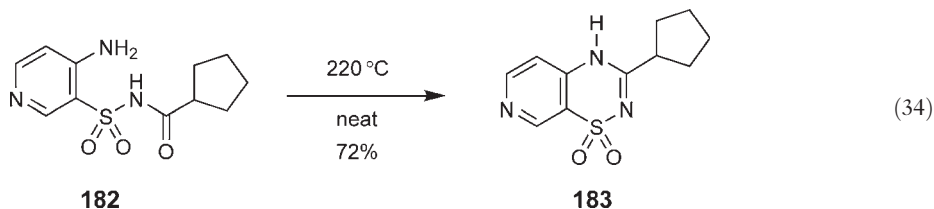
Scheme 14

Condensation reactions offer a convenient route to the benzo-1-thia-2,4-diazine 1,1-dioxide system. Thus, exposure of sulfonamide **179** to acid in boiling 1,4-dioxane results in formation of the 3-(bromomethyl) derivative **180** (Equation 32) [<2005BML1185>](#). The analogous compound **181** is cyclized readily in the presence of base to afford the 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **135** in 71% yield (Equation 33) [<2001JME3488>](#). Reaction of the carboethoxy group of **135** with amines is discussed in [Section 9.05.7.5](#).

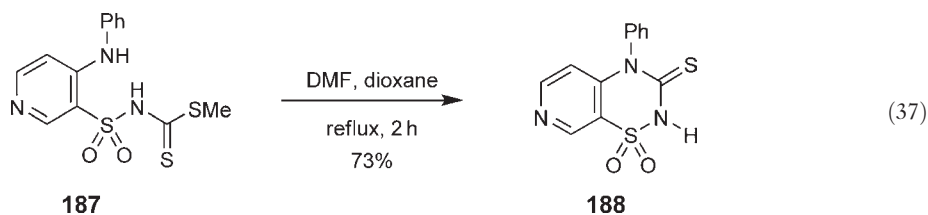
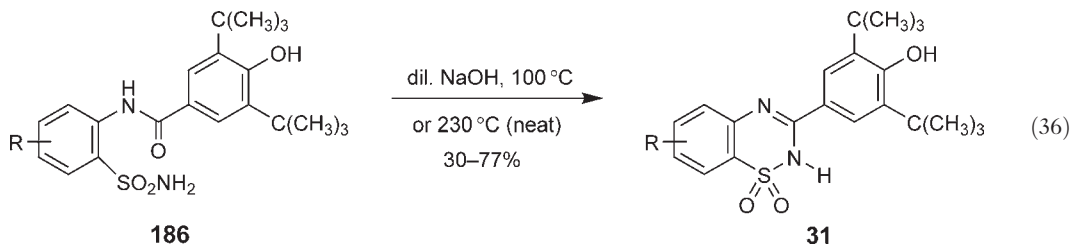


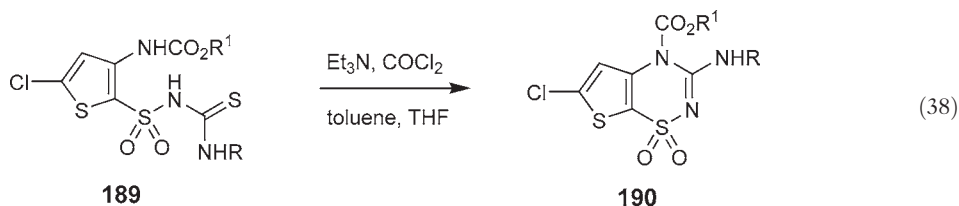


Heating substrates such as sulfonamide **182** without solvent also results in cyclization via condensation ($-\text{H}_2\text{O}$) to provide 3-cyclopentyl-4*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxide **183** (Equation 34) <1996JME937>. Similarly, heating sulfonamides **184** ($\text{R} = \text{Me}, \text{Ar}$; $\text{R}^1 = \text{H}, \text{Br}$) neat gives access to potential cholecystokinin/gastrin receptor ligands such as **185** (Equation 35) <1998EJP29>.

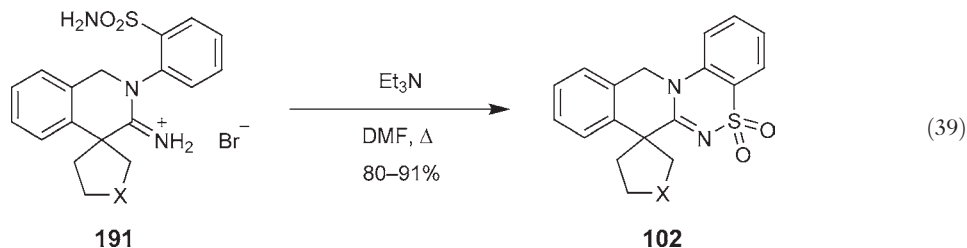


Sulfonamide **186** undergoes base-induced cyclization to yield the 5-aryl-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **31** ($\text{R} = \text{Cl}, \text{Br}, \text{Me}, \text{CF}_3, \text{OCH}_3, \text{NO}_2$) (Equation 36) <1996T12587>, which have useful antioxidant properties (see Section 9.05.3.1.1). The same products are produced if the precursors **186** are heated without solvent. Similar chemistry has been applied to the synthesis of 5-(methanoyl)-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides <2001CHE237, 2000CHE346>. An interesting application of the condensation method involves heating methyl (4-phenylaminopyridine-3-sulfonyl) carbodithionate **187** in refluxing DMF/1,4-dioxane, which gives access to the 3-thioxo derivative **188** (Equation 37) <1998EJP29>. Exposure of the thioureas **189** ($\text{R} = \text{alkyl}, \text{Ar}$; $\text{R}^1 = \text{Me}, \text{Et}$) to phosgene and triethylamine results in cyclization to afford the 3-(aminoalkyl)-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **190** (Equation 38) <2002JME4171>, derivatives of which are of interest as K_{ATP} channel modulators <1999WO9932494>.

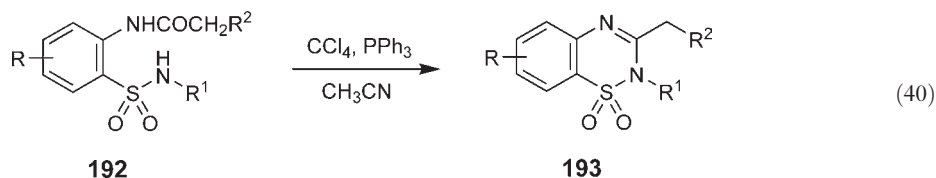




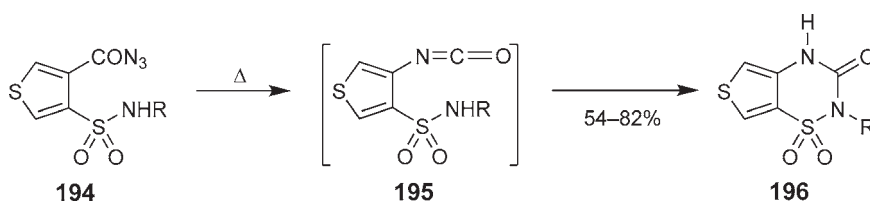
Heating the salts **191** ($X = \text{CH}_2, \text{CH}_2\text{O}$) in DMF in the presence of triethylamine effects cyclization to the 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **102** (Equation 39) <2002CHE1130, 2000CHE1116>. The reduction of the cyclization products **102** with NaBH_4 is addressed in Section 9.05.6.2.4.



Dehydration of sulfonamides **192** using CCl_4 and PPh_3 has been used as a route to 3-alkylated-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **193**, which are useful intermediates for photographic dyes (Equation 40) <2004JPP2004035415>.

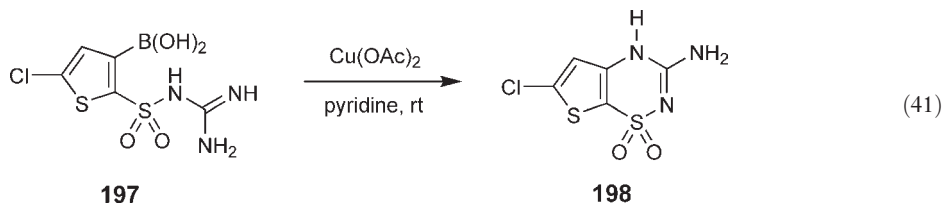


Construction of the 1-thia-2,4-diazine 1,1-dioxide system by employing the Curtius rearrangement is also a useful approach. Thermolysis of acyl azides **194** ($R = \text{Pr}^n, \text{Bn}, \text{Ar}$) in benzene, chloroform, or xylene solution leads to the intermediate isocyanate **195**, which cyclizes to give the isolated product **196** (Scheme 15) <2000EJM751, 1999BMC2811, 1997H(45)1767>. N-Alkylation of compounds related to **196** is addressed in Section 9.05.6.2.2.

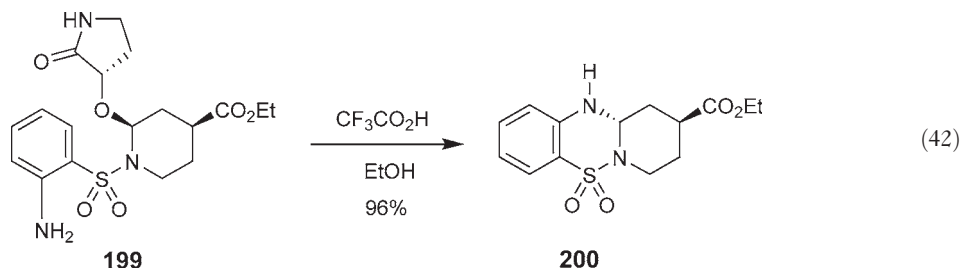


Scheme 15

Boronic acids such as **197** undergo cyclization upon treatment with copper(II) acetate to produce the 4*H*-thieno-1-thia-2,4-diazine 1,1-dioxide **198** (Equation 41) <2002WO2002050085>.



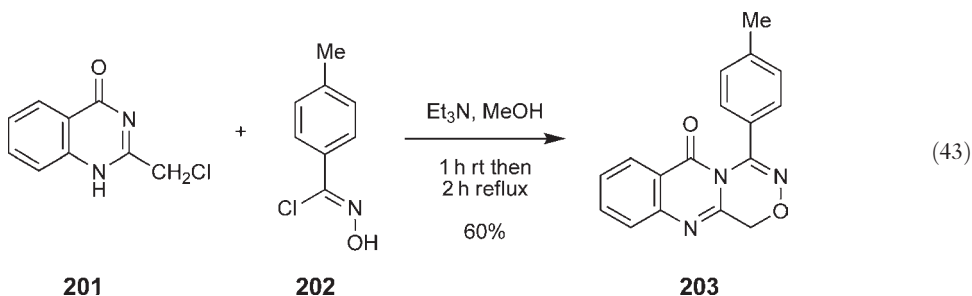
Exposing sulfonamide **199** to trifluoroacetic acid results in formation of the 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxide **200** in high yield, presumably via an iminium ion intermediate. The *trans:cis* ratio for **200** was found to be 2.5:1 (Equation 42) <2006JA2587>.



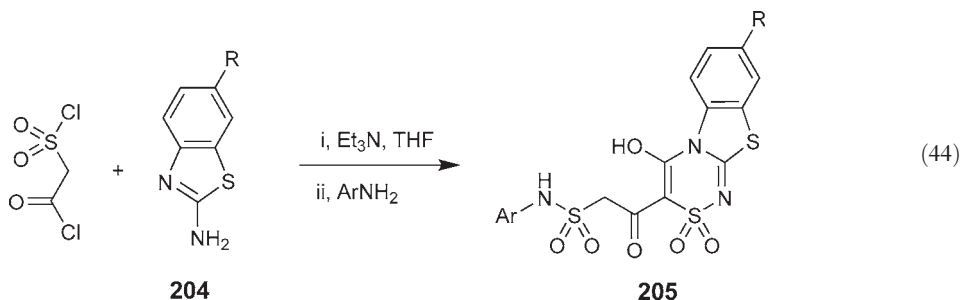
9.05.9.2 Formation of Two Bonds

9.05.9.2.1 [3+3] fragments

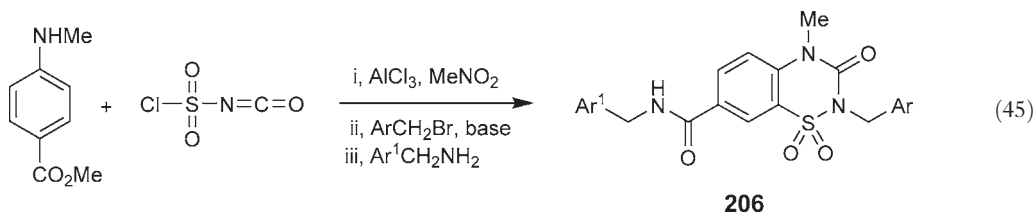
Reacting alkyl chloride **201** with *N*-hydroxyimidoyl chloride **202** in the presence of base results in the formation of the 1-oxa-2,4-diazine **203** (Equation 43) <2003IJC2119>.



When 2-aminobenzothiazoles **204** ($\text{R} = \text{H}, \text{OMe}, \text{OEt}, \text{F}, \text{Cl}, \text{NO}_2, \text{SO}_2\text{NH}_2$) are treated with 2 molar equiv of chlorosulfonylacetly chloride and base, the fused 4*H*-1-thia-2,4-diazine 1,1-dioxides **205** result, which are of interest as potential platelet ADP receptor inhibitors (Equation 44) <1999WO9939525>.

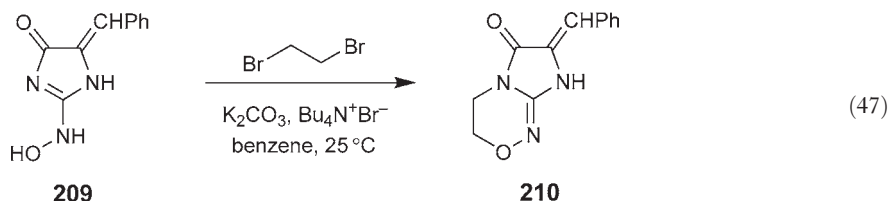
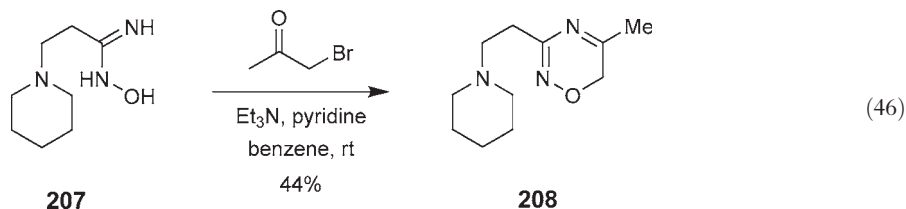


Treating methyl 4-methylaminobenzoate with *N*-chlorosulfonyl isocyanate in the presence of AlCl_3 leads to the benzo-1-thia-2,4-diazine 1,1-dioxide adduct, which after *N*-alkylation and reaction with benzylic amines affords the 3,4-dihydro-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **206** as matrix metalloproteinase inhibitors (Equation 45) <2002WO2002064578, 2002WO2002064080>.

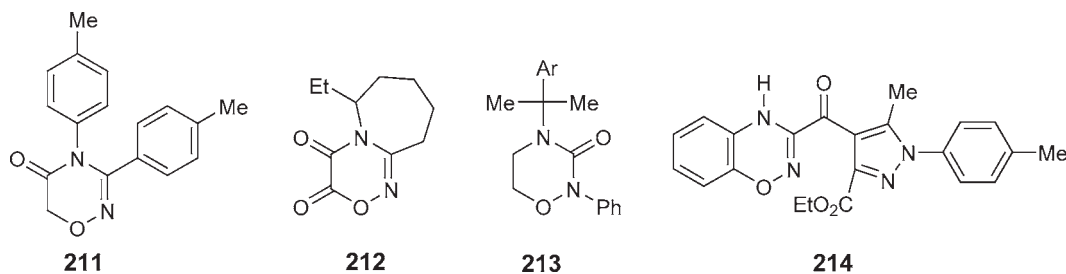


9.05.9.2.2 [4+2] fragments

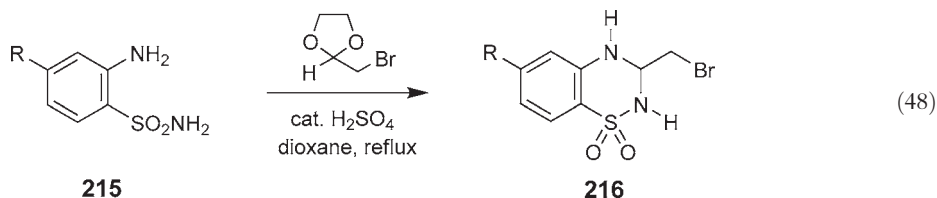
Reaction of amidoximes with α -haloketones or 1,2-dibromoalkanes in the presence of base leads to the 1-oxa-2,4-diazine system; β -aminopropionamidoxime **207** and α -bromoacetone yield **208** (Equation 46) <2004IZK56>, whereas hydantoin-derived amidoxime **209** and 1,2-dibromoethane give **210** (Equation 47) <2002EJC777>.



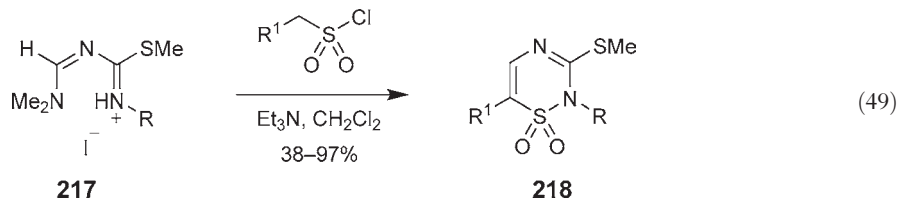
Similar chemistry leads to 3,4-disubstituted 1-oxa-2,4-diazine **211** <1999PS39>, the 1-oxo-2,4-diazolo[4,3-*a*]azepine **212** <1999WO9964426>, and the 2,4-disubstituted 3-oxo-1-oxa-2,4-diazine **213** <1998WO9806709>. The benzo-1-oxa-2,4-diazine **214** results from treating a pyrazolylhydroximoyl chloride with *o*-aminophenol <1997JCCS617>.



Acid-catalyzed reaction between 4-substituted 2-aminosulfonamides **215** ($R = \text{H, Me, Cl}$) and 2-bromomethyl-1,3-dioxolane provides access to 3-(bromomethyl)-benzo-1-thia-2,4-diazine 1,1-dioxide **216** (Equation 48). Related compounds have been used as precursors to 3-(*N*-alkyl) derivatives as potential ligands for α_1 and 5-HT_{1A} receptors (see Section 9.05.7.7) <2005BML1185>.

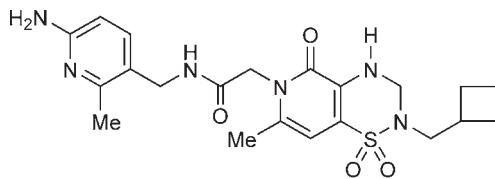
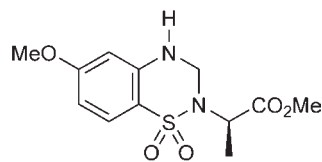


Cationic 2-methylthio-1,3-diazines **217** serve as convenient precursors to the 2*H*-1-thia-2,4-diazine 1,1-dioxides **218** ($R = \text{Me, Ph}$; $R^1 = \text{H, Me, Ph}$) through reaction with various sulfonyl chlorides (Equation 49) <2001JHC93, 2000S695>.



9.05.9.2.3 [5+1] fragments

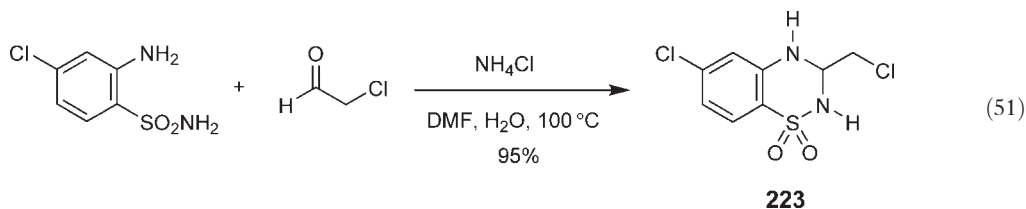
2-Amino sulfonamides are readily condensed with formaldehyde to produce 3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides; application affords **219**, which was studied as a potential thrombin inhibitor <2003BML1441> while benzo derivative **220** was used as a precursor to potentially selective inhibitors of tumor necrosis factor- α -converting enzyme <2003JME1811>.

**219****220**

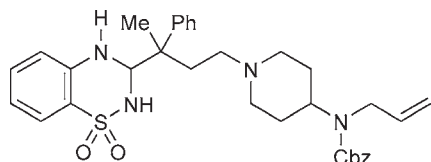
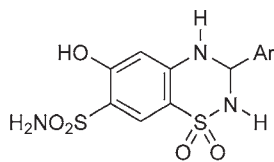
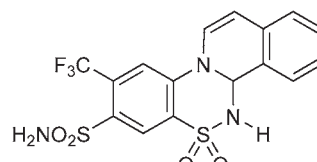
Acid-catalyzed reaction of *o*-aminobenzenesulfonamides such as **221** has been used in a combinatorial synthesis of new 3-alkyl-3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides (**222**; R = alkyl) as improved AMPA receptor modulators (Equation 50) <2002BMC1229>. Similar chemistry affords racemic 3-aryl-3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides, which are resolved into the individual enantiomers on Chiralcel[®] stationary phases <2002JME2355>. Acid-catalyzed condensation of enantiomerically pure aldehydes yields cyclothiazide (**61**) analogs that have been used to examine stereospecificity in the activity of such compounds at AMPA-type glutamate receptors <1996JA4550>.

**221****222**

Heating 2-amino-4-chlorobenzenesulfonamide with chloroacetaldehyde in the presence of NH₄Cl in aqueous DMF results in a high yield of the corresponding 3-chloromethyl-3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxide **223** (Equation 51) <2005BMC1393>.

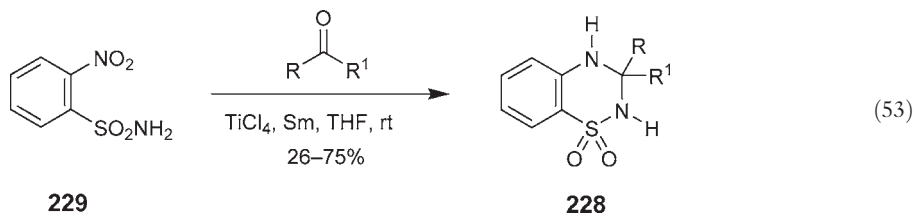
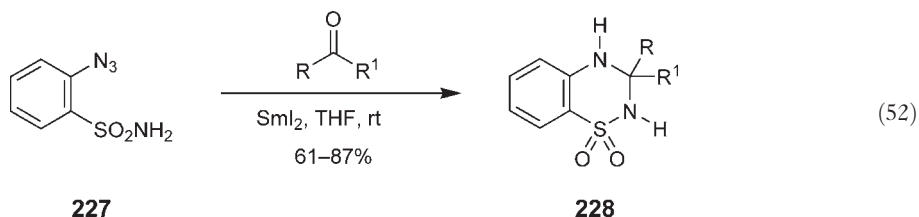
**223**

The 3-alkyl-3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxide **224** is produced by heating the appropriate aldehyde with 2-aminobenzenesulfonamide in *N*-methyl-2-pyrrolidone (NMP) at 100 °C <2001BML3103>. 3-Aryl-3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides **225** are the products of heating preformed bis(sulfonamides) with aryl aldehydes in dimethyl sulfoxide (DMSO) <2004OJC373>. The 3,4-annulated derivative **226** is the result of a reaction between the corresponding 2-aminobenzenesulfonamide and homophthalaldehyde <1996AP51>.

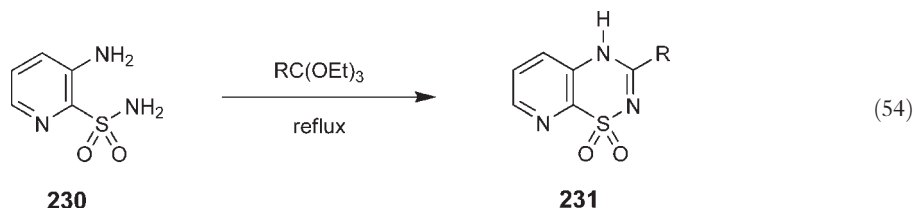
**224****225****226**

A variant of the condensation route to 3-mono- and disubstituted 3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides **228** involves the *in situ* reduction of *o*-azidobenzenesulfonamide **227** in the presence of an aldehyde or a ketone (R = H, alkyl, Ar; R¹ = alkyl, Ar) (Equation 52) <2003JIC637>. Replacing the azido precursor with 2-nitrobenzenesulfonamide

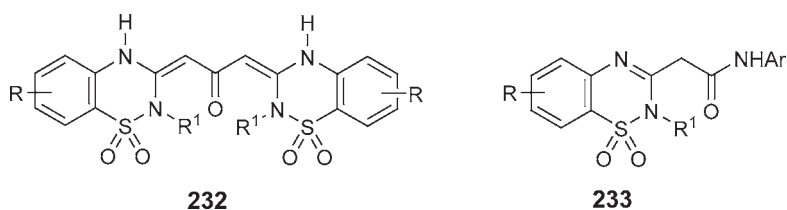
229 allows for a similar transformation using TiCl_4/Sm as the reductant (Equation 53) <2000CHJ786>. Employing SmI_2 gives similar results <2000JCM292>.



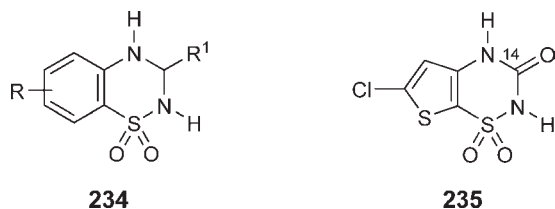
Orthoformates react with pyrido aminosulfonamides such as **230** to produce the corresponding 4*H*-1-thia-2,4-diazine 1,1-dioxides **231** ($\text{R} = \text{H, Me}$) (Equation 54) <1998JME2946, 2003S1603>. These compounds are reduced readily to the 3,4-dihydro-2*H*-pyrido-1-thia-2,4-diazine 1,1-dioxide derivatives (see Section 9.05.6.2.4), which are of significant interest as positive allosteric modulators of AMPA receptors <2001WO2001040210, 2004FRP2854634>.



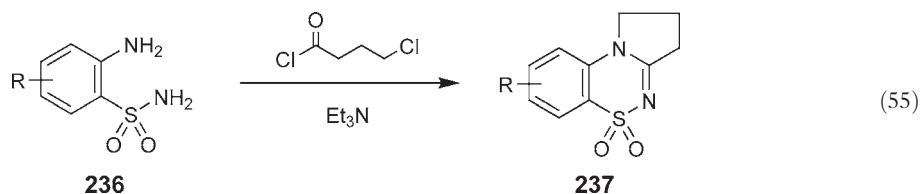
Treatment of substituted 2-aminobenzenesulfonamides with 1,1,1-triethoxyethane serves as a route to the precursor of **232** <2004JPP2004224957> and similar chemistry using more highly substituted orthoesters leads to 2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **233** <2005JPP2005289982>. Compounds such as **232** and **233** are of interest as yellow photographic dyes.



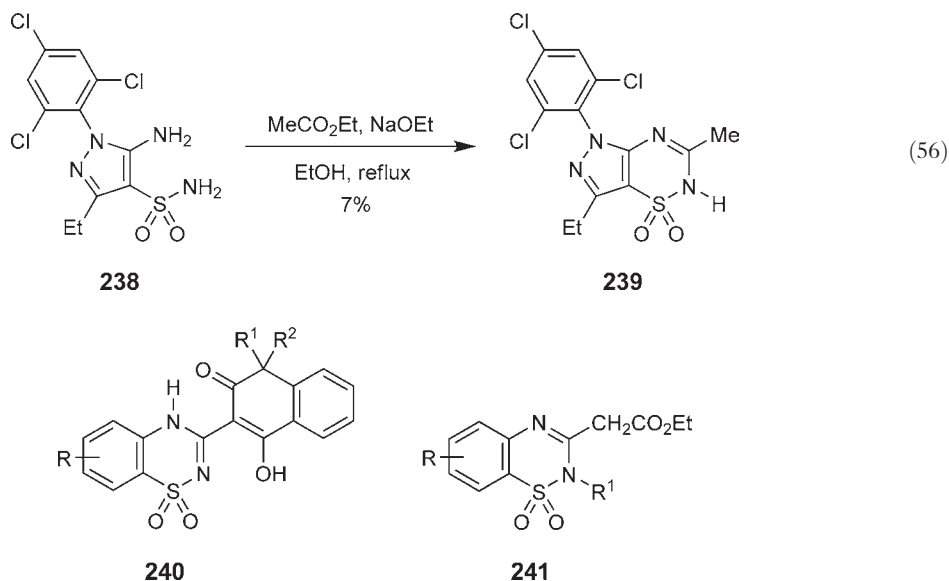
Acid chlorides react with 2-aminobenzenesulfonamides to produce 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides, which are then reduced to yield 3,4-dihydro-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides such as **234** ($\text{R} = \text{Cl, I, MeO, Ar, NH}_2, \text{SO}_2\text{NH}_2$; $\text{R}^1 = \text{cycloalkyl}$) as positive AMPA receptor modulators <1999WO9942456>. C-3-Labeled thieno[3,2-*e*]-1-thia-2,4-diazine 1,1-dioxide **235** has been made from the corresponding 3-aminothiophene-2-sulfonamide and ^{14}C -labeled ethyl chloroformate <2004JLR127>.



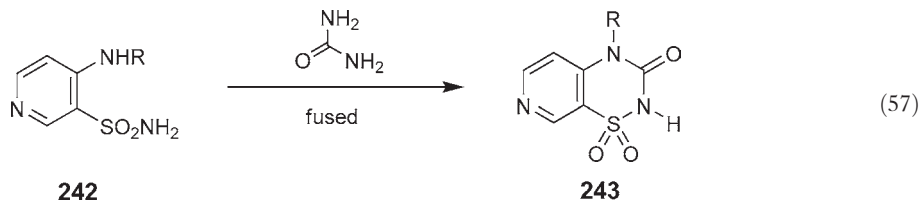
A variant on this reaction involves treating various 2-aminobenzenesulfonamides **236** with 4-chlorobutyl chloride in the presence of base, which gives the pyrrolo-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **237** (R = H, OAr), which are also of interest for their potential as AMPA receptor modulators (Equation 55) <1996EPP692484, 2002EPP1176148, 2003FRP2833955, 2003FRP2833956, 2004EPP1486502>. Pyrido analogs of **237** have been reported also using succinic anhydride in place of 4-chlorobutyl chloride <2005RUP2263667>.

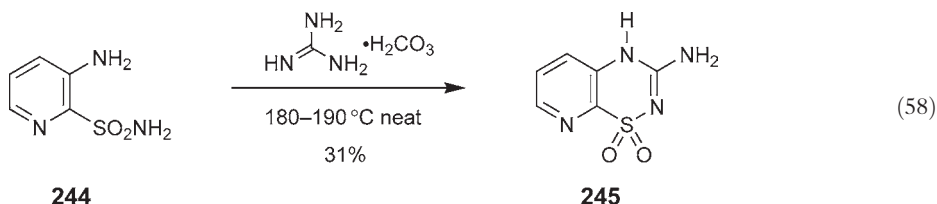


Esters also react with suitable sulfonamides to afford the 1-thia-2,4-diazine system; the pyrazole-derived sulfonamide **238** reacts with ethyl acetate in the presence of base to afford **239**, albeit in very low yield (Equation 56) <2004JME5894>. Using more highly functionalized esters with 2-aminobenzenesulfonamides leads to 3-substituted-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **240** (R = OCH₂CONH₂, NHSO₂Me; R¹, R² = alkyl), which are of significant interest as antiviral agents <2005USP2005107364>. A variation on this chemistry involves using imidates in place of esters, which has been employed in the synthesis of 2-N-alkylated-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **241** (R = H, alkyl; R¹ = alkyl, aryl) as yellow dyes <2003JPP2003286271, 2003JPP2003286272>.

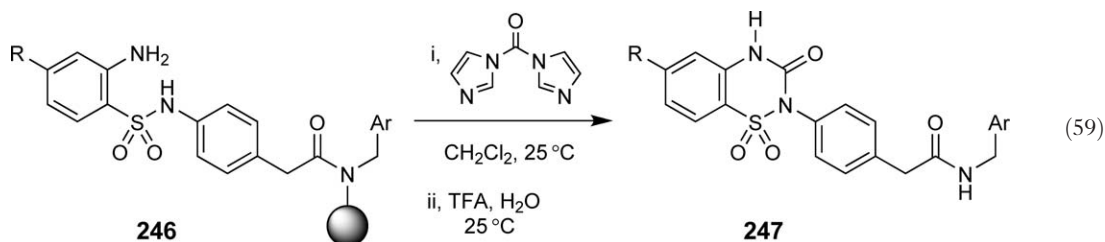


Fusing urea or guanidine with pyridine-derived aminosulfonamides gives access to 2*H*-pyrido-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides and 3-amino-4*H*-pyrido-1-thia-2,4-diazine 1,1-dioxides, respectively. Thus, 4-aminopyridine-3-sulfonamides **242** (R = H, Me) serve as precursors to 2*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **243** (Equation 57) <1999T5419>, which are used in the synthesis of 3-alkylamino-pyrido-1-thia-2,4-diazine 1,1-dioxides, the tautomeric identity of which has been addressed in Sections 9.05.3.1.1 and 9.05.3.1.2. 3-Aminopyridine-2-sulfonamide **244** is used to construct 3-amino-4*H*-pyrido[2,3-*e*]-1-thia-2,4-diazine 1,1-dioxide **245** (Equation 58) <2002JME90>.

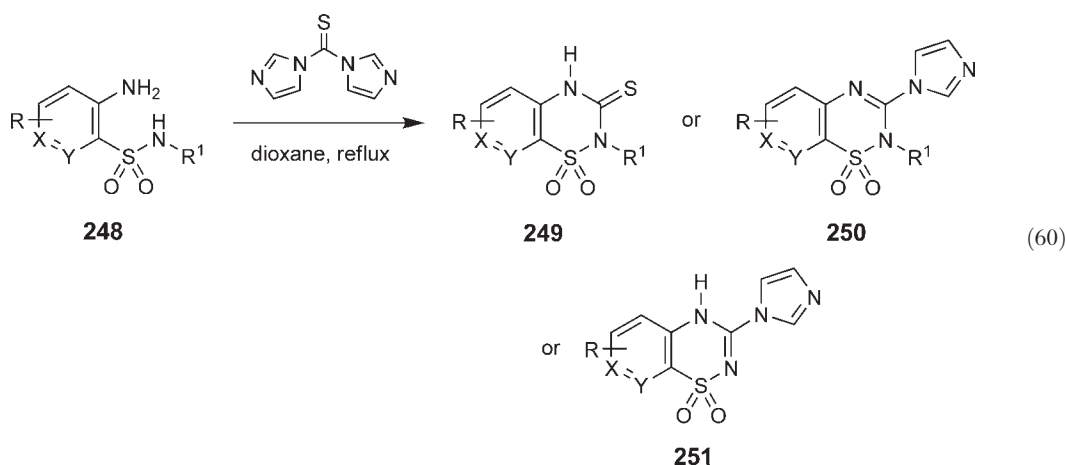




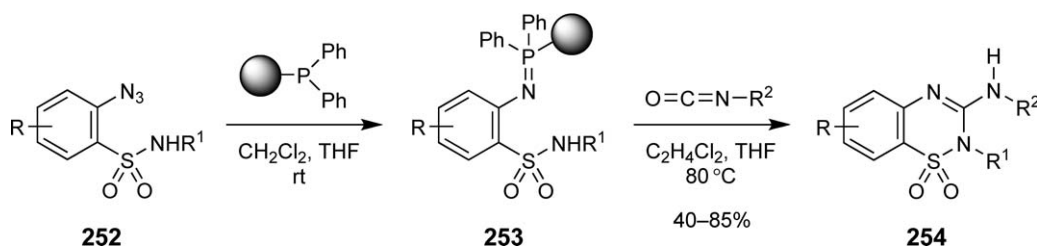
Carbonyldiimidazole has been used in a combinatorial synthesis of 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides; polymer-supported sulfonamides **246** react to produce the corresponding heterocycles, which are cleaved from the support using trifluoroacetic acid to give 85–96% of the *N*-2-aryl-2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides **247** (R = H, CF₃, OMe) in 91% to >95% purity, as determined by HPLC (Equation 59) <2003JCO73>. Further chemistry of the 1-thia-2,4-diazine heterocycle on the polymer support has been discussed in Section 9.05.6.2.2.



The reactions between various benzene- and pyridine-derived aminosulfonamides **248** and 1,1'-thiocarbonyldiimidazole have been studied in detail. For 2-amino-*N*-methylbenzenesulfonamide (X = Y = C, R = H, R¹ = Ph) and a 4-aminopyridine sulfonamide analog (X = N, Y = C, R = H, R¹ = Me), this leads to the *N*-2-substituted-2*H*-benzo-(pyrido)-1-thia-2,4-diazine-3(4*H*)-thio 1,1-dioxides **249** in 75% and 86% yield, respectively (Equation 60) <1998T4935>. When **248** features a substituent at the sulfonamide nitrogen (X = N; Y = C; R = H; R¹ = alkyl; Ph), the 2-*N*-substituted-3-(1*H*-imidazol-1-yl)-2*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides **250** are formed. Unsubstituted sulfonamides **248** (X = C or N; Y = C or N; R = H, Cl; R¹ = H) give the 3-(1*H*-imidazol-1-yl)-4*H*-pyrido[4,3-*e*]-1-thia-2,4-diazine 1,1-dioxides **251**. Displacement of the 3-imidazolyl substituent on **251** by amines serves as a convenient pathway to 3-alkylamino-4*H*-pyrido[2,3-*e*]-1-thia-2,4-diazine 1,1-dioxides (see Section 9.05.7.4) <2000JME1456>.

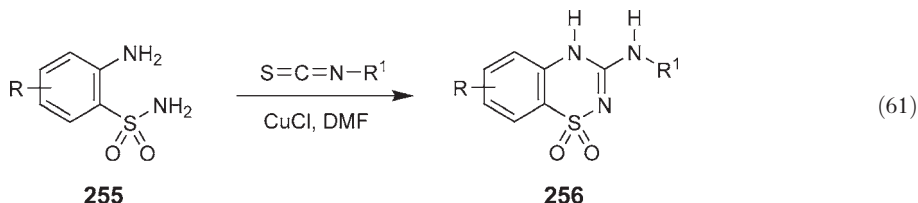


Aza-Wittig chemistry using polymer-supported triphenylphosphine provides access to 3-amino-2*H*-benzo-1-thia-2,4-diazine 1,1-dioxides. Various *N*-substituted 2-azidobenzenesulfonamides **252** react with the phosphine to produce the intermediate phosphinimine **253**, which undergoes aza-Wittig reaction with isocyanates and subsequent cyclization to produce the 3-amino-substituted products **254** (R = H, Me, OMe, Cl; R¹ = alkyl, R² = alkyl, aryl) (Scheme 16) <2005JOC10206>.

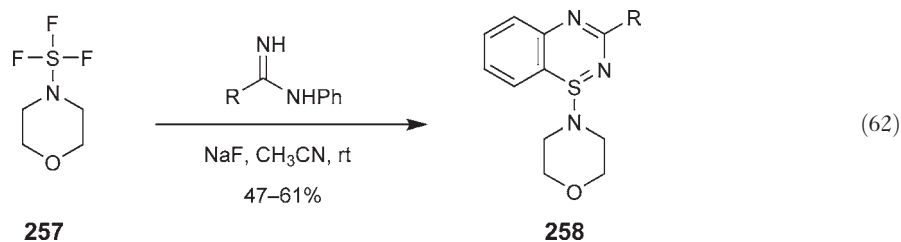


Scheme 16

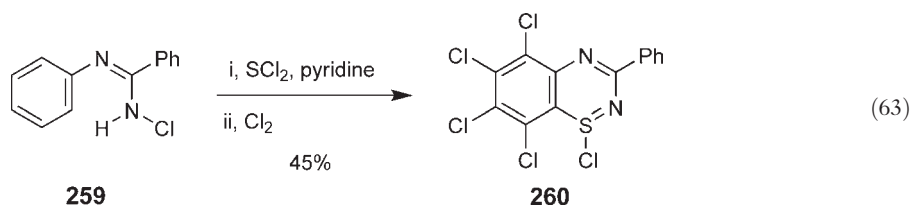
Reacting various 2-aminobenzenesulfonamides **255** with isothiocyanates provides the 3-(aminoalkyl)-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides **256** as potential potassium channel openers (Equation 61) <1997WO9749692>.



N-Phenylamidines react with morpholino sulfur trifluoride **257** to produce the benzo-1-*N*-morpholino-1*λ*⁴-thia-2,4-diazines **258** ($\text{R} = \text{CF}_3$, CCl_3 , Ph) (Equation 62) <2002UKZ44>. An alternative synthesis of compounds related to **258** has been discussed in Section 9.05.8.

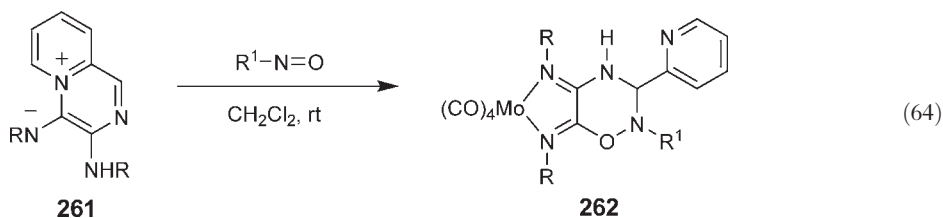


Treatment of chloramine **259** with sulfur dichloride, followed by addition of chlorine to the reaction mixture, results in the isolation of sulfiminyl chloride **260** (Equation 63) <2004JOC7525>, which was used without further purification for the synthesis of the corresponding perchlorinated benzo-4*H*-1-thia-2,4-diazine (see Section 9.05.8).

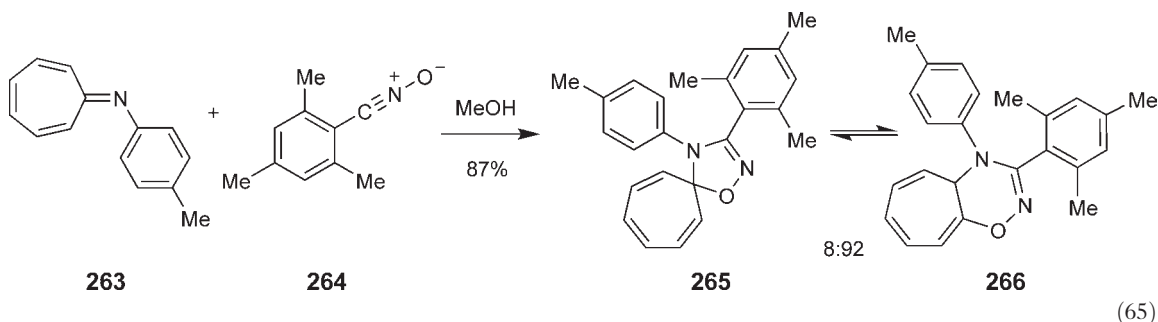


9.05.10 Ring Syntheses by Transformations of Another Ring

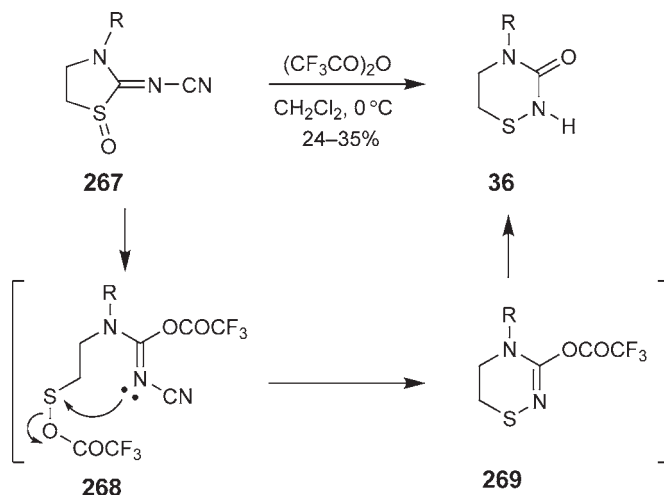
Cycloaddition of nitrosobenzenes to pyrido[1,2-*a*]pyrazines **261**, followed by Dimroth rearrangement of the initial cycloadduct, leads to 1-oxa-2,4-diazine intermediates that are trapped in solution using $(\text{CO})_4\text{Mo}$ (norbornadiene) to produce the complexes **262** ($\text{R} = \text{Aryl}$; $\text{R}^1 = \text{alkyl, Aryl}$) (Equation 64) <1999JHC627>.



When 8-azaheptafulvene **263** and nitrile oxides such as **264** are mixed in MeOH at room temperature, two interconverting heterocyclic products are formed: 1-oxa-2,4-diazaspiro[4,6]undeca-2,6,8,10-tetraene **265** and [4,9-*a*]-dihydrocyclohepta-1-oxa-2,4-diazine **266** (Equation 65) <2002EJO569>. The X-ray structure of a cycloadduct of **266** (i.e., **35**) has been described in Section 9.05.3.1.5 and the thermal decomposition of compounds related to **266** is considered in Section 9.05.6.1.1.



3-Alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxides **267** ($R = \text{CH}_2\text{Ar}$) undergo a ring-enlargement process in the presence of trifluoroacetic anhydride to afford 5,6-dihydro-2*H*-1-thia-2,4-diazin-3(4*H*)-ones **36** (Scheme 17). Initial reaction of **267** with the anhydride leads to open-chain imidate **268**, and the intramolecular displacement of triflate gives 4*H*-1-thia-2,4-diazine **269**, which finally hydrolyzes to the isolated product **36** <1997SL316>. The crystal structure of **36** ($R = \text{CH}_2\text{C}_6\text{H}_4\text{-}p\text{-OMe}$) is detailed in Section 9.05.3.1.5.



Scheme 17

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

9.05.11.1 1-Oxa-2,4-diazines

The 1-oxa-2,4-diazine system is formed by Mitsunobu reactions on β -lactam-derived oximes, and 1-oxa-2,4-diazine-5-ones result from ring closure of suitably substituted carboethoxy amidoximes (Section 9.05.9.1.1). Related 1-oxa-2,4-diazine-3-thioxo-4-ones are produced by dehydrative cyclization of thioureas (Section 9.05.9.1.3). Treating α -chloroimidates with *N*-hydroxyimidoyl chlorides serves as a route to annulated 1-oxa-2,4-diazines (Section 9.05.9.2.1), as does the reaction of amidoximes with α -haloketones or 1,2-dibromoalkanes (Section 9.05.9.2.2). Cycloaddition of pyrido[1,2-*a*]pyrazines with nitrosobenzenes, followed by Dimroth rearrangement of the cycloadduct, leads to 5,6-diimino derivatives of 1-oxa-2,4-diazines, which are trapped as Mo complexes (Section 9.05.10).

9.05.11.2 Benzo-1-oxa-2,4-diazines

Intramolecular displacement on an amidoxime aryl fluoride affords a tricyclic benzo-1-oxa-2,4-diazine system (Section 9.05.9.1.1), while reacting pyrazoylhydroximoyl chlorides with *o*-aminophenol gives 5-acyl-benzo-1-oxa-2,4-diazines (Section 9.05.9.2.2).

9.05.11.3 1-Thia-2,4-diazines

Ring expansion of 3-alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxides initiated by trifluoroacetic anhydride produces 5,6-dihydro-2*H*-1-thia-2,4-diazin-3(4*H*)ones (Section 9.05.10). 2-Aminobenzothiazoles react with chlorosulfonylacetyl chloride to form fused 4*H*-1-thia-2,4-diazine 1,1-dioxides (Section 9.05.9.2.1) and cationic 2-methylthio-1,3-diazines react with similar sulfonyl chlorides to produce 3-(methylthio)-2*H*-1-thia-2,4-diazines (Section 9.05.9.2.2). Condensing 2-amino sulfonamides with formaldehyde leads to the 3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxide system (Section 9.05.9.2.3).

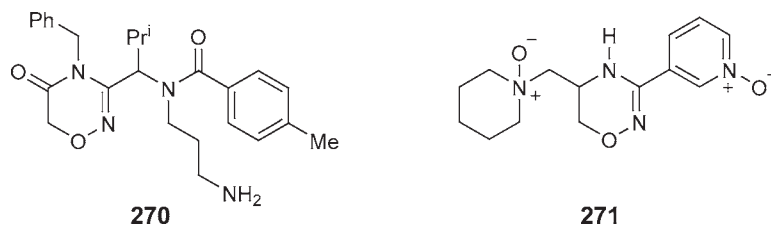
9.05.11.4 Benzo-1-thia-2,4-diazines

The most common method for the formation of benzo-1-thia-2,4-diazines involves reaction of 2-aminoarenesulfonamides with various one-carbon units (Section 9.05.9.2.3). Treatment of *N*-alkylated anilines with chlorosulfonyl isocyanate, followed by addition of a Lewis acid, results in 2*H*-benzo-1-thia-2,4-diazine-3(4*H*)-one 1,1-dioxides (Section 9.05.9.1.2) as does use of the Curtius rearrangement; isocyanates produced at C-2 of the aryl ring that are then trapped by a sulfonamide function at C-1 (Section 9.05.9.1.3). Variants of intramolecular condensation reactions of 2-*N*-acyl-2-aminobenzenesulfonamides serve as a general route to 3-acyl or 3-alkyl 2*H*- and 4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides (Section 9.05.9.1.3).

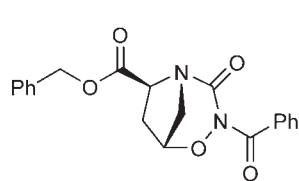
The *N*-morpholino-benzo-1- λ^4 -thia-2,4-diazine system results from reacting *N*-phenylamidines with morpholino sulfur trioxide and *N*-chloroimidates react with SCl_2 to give 1-chloro-benzo-1 λ^4 -thia-2,4-diazines (Section 9.05.9.2.3).

9.05.12 Important Compounds and Applications

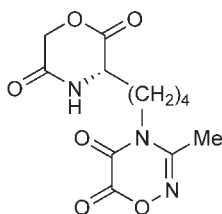
The 3,4-dialkylated-4*H*-1-oxa-2,4-diazine-5(6*H*)-one ring features in a series of compounds such as **270** designed as inhibitors of kinesin spindle protein (KSP) that have potential in the treatment of proliferative diseases such as cancer, hyperplasias, restenosis, and cardiac hypertrophy <2004WO2004091547>. 3,5-Disubstituted-5,6-dihydro-4*H*-1-oxa-2,4-diazines such as **271** have been prepared for their use in the treatment of vascular diseases <2003WO2003057664>.



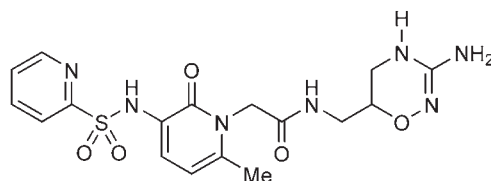
Bicyclic 1-oxa-2,4-diazine **272**, in combination with other known antibacterials, has proven effective against bacteria such as *Escherichia coli* and *Staphylococcus aureus* <2003FRP2835186, 2002WO2002010172>. 3,4-Dialkylated-4*H*-1-oxa-2,4-diazine-5,6-diones such as **273** are found to be useful as inhibitors of nitric oxide synthase <2000WO2000063195, 1999WO9905131>. 5-Alkylated-3-amino-4*H*-1-oxa-2,4-diazines **274** show promise as protease inhibitors capable of inhibiting the formation of blood platelet aggregates <2002WO2002006248, 2000WO2000073302>.



272

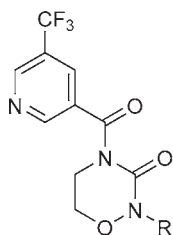


273

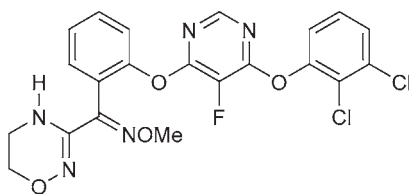


274

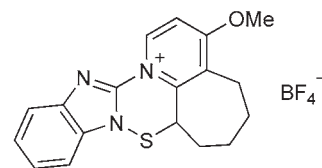
Pyridinecarboxamides **275** ($R = \text{alkyl}$) have been prepared as pesticides and found to be effective in a black bean aphid assay [<2003WO2003097604>](#). A series of 3-substituted-5,6-dihydro-4*H*-1-oxa-2,4-diazines **276** have been shown to have useful fungicidal properties [<1999DEP19737723, 1996DEP19510297>](#). Polycyclic sulfenamides such as **277** have interesting properties as proton pump inhibitors [<1996CPB215, 2004WO2004077367, 1997JPP09020784>](#).



275

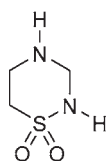


276

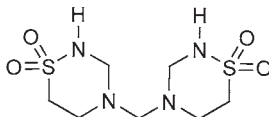


277

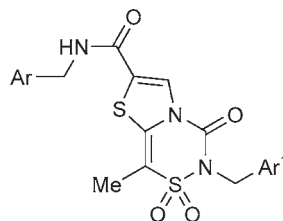
Taurultam **278** is known to have significant antibacterial and antifungal properties and the related bis[4-(1,1-dioxo-3,4,5,6-tetrahydro-2*H*-1-thia-2,4-diazinyl)]methane (Taurolidine, **279**) is an important antibacterial with uses, for example, in the treatment of various skin disorders [<2001EPP1103251>](#). Fused bicyclic derivatives of 3-oxo-1-thia-2,4-diazine 1,1-dioxides **280** have potential in treating arthritis and inflammation through their action as inhibitors of metalloproteinases [<2004WO2004014923>](#).



278

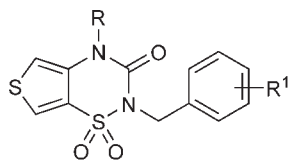


279

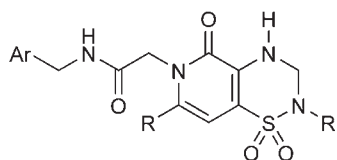


280

Thieno[3,4-*c*]-1-thia-2,4-diazine 1,1-dioxides **281** ($R = \text{alkyl}$; $R^1 = \text{H, Cl, F}$) are inhibitors of HIV-1 reverse transcriptase and have significant anti-HIV-1 activity [<1998AAC618>](#). Pyridone-fused 3,4-dihydro-2*H*-1-thia-2,4-diazine 1,1-dioxides **282** ($R = \text{H, alkyl, cycloalkyl}$; $R^1 = \text{H, Ar}$) are useful for inhibiting thrombin and thrombotic occlusions [<2000WO2000018762>](#).

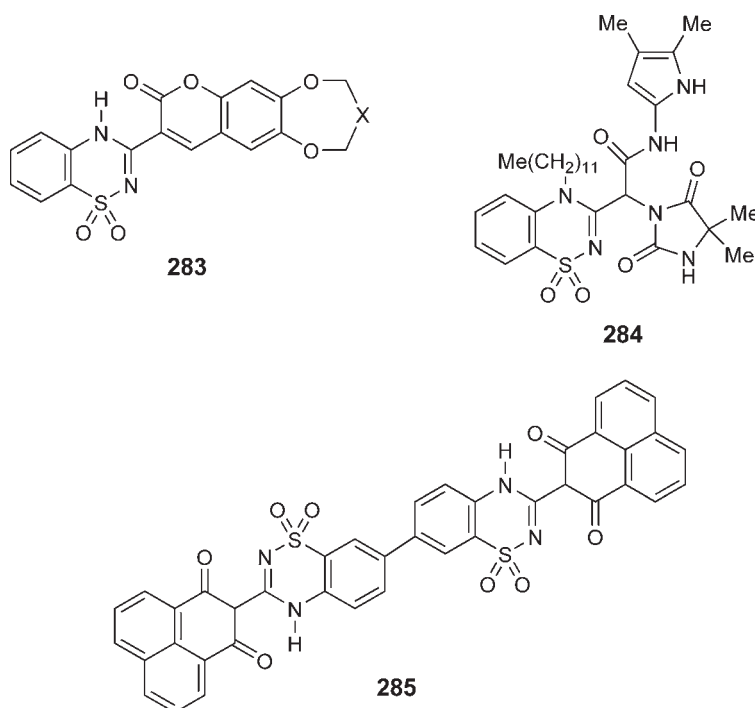


281



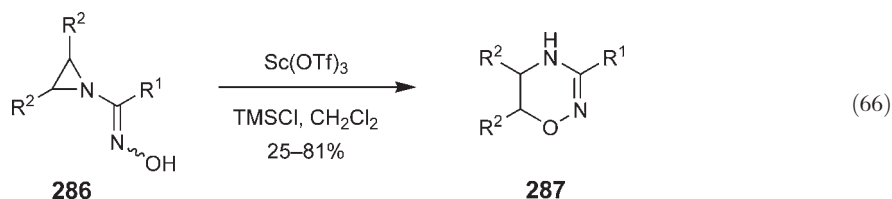
282

Coumarin-linked benzo-4*H*-1-thia-2,4-diazine 1,1-dioxides **283**, where X is a cryptand or crown ether, have been studied for their potential in measuring metal cation concentrations [<1998EPP861843>](#). 3,4-Dialkylated benzo-4*H*-1-thia-2,4-diazine 1,1-dioxides **284** are useful as couplers in the formation of photographic dyes [<2002JPP2002318441>](#). Bis(3-substituted-4*H*-benzo-1-thia-2,4-diazine 1,1-dioxides) such as **285** are useful as materials in the recording layers of optical disks that use lasers in the 300–900 nm range [<2006JPP2006076209>](#).

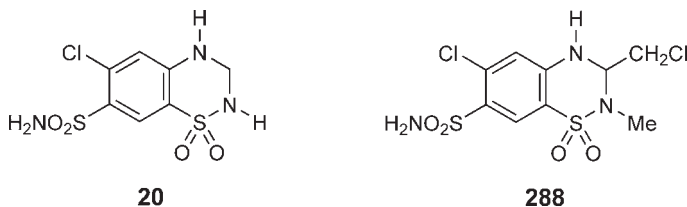


9.05.13 Further Developments

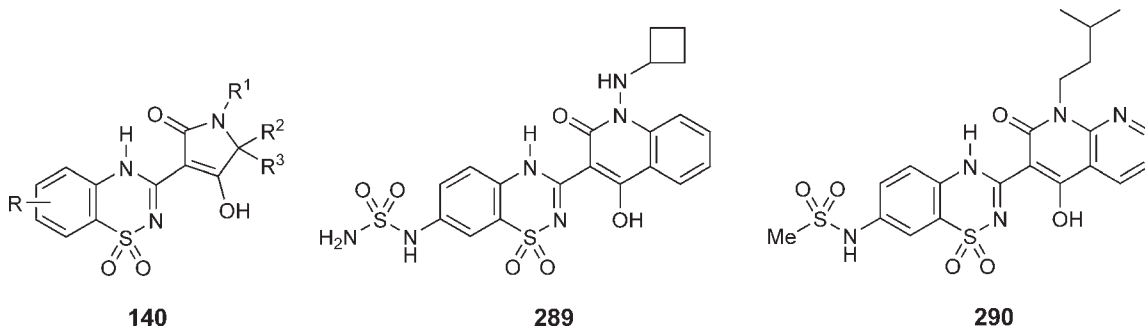
Aziridinybenzaldoximes **286** undergo Lewis acid promoted cyclization with scandium triflate in the presence of TMSCl to produce 5,6-dihydro-4*H*-1-oxa-2,4-diazines **287** (Equation 66) <2006TL9029>. The method was further developed to produce a one-pot synthesis of **287** beginning with the aldoxime precursors, i.e., the appropriate aziridines and chlorooximes.



A series of reports have detailed the X-ray crystal structure of a number of hydrochlorothiazide **20** solvates including those with DMF <2006AXE1730>, DMSO <2006AXE2288>, dimethylacetamide <2006AXE2926>, and *N*-methyl-2-pyrrolidone <2006AXE5169>. The different potential intermolecular hydrogen bonding alignments of **20** have been investigated also by X-ray diffraction <2007CGD705>. The solid state structure of methylclothiazide **288** reveals three types of intermolecular N–H to O–H bonds that generate an overall sheet structure in the solid state <2006AXE3009>.



An asymmetric, polymer-supported route to benzo-1-thia-2,4-diazine-substituted tetramic acids such as **140** has allowed for their evaluation as inhibitors of the hepatitis C virus RNA-dependent RNA polymerase with compounds having IC₅₀ as low as 1.7 nM <2006BMCL2205>. The related sulfamides **289** <2006BMCL3367> and **290** <2006BMCL3833> are potent inhibitors of the hepatitis C polymerase.



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Biographical Sketch



Peter Norris is a Professor of Organic Chemistry in the Department of Chemistry at Youngstown State University in northeastern Ohio, USA. He was born in Whiston, a suburb of Liverpool in England in 1965, and grew up near Wigan in Lancashire. After receiving his B.Sc. (Honors) degree from Salford University in 1986 Norris headed to the United States for doctoral training at The Ohio State University under the direction of Harold Shechter. After graduating with his Ph.D. in 1992 he moved to Washington, DC, to pursue post-doctoral work with Derek Horton at American University and in 1996 joined the faculty at Youngstown State as an Assistant Professor; he received tenure, and promotion to Associate Professor, in 2000 and promotion to Full Professor in 2004. Norris has interests in the chemistry of monosaccharides and other heterocycles such as triazoles; he has received funding from the National Institutes of Health, the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, and Research Corporation. Norris has mentored 32 master's degree students and numerous undergraduates at Youngstown State and produced 40 publications thus far. Outside of chemistry he enjoys traveling, spending time with his wife Dr. June Yun, and following the fortunes of Liverpool Football Club.

9.06

1,2,5-Oxadiazines and 1,2,5-Thiadiazines

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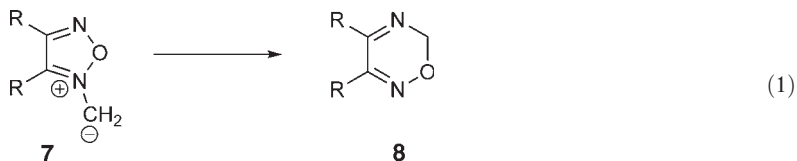
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9.06.1 Introduction

1-Oxa-2,5-diazines and 1-thia-2,5-diazines **1–4** and their benzo analogs **5** and **6** remain relatively obscure heterocyclic systems. While 1-oxa-2,5-diazinanes **1** and 5,6-dihydro-4*H*-1-oxa-2,5-diazines **2** continue to appear in recent studies, 4*H*-1-oxa-2,5-diazines **3** remain unknown. Several examples of the previously elusive 6*H*-1-oxa-2,5-diazine system **4** as well as a number of synthetic studies leading to 1-*H*-benzo-1-thia-2,5-diazines **6** have now been reported (**Figure 1**) and will be examined in this chapter. Additional information on these systems is available in Chapter 6.15 in CHEC-II(1996) <1995CHEC-II(6)681>, though the corresponding section in CHEC(1984) contains limited information on the 1-oxa-2,5-diazines and none on 1-thia-2,5-diazines <1984CHEC(3)1039>.



A brief theoretical study using the 6-31G basis set was undertaken to complement the experimentally observed ring enlargement of furazan-*N*-methanamides **7** to the corresponding 8*H*-1-oxa-2,5-diazines **8** (Equation 1).

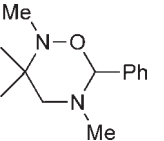
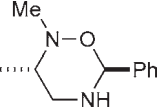
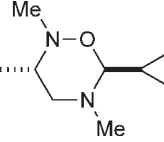
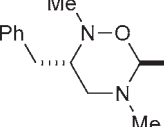


The overall free-energy change for the **7** $\rightarrow$ **8** transformation was calculated to be a relatively favorable $-53.6 \text{ kcal mol}^{-1}$ <1995JP11083>.

9.06.3.1 Ultraviolet, Infrared, and Mass Spectra

No data related to UV spectra for these ring systems have been recorded in the last decade, but IR and MS data have been reported for a number of 1,2,5-oxadiazinanes as shown in **Table 1** <2000J(P1)3292>.

Table 1 Infrared and mass spectral data for some selected 1,2,5-oxadiazinanes^a

<i>Compound</i>	<i>IR</i> $\nu_{\max}$ (cm^{-1})	<i>MS</i> m/z (% intensity)
	941	220(40), 174(6), 133(57), 119(48), 118(100), 91(16)
	3301, 915	192(59), 175(9), 146(30), 118(54), 106(12), 105(36), 91(40), 77(38), 74(100)
	912	170(8), 131(6), 124(9), 122(9), 113(33), 96(18), 84(100) 82(25), 70(11), 68(15), 58(15), 41(27)
	900	282(41), 265(7), 191(25), 175(100), 132(99), 118(63)

^aData from 2000JCS(P1)3292.

In their infrared (IR) spectra, characteristic N–O bands in the $900\text{--}950\text{ cm}^{-1}$ range were observed for the above systems, while IR data for 4-trifluoromethyl-6*H*-[1,2,5]oxadiazine showed principal bands at 1185 , 1125 , and 1115 cm^{-1} <1999JHC917>. For [1,2,5]oxadiazine-3,6-diones **10** and **11**, carbonyl stretching at C-3 occurred at 1747 and 1772 cm^{-1} , respectively, while the C-6 carbonyl stretches appeared at 1688 versus 1692 cm^{-1} for amide I and 1590 versus 1594 cm^{-1} for amide II-type stretches <2003MI175>. For 1-thia-2,5-diazine **12**, bands were observed at 3390 and 3450 (N–H) , 1614 (C=N) , 1334 (CN) , $751\text{ (1,2-disubstituted benzene)}$, and $697\text{ cm}^{-1}\text{ (C–S)}$ (**Figure 2**) <2004JIC775>.

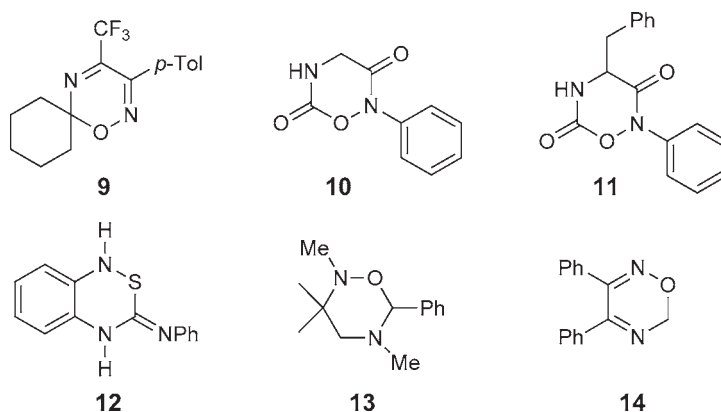


Figure 2

Some ^1H and ^{13}C NMR data for selected 1-oxa-2,5-diazine systems are shown in **Table 2**. Additional examples may be found in the indicated references. No recent nuclear magnetic resonance (NMR) data are available for the corresponding thiadiazine derivatives. The reader is referred to Section 6.15.2.1.2 in CHEC-II(1996) for some earlier data.

Table 2 Some ^1H and ^{13}C NMR shifts (ppm) of 1-oxa-2,5-diazine derivatives

Compound	^1H NMR	^{13}C NMR	Reference
9	1.10–2.35 (C_5H_{10}), 2.35 (ArMe), 7.18, 7.55 (aryl)		1999JHC917
10	4.10 (2-H), 7.56–7.34 (Ph) 8.72 (N-H)	44.2 (CH_2), 122.4, 127.6, 129.1 137.4 (Ph), 152.8, 164.6 (C=O)	2003MI175
13	1.05 (3-Me), 1.40 (3-Me) 1.91 (5-Me), 2.34 (4-H) 2.54 (2-Me), 2.75 (4-H) 4.58 (6-H), 7.26–7.37 (Ph) 7.48–7.52 (Ph)	15.7, 25.3 (3-Me), 37.7 (5-Me) 40.3 (2-Me), 67.4 (4- CH_2) 99.3 (6-CH), 128.4, 128.5 129.3 (PhCH), 138.0 (PhC)	2000J(P1)3292
14	5.28 (NCH_2O), 7.1–7.3 (Ph)	78.3 (CH_2), 157.4 (C-3), 156.3 (C-4), 135.1, 128.3 128.5, 130.4, 132.1, 127.9, 128.3, 130.1 (Ph)	1995J(P1)1083

9.06.3.2 X-Ray Crystallography

Single crystals of **15**, a member of the relatively obscure oxadiazinane family of heterocycles, were obtained by recrystallization from ethyl acetate:hexane. Subsequent X-ray analysis was useful in confirming structural assignments based on NMR data for both **15** and **16** (**Figure 3**), which were obtained from reaction of a carbohydrate-derived nitron with allyl amine (see Section 9.06.9.2). Thus, the structure of the major *trans* isomer **16** was inferred from the crystal data obtained for minor isomer **15**, though some doubt remained as to which centers in **16** were opposite in configuration to those in **15** <2000J(P1)3292>.

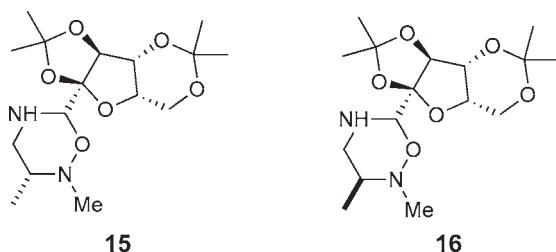


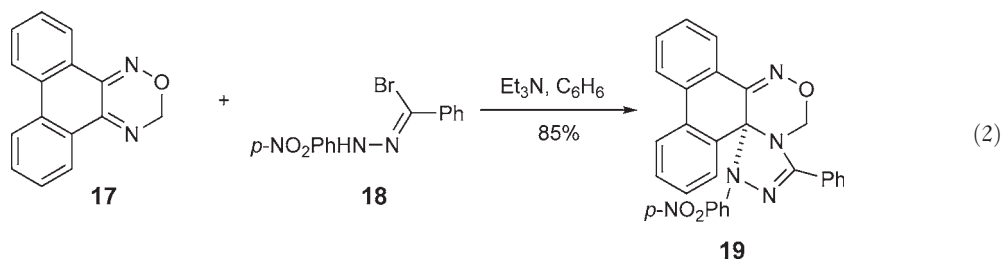
Figure 3

9.06.4 Thermodynamic Aspects

Because of the variety of substitution, unsaturation, and heteroatom arrangements possible in oxadiazines and oxathiadiazines, it is difficult to generalize with regard to trends in boiling points, melting points, solubilities, and related properties. Compound **9** was reported to be a crystalline solid with m.p. 110–111 °C after isolation via chromatography with 4:1 benzene–dichloromethane <1999JHC917>. Similarly, chromatography with 95:5 dichloromethane–hexane gave solid **14** with m.p. 116–118 °C <1995J(P1)1083>, while chromatographic purification of **10** used 1:1 cyclohexane–ethyl acetate to give pure material with m.p. 115–117 °C <2003MI175>. TLC analysis of **13** showed R_f 0.36 using 1:8 ethyl acetate–hexane <2000J(P1)3292>. Thiadiazine **12** was recrystallized from aqueous ethanol to give m.p. 141 °C <2004JIC775>. None of the ring systems in this chapter is aromatic, and no tautomeric equilibria data are available. Beyond what may be judged from the available X-ray data for oxadiazinane **15** (Section 9.06.3.2), information regarding conformational aspects of these systems is very limited (see Section 2.28.2.5.6 in CHEC(1984) for additional information).

9.06.5 Reactivity of Fully Conjugated Rings

Since none of these systems is fully conjugated or aromatic, no information is available for this section. Previously unknown π -conjugated 6*H*-1-oxa-2,5-diazine systems such as **9** <1999JHC917> and **14** <1995J(P1)1084> have now been reported, but little information is available beyond their preparative chemistry except for the reported cycloaddition of phenanthro-1-oxa-2,5-diazine **17** with a nitrile imide derived from phenylhydrazonoyl bromide **18** to give the corresponding cycloadduct **19** (Equation 2) <1997J(P1)1047>.

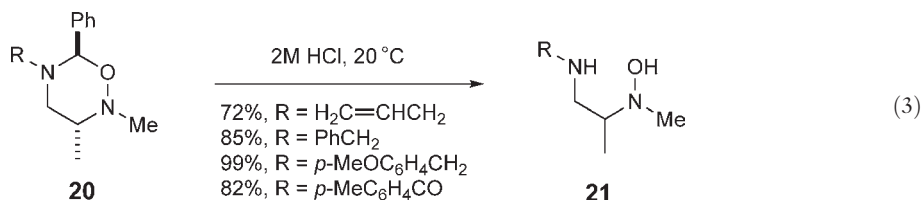


9.06.6 Reactivity of Nonconjugated Rings

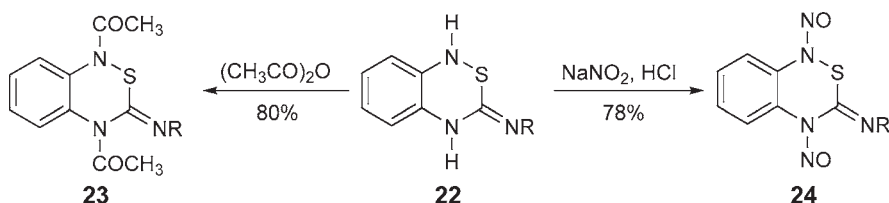
Available information in this section is limited to a few examples of reactions of oxadiazinanes and benzothiadiazine systems. Additional earlier examples of the chemistry of these and related systems may be found in Section 6.15.4 of CHEC-II(1996).

9.06.6.1 Electrophilic Attack at Ring Nitrogen, Sulfur, or Carbon

Treatment of oxadiazinanes **20** with dilute hydrochloric acid affords the corresponding aminohydroxylamines **21** (Equation 3). Such products are not readily obtained by other means and may prove to be useful as synthetic intermediates or as metal ligands <2000J(P1)3292, 1997TL8545>.



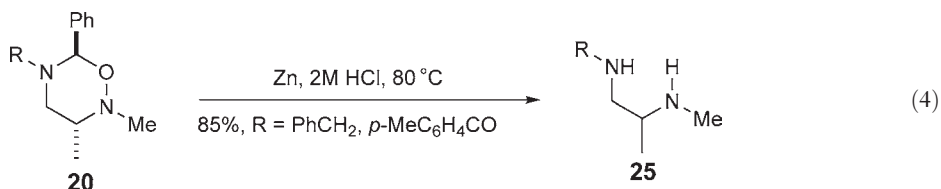
Benzothiadiazine **22** underwent *N*-acylation when treated with acetic anhydride in acetic acid (1:2) at reflux temperature to give **23** as a white solid, m.p. 265 °C (Scheme 1). Treatment of an ethanolic solution of **22** with sodium nitrite and aqueous HCl gave the corresponding *N*-nitroso derivative **24** as a greenish-yellow precipitate, m.p. 92 °C <2004JIC775>.



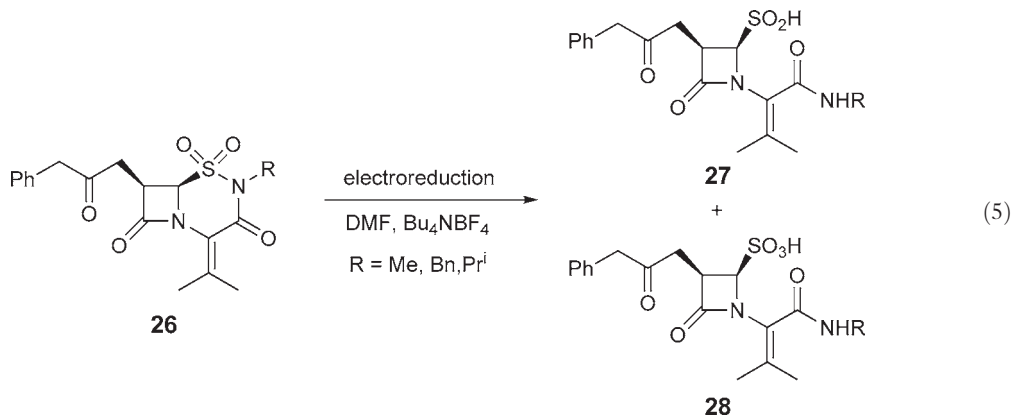
Scheme 1

9.06.6.2 Reduction

Treatment of oxadiazinanes **20** with Zn metal in aqueous HCl afforded the corresponding 1,2-diamines **25** in good yield (Equation 4). Where R = *p*-MeC₆H₄CO, the product is a monoacylated diamine; such derivatives are accessible by other means only with difficulty <2000J(P1)3292>.

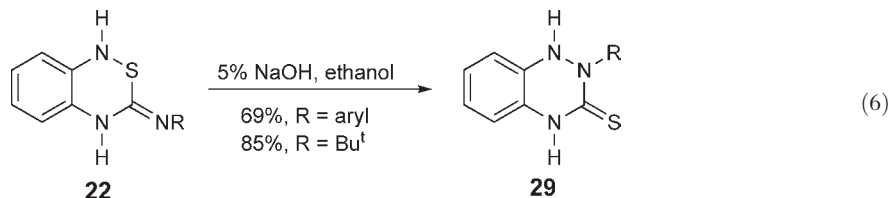


Studies on the electrochemical reduction of anhydro-2-azacephams **26** at a mercury electrode gave azetidine-type products **27** and **28** resulting from exclusive S–N bond cleavage (Equation 5). Formation of an organomercury compound was postulated as an intermediate in the reduction process <2001MI229>.



9.06.6.3 Base Induced Isomerization

Benzo-1-thia-2,5-diazines **22** rearrange readily to benzo-1,2,4-triazines **29** upon treatment with 5% aqueous sodium hydroxide solution in ethanol (1:1) at reflux temperature for 1 h (Equation 6) <2004JIC775>. Desulfurization of **29** with alkaline lead acetate solution was indicative of the presence of the expected -NH-C=S linkage.



9.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

No information was available under this heading in Section 6.15.5 in CHEC-II(1996) and since 1995 there has been no new chemistry to report.

9.06.8 Reactivity of Substituents Attached to Ring Heteroatoms

No information was available under this heading in Section 6.15.5 in CHEC-II(1996) and since 1995 there has been no new chemistry to report.

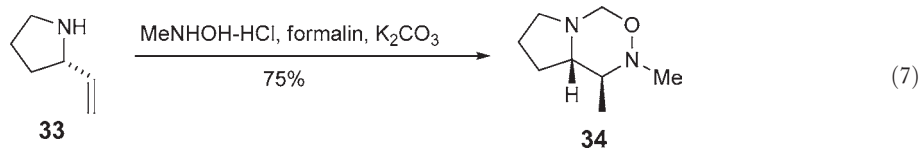
9.06.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

This section treats several important synthetic approaches to the ring systems of this chapter, including intramolecular cyclizations whose substrates were derived from prior condensation of separate acyclic components ultimately contributing ring fragments to the final heterocycle.

9.06.9.1 [3+3] Fragments: Reaction of Nitrones with Allyl Amines

Allyl amines **30** react with aldehyde-derived nitrones **31** to give oxadiazinanes **32** in excellent yield. The reaction proceeds via initial nucleophilic attack on the nitron by the amine, followed by a reverse-Cope elimination and subsequent Meisenheimer rearrangement to give the observed products as shown in **Figure 4** <2000J(P1)3292>.

An *in situ* method for capturing nitrones too unstable for isolation involved reaction of allylic amines such as proline derivative **33** with *N*-methylhydroxylamine in basic formalin solution to give, in this instance, chiral oxadiazinane **34** (Equation 7) <1997TL8545>.



9.06.9.2 [4+2] Fragments: Intramolecular Cyclizations of Hydroxamic Acids and Aminophenylthiocarbamides

Hydroxamic acids **35**, derived from *N*-(1-benzotriazolylcarbonyl)-amino acids, were found to cyclize under basic conditions to give the corresponding 1,2,5-oxadiazine-3,6-dione derivatives **36** in modest yield (Equation 8) <2003MI175>.

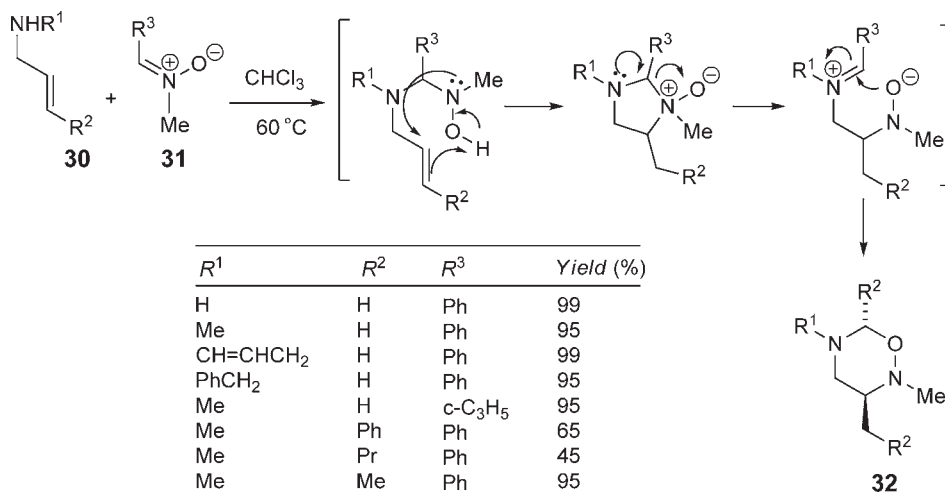
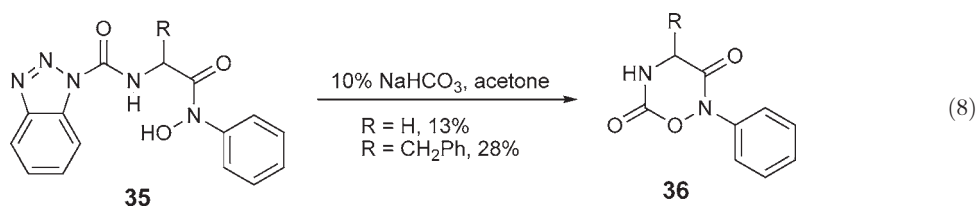
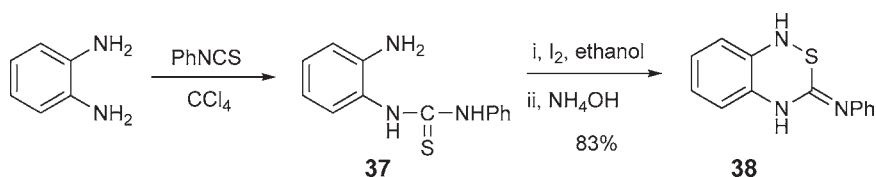


Figure 4



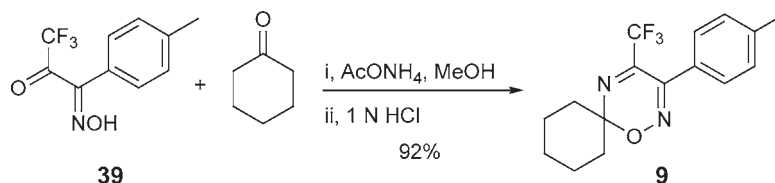
Reaction of *o*-phenylenediamine with phenyl isothiocyanate in CCl₄ gave thiocarbamide **37** which underwent oxidative cyclization to benzothiadiazine **38** upon treatment with ethanolic iodine followed by basification with ammonium hydroxide solution (Scheme 2). Analogous results were obtained using a variety of ring-substituted phenyl isothiocyanates as well as *t*-butyl isothiocyanate in this sequence, with overall yields ranging from 69% to 87% <2004JIC775>.



Scheme 2

9.06.9.3 [5+1] Fragments: Reaction of Trifluoroalkane-2,3-Dione-3-Oximes with Ketones

Aryl-substituted oxadiazine **9** (also see Section 9.06.3.1) was obtained in excellent yield by treatment of trifluoromethyl-2,3-diketone-3-oxime **39** with methanolic ammonium acetate solution at reflux temperature over 18 h followed by acidification of the reaction mixture with aqueous HCl (Scheme 3) <1999JHC917>.



Scheme 3

9.06.10 Ring Syntheses by Transformations of Another Ring

9.06.10.1 Ring Expansion of *N*-Methyloxadiazolium and *N*-Methylphenanthroazolium Salts

Treatment of toluene solutions of *N*-methyloxadiazolium salts **40** with potassium *t*-butoxide at room temperature afforded the corresponding oxadiazines **41** in good to excellent yield (Figure 5). Slightly lower yields were observed using lithium diisopropylamide as base in tetrahydrofuran and yields of less than 15% were obtained using sodium ethoxide. The starting quaternary ammonium salts were readily obtained from the corresponding furazans by treatment with dimethyl sulfate followed by ion exchange with sodium perchlorate <1997J(P1)2919, 1995J(P1)1083>.

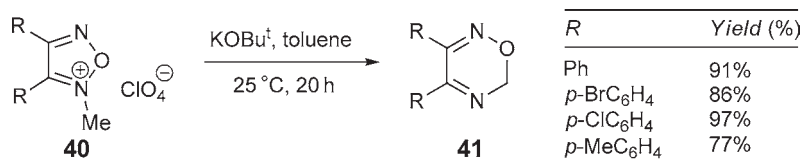
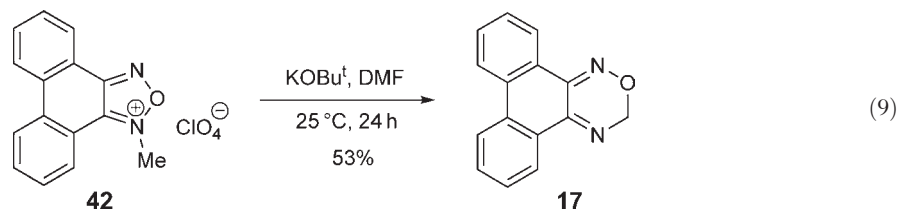


Figure 5

Similarly, *N*-methylphenanthroazolium salt **42** undergoes base-induced ring expansion (Equation 9) to give phenanthro-1-oxa-2,5-diazine **17** in reasonable yield (also see Section 9.06.5) <1997J(P1)1047>.



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

Review of Sections 9.06.9 and 9.06.10 reveals that each of the 1-oxa-2,5-diazine and 1-thia-2,5-diazine ring systems covered in this chapter is unique with respect to degree of unsaturation, oxidation or substitution and synthetic approach, except for 6*H*-1-oxa-2,5-diazines such as **9** (see Scheme 3) and **41** (see Figure 5).

In the case of **9**, the approach involved reaction of a trifluoroalkane-2,3-dione-3-oxime with cyclohexanone, while synthesis of **41** was achieved via ring expansion of *N*-methyloxadiazolium salts. The scope and limitations of the 2,3-dione-3-oxime route to **9** is difficult to evaluate since only a single example was reported, though a trifluoromethyl group may be required for activation of this system and thus would limit possible substitution patterns on the resulting oxadiazine ring. However, the reaction would presumably tolerate a number of different ketone partners, thereby increasing its scope.

For the ring expansion approach to **41**, only symmetrical 1,2-diaryl substitution of the five-membered ring of the oxadiazolium salt is possible, since unsymmetrical ring substitution of the starting furazans would yield a mixture of

N-methyloxadiazolium salts. Substitution of the furazan ring system is also limited to substituents lacking acidic hydrogens (as in aryl substitution) since the resulting rearrangement of the *N*-methyloxadiazolium salt requires strongly basic conditions.

For additional comparison of syntheses of these systems, see Section 6.15.8 in CHEC-II(1996).

9.06.12 Important Compounds and Applications

No new applications of these compounds have been reported, though benzothiadiazine **43** (Figure 6) was found to be highly active in an antimicrobial screen, while **44** was active in an antifungal screen and **45** was active in both <2004JIC775>. Oxadiazines **10** and **11** were evaluated for potential cytotoxic and cytostatic properties and were found to inhibit cell growth significantly in HeLa and GMK cell lines, but possessed only minor antiviral effects against adenovirus, herpesvirus, and enteroviruses <2003MI175>, see Section 6.15.9 in CHEC-II(1996) for some additional examples of applications of these systems.

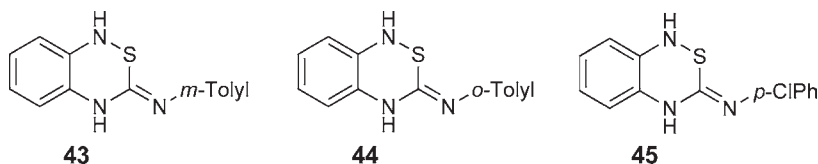


Figure 6

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Biographical Sketch



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9.07

1,2,6-Oxadiazines and 1,2,6-Thiadiazines

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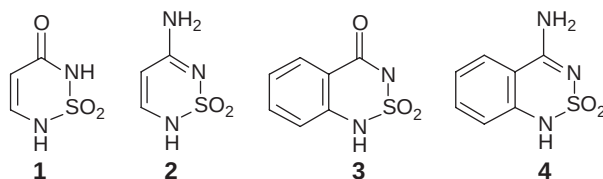
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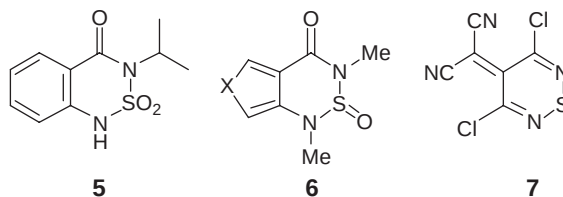
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9.07.1 Introduction

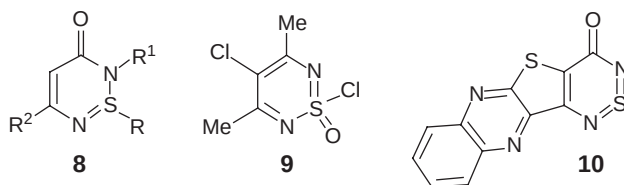
The most common ring systems discussed in this chapter are the 1,2,6-thiadiazin-3-one 2,2-dioxides **1**, the corresponding amino analog **2**, and their benzologs **3** and **4**.



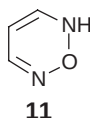
The most important example of the ring system continues to be the herbicide Bentazone **5** <1989CIM30>. A review on Bentazone and the molecular mechanism of selectivity of two rice mutants appeared <2004NY217>. Also prepared were monoxides such as **6** (Section 9.07.9.2.2) and sulfides **7** (Section 9.07.9.2.2).



Examples of the 1 λ^4 -thiadiazines **8** (Sections 9.07.8) and **9** (Section 9.07.6.3.1) have been described as well as S(IV) compounds such as **10** (Section 9.07.9.2.2).

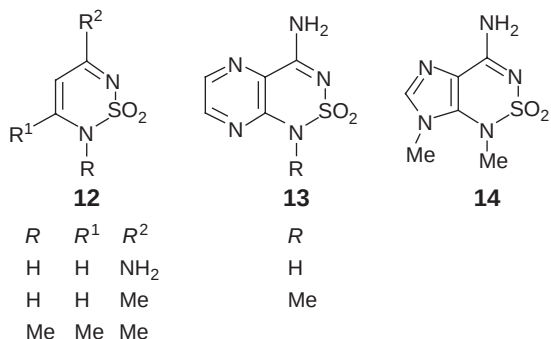


The 1,2,6-oxadiazine ring **11** remains an unexplored ring system (Sections 9.07.9.1.2 and 9.07.11.1).

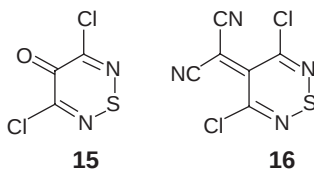


9.07.2 Theoretical Methods

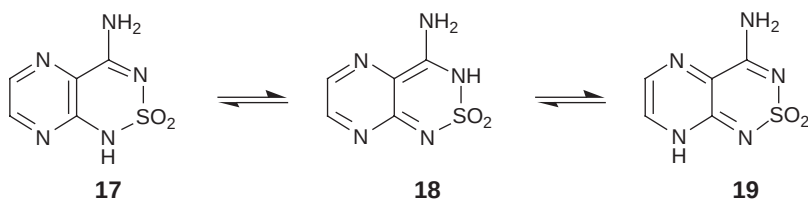
Theoretical analyses of aminosulfonylamino (sulfamoyl) moieties **12–14** were carried out using several methods, none of which best described the geometry and electronic distribution of these compounds. The best geometric descriptors were obtained with Hartree–Fock (HF) *ab initio* calculations, while methods using electronic correlation (Møller–Plesset) gave longer bond lengths but more closely reproduced experimental dipole moments <1996JPO203>.



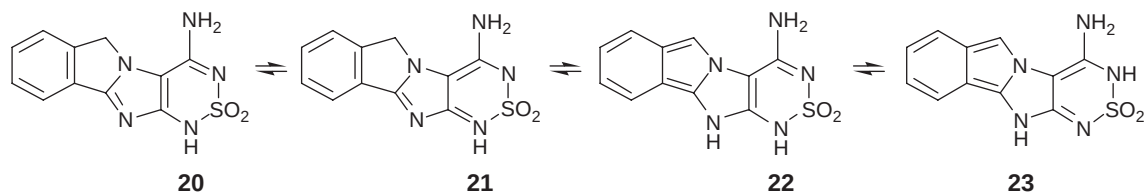
Thiadiazine **15** has an aromaticity index (I_A) of 54 indicating a moderately aromatic compound <2000CC303> and is consistent with its almost-planar structure <1978AXB2927>. The dicyano analog **16** has a slightly higher aromaticity index ($I_A = 60$) despite being less planar. It was proposed that greater contribution from dipolar resonance forms could account for this.



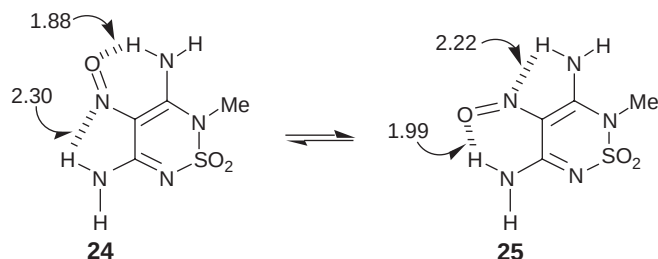
Gas-phase calculations of tautomers **17–19** using semi-empirical density functional theory (DFT) and molecular orbital *ab initio* calculations indicated tautomer **17** is the most stable by 40 and 65 kJ mol⁻¹ over **18** and **19**, respectively <1998J(P2)1889>. Thus, only **17** should be present in apolar media, which is in agreement with experimental results obtained for related 4-aminopyrazino[2,3-*c*][1,2,6]thiadiazines <1984JHC861, 1988H(27)2201>. Continuum solvation models indicated the stabilization of tautomer **19** in aqueous media with larger ρ values and shorter hydrogen bond distances indicating stronger interactions.



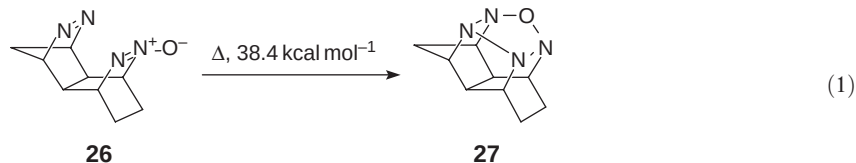
Similarly, tautomerism of **20** was studied by theoretical molecular orbital calculations with total and relative energies in the gas phase indicating that tautomers **20** and **21** are more stable than **22** and **23**. The relative low stability and lower dipole moments of the latter pair should make **20** and **21** favored in aqueous media. Self-consistent reaction field calculations indicate **20** is more stable (9–12 kcal mol⁻¹) in water than **21** <1998H(48)1833>.



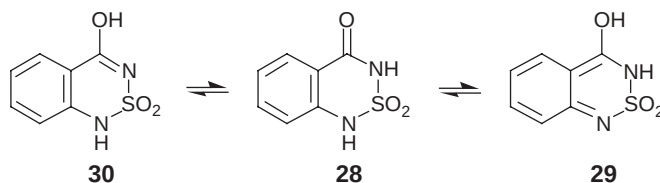
In accord with the small experimental energy difference observed in solution, molecular orbital calculations indicated that conformer **24**, in the gas phase, is more stable ($0.54 \text{ kcal mol}^{-1}$) than conformer **25** <1996J(P2)293>. The calculations predict the SO_2 group to be out of the plane defined by the rest of the atoms in the ring. Similar results were seen in X-ray structures of 1,2,6-thiadiazine <1988AHC81>. The C–NH₂ bond distances of $1.33 \text{ \AA}$ are similar to the experimental C=N bond distances of pyridine ($1.337 \text{ \AA}$), indicating partial double bond character that is borne out in the high rotational barrier of the C–NH₂ bond as seen from the proton nuclear magnetic resonance (NMR) spectrum. The smaller hydrogen bond distance calculated for **24** ($1.88 \text{ \AA}$ vs. $1.99 \text{ \AA}$) may explain the chemical shift displacement in the proton NMR of **25** <1996J(P2)293>.



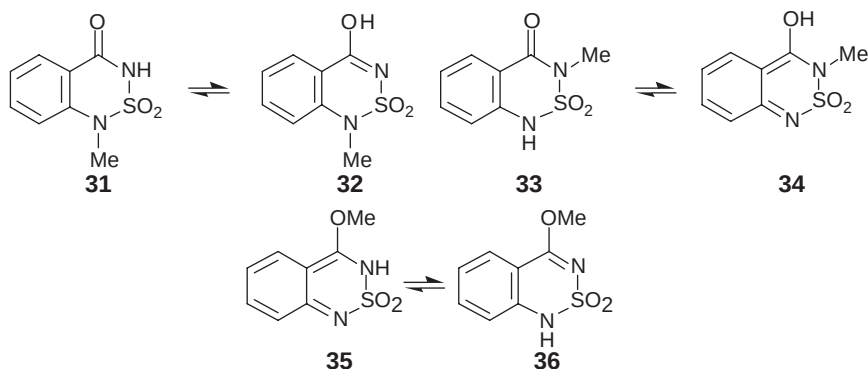
The potential of the novel *syn*-periplanar N=N=N motif exemplified in **26** was explored by calculations and experimentally <2000EJO763>. DFT calculations for [3+2] cycloaddition of compound **26** indicated that a diazine/diazenoxy cycloaddition (**26** → **27**) was unlikely and other reaction manifolds were operative (Equation 1).



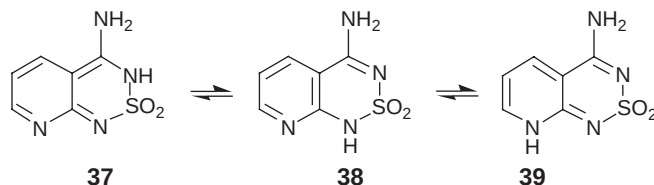
The tautomeric equilibrium of **28** was studied in the gas phase using molecular orbital calculations following the *ab initio* method at the HF with the 6-31G* basis set (HF/6-31G*). The tautomer **29** is quite unstable, whereas the keto form **28** is the most stable tautomer in the gas phase. Since the form **30** is more polar than the keto form, electrostatic stabilization in polar solvents or in the solid state could favor the OH tautomer, which is in agreement with experimental results <1999T12405>.



Monosubstituted benzothiadiazinone tautomerism was also investigated. The HF/6-31G* level calculations showed a clear preference for the keto tautomers **31** and **33** in the N-1- and N-3-monosubstituted compounds over the respective hydroxy tautomers **32** and **34**. The *O*-alkyl derivative tautomer **35** is preferred over **36** because of better π -bond delocalization in the fused benzene ring <1999T12405>.



Compound **37** represents an interesting case of annular tautomerism. As above, the molecular orbital *ab initio* method at the HF/6-31G* level was employed. The calculations suggested that only tautomer **38** is present in the gas phase because of the large energy difference between the other two tautomers. However, the relative lower dipole moment of tautomer **38** should make tautomers **37** and **39** more favored in aqueous solution <2004JMT83>.

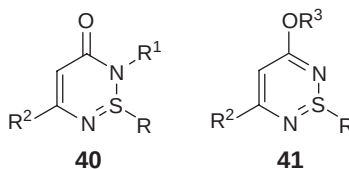


9.07.3 Experimental Structural Methods

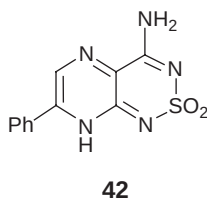
9.07.3.1 Spectroscopic Studies

9.07.3.1.1 Ultraviolet and infrared spectra

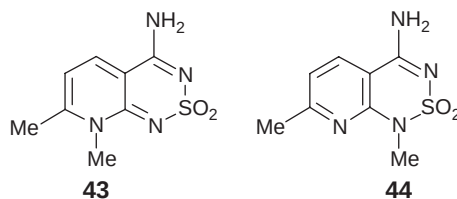
In contrast to the *N*-alkyl-substituted **40** ($R^1 = \text{alkyl}$) and *NH*-1 λ^4 -thiadiazin-3-ones **40** ($R^1 = \text{H}$) (λ 337 (4096)), absorption maxima of the *O*-alkylated thiadiazines **41** (λ 373 nm (2265)) are shifted to higher wavelengths (bathochromic effect). Thus, crystals, as well as solutions of **41**, are yellow whereas **40** appear colorless <2003JOC3817>.



Rate equations with temporal, spectral, and spatial dependence were derived to obtain characteristics of the laser emission of the monoprotonated species of 4-amino-7-phenyl-8*H*-pyrazino[3,2-*c*][1,2,6]thiadiazine 2,2-dioxide **42** in acetonitrile. The phenomenology indicated the possibility of observing simultaneous laser emissions at two different frequencies of both acid-base species <1995OQE1027>.

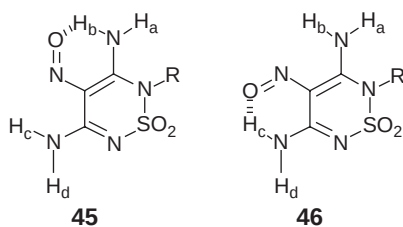


In dimethyl sulfoxide, a single neutral species was detected for both **43** and **44**. However, in acetonitrile, an acid-base process between the neutral and an acidic form was detected and characterized through pK values in the ground state and pK^* values in the excited state (**44**: $pK = 2.0$, $pK^* = 2.3$; **43**: $pK = 2.9$, $pK^* = 4.0$). Absorption maxima in the range of 326–304 nm were observed. Fluorescence maxima in the range of 413–469 nm, with relatively high quantum efficiencies (0.3–0.7), were obtained <1995JPH35>.

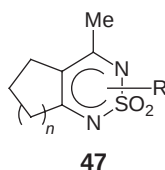


9.07.3.1.2 NMR spectra

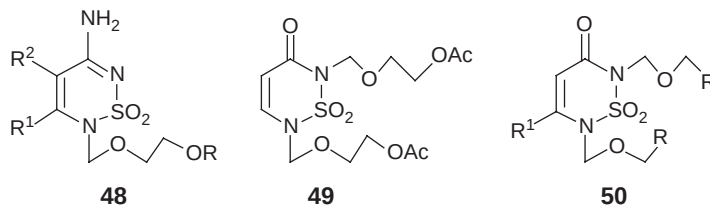
In the ^1H NMR spectrum of **45**, one of the amino groups hydrogen-bonded to the nitroso group appears at ca. 10.5 and 8.0 ppm with a coupling constant of 4.5 Hz. These signals correspond to H_c and H_d of conformer **46**. The remaining two NH signals of conformer **46** were assigned based on the larger variability of H_a due to effects of substituents attached to position N-2 and the electrostatic interaction of H_b with the nitroso nitrogen leading to larger δ shifts. Compound **45** ($\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$) shows four signals that coalesce to two signals at 363 K (conformer **46**) and 373 K (conformer **45**). These signals should correspond to the amino groups that are not forming a hydrogen bond with the nitroso group in either conformation (8.80 and 8.30 ppm in conformer **45** and 9.87 and 9.04 ppm in conformation **46**). Using these values, the rotation barriers of these amino groups were calculated to be 17.7 and 16.8 kcal mol $^{-1}$, respectively. The ^{13}C NMR spectra of these compounds show a large influence in the chemical shift of the C-3 and C-5 carbons depending on the conformation of the nitroso group. In both cases, the carbon in the (Z)-position to the nitroso group shows the smaller chemical shift <1996J(P2)293>.



N-Substitution at the N-3 position of the bicyclic thiadiazine 2,2-dioxide ring system **47** ($n = 1, 2$) produces a 6 ppm downfield shift of the C-4 methyl carbon. This observation should help with future structural elucidations <1995BMC179>.

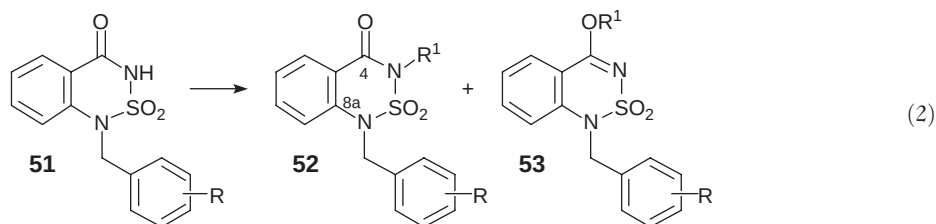


The sites of glycosylation on **48–50** were determined by nuclear Overhauser effect (NOE) experiments. Unequivocal assignment of all ^1H and ^{13}C signals was achieved using sequences of heteronuclear multiple quantum correlation (HMQC) for one bond correlation and heteronuclear multiple bond correlation (HMBC) for long-range correlation <1995BMC1527, 1997NN265>.

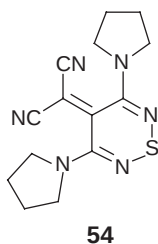


Deprotection of the acyclic moiety in **48** ($\text{R} = \text{Ac}$ to $\text{R} = \text{H}$) produced a shielding effect on the adjacent methylene protons with the AA'BB' splitting present in the acetoxyethoxy chain changed to an AA'A''A''' system in the hydroxyethyl chain group present <1995BMC1527>. For the diacyclonucleoside analog **49**, ^{13}C NMR chemical shifts of the N-CH $_2$ were between 79 and 72 ppm, ruling out possible alkylation on the oxygen <1995BMC1527>.

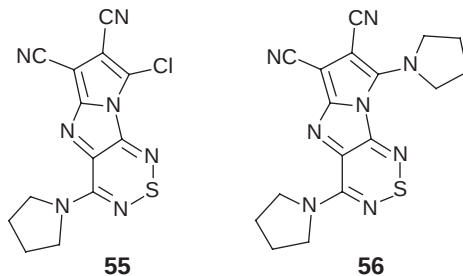
Both possible disubstituted compounds **52** and **53** were obtained from alkylation (halides and sulfate) of **51**. In determining the structures, the N(1)-CH $_2$ correlated exclusively with the quaternary carbon C-8a, while the N(3)-CH $_2$ or O-CH $_2$ correlated with carbon C-4. In the latter case, a deshielding in both proton and carbon signals was observed that additionally confirmed the O-substitution (Equation 2) <2003BMC2395, 2000JMC3218>.



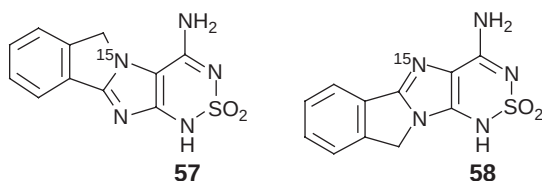
The structure of **54** was supported by analysis of its ^{13}C (symmetry seen) and ^1H NMR spectra and showed less negative charge delocalized onto the central carbon of the dicyanomethylene group as compared to the starting dichloride used to prepare it. A significant barrier to rotation of the pyrrolidino groups was observed as four separate and well-defined carbon resonances (66.1, 65.7, 48.4, 45.6 ppm) were observed, whereas the starting dichloride had only two resonances (66.1, 48.6 ppm).



The ^1H and ^{13}C NMR spectra showed that rotation of the pyrrolidine ring on the thiadiazine was significantly slower than the one on the pyrrole. Four carbon resonances (51.4, 49.3, 27.0, 24.3 ppm) were detected for the pyrrolidine in compound **55**, whereas in compound **56** these resonances had merged into two broad signals (49.5, 25.4 ppm) and the second pyrrolidine showed two sharp signals (51.4, 25.5 ppm). Presumably, replacement by the second pyrrolidine increases the electron density in the ring system and reduces the amidine-like conjugation between the other pyrrolidine and the thiadiazine ring, thus reducing the energy barrier to rotation. This indication of electron delocalization across the tricyclic 14π aromatic system was supported also by the observed 50 nm red shift of the first ultraviolet (UV) absorption band on introduction of each pyrrolidine substituent [<2000J\(P1\)1081>](#).

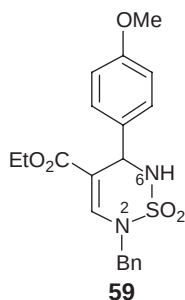


Compounds **57** and **58**, which are possible products from the reaction of *o*-phthalaldehyde and 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide, contain two types of nitrogen in the imidazole ring: an sp^2 -type nitrogen that appears at lower field ($\delta = 154.8$ ppm) and an sp^3 -type nitrogen at higher field ($\delta = 292.1, 265.7, 260.4$ ppm). The ^{15}N NMR spectrum of the ^{15}N -labeled compound showed only one signal ($\delta = 259.0$ ppm) corresponding to an sp^3 -type nitrogen atom (N-5) and, thus, was compatible only with structure **57** [<1998H\(48\)1833>](#).

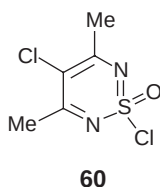


9.07.3.1.3 X-Ray crystallography

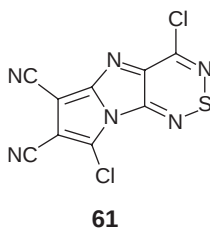
The crystal structure of **59** was determined. The sulfone group displayed a distorted tetrahedral structure and N-6 deviated from the plane of the thiadiazine ring <1995JKCS344>.



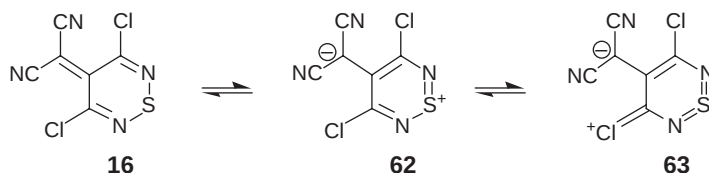
The structure of the tetracoordinate sulfur compound **60** was confirmed by X-ray crystallography. The presence of the N=S(O)Cl functionality was confirmed and the S(vi) atom was shown to lie 0.43 Å out of the plane of the ring. The C=C (1.394 Å) and C=N (1.348 Å) bond distances indicated some π -delocalization <1998ZNB532>.



Two polymorphs of **61** were identified, both being monoclinic, but one is in a centrosymmetric space group and the other polar. The geometries of the two forms do not differ significantly, being relatively planar. There is distinct bond ordering in the thiadiazine ring and to a lesser degree in the imidazole, but the pyrrole exhibits delocalization. The ring system is planar and delocalized and can be considered a 14 π -aromatic system <2000CC303, 2000J(P1)1089>.

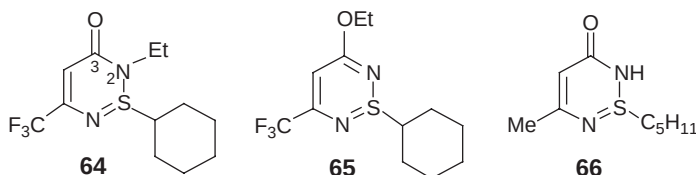


The dicyanomethylene compound **16** has a nonplanar shallow boat conformation. The N–S–N and C–C–C planes are inclined nearly 25°, thus distancing the cyano groups from the chlorines. The two C=N bonds have pronounced double bond character and the exocyclic C=C bond is delocalized. Compound **16** was calculated to have a higher aromaticity index ($I_a=60$) than the keto analog despite being less planar. This was attributed to strong electron withdrawal of the two cyano groups allowing for resonance forms such as **62** and **63**. In agreement with this, the ^{13}C resonance of the exocyclic carbon (C-7) at 81.8 ppm, as compared with tetracyanoethylene at 108.2 ppm, <1987S749> indicates substantial negative charge on the dicyanomethylene group <2000CC303, 2000J(P1)1089>.

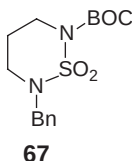


X-Ray analysis of the N-alkylated by-product **64** confirmed that the ethyl group is attached to N-2. The heterocyclic ring is not planar, the tetrahedral sulfur atom projects out of the plane, and its fourth valence is occupied by the

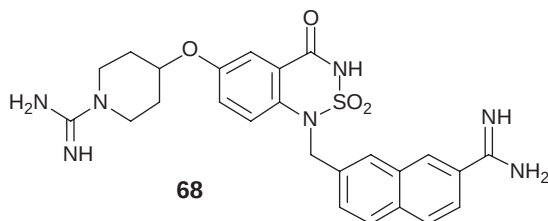
nonbonding lone pair. The position of the S-cyclohexyl is perpendicular to the plane and both S–N bonds are almost the same length. The same is true for the differently substituted $1\lambda^4,2,6$ -thiadiazines **65** and **66** <2003JOC3817>.



Structural proof for **67** was obtained from X-ray analysis <2003T6051>.



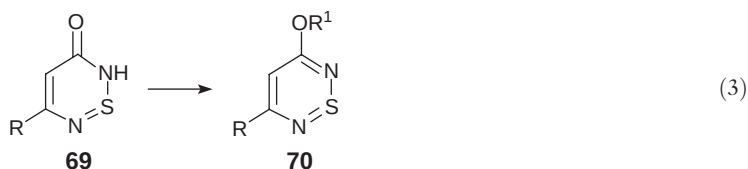
The binding of **68** in the active site of Factor Xa (FXa) was proposed on the basis of X-ray crystallographic analysis of this compound complexed to the related enzyme trypsin <2003BMC367>.



9.07.4 Thermodynamic Aspects

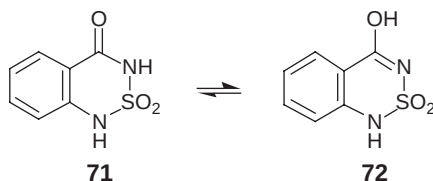
9.07.4.1 Aromaticity

For the O-alkylation of **69** leading to **70**, the exocyclic carbonyl double bond present on **69** is formally 'shifted' into the heterocyclic ring system, thereby enlarging the conjugated π -electron system, yet, the tetrahedral-configured sulfur atom is not included in the ring delocalization. Consequently, even the O-alkylated thiadiazines **70** are nonaromatic heterocycles <2003JOC3817>. The delocalized π -electron system may be described as a 1,5-diazapenta-1,3-diene anion that is analogous to $1\lambda^4,2,4,6$ -thiatriazine (Equation 3) <1993CB2601, 1992SR257>.

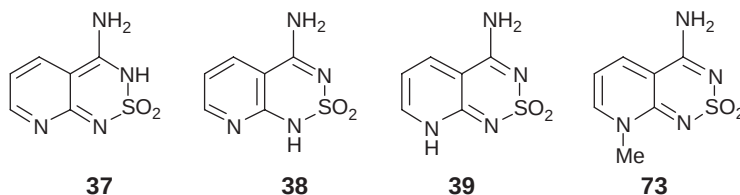


9.07.4.2 Tautomerism

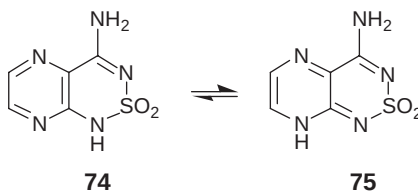
It was concluded from ^{13}C NMR studies on benzothiadiazinone **71** and several alkylated derivatives that **71** exists mainly as the hydroxy tautomer **72** in the polar aprotic solvent dimethyl sulfoxide, while in nonpolar solvents such as tetrahydrofuran, the population of the keto form **71** increases considerably. Protic solvents, such as methanol, increase the rate of prototropic exchange, and an equal population of these two tautomers is seen <1999T12405>.



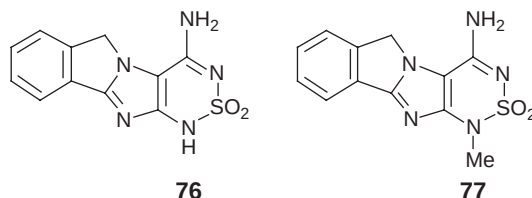
Compound **37** is an acid ($pK_a = 5.85$). In aqueous solution, information about the predominant species can be obtained from the two UV wavelength absorption bands of the neutral species. The band at 365 nm is characteristic of the tautomer **39** whereas the second band at 320 nm indicates the presence of tautomer **38**. A comparison of the UV spectrum with that of the 8-methyl derivative **73** indicated that compound **37** exists in aqueous solution as the 8*H*-tautomer **39**. It was concluded that **37** exists as tautomer **39** in dimethyl sulfoxide and in aqueous solution <2004JMT83>.



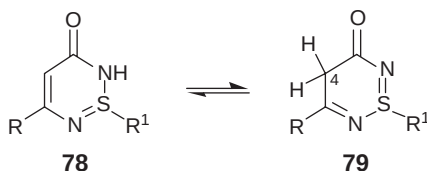
Similar arguments were made for the pyrazino[3,2-*c*][1,2,6]thiazine 2,2-dioxide **74**. It was concluded that compound **74** exists in aqueous solutions as an equimolar mixture of the two tautomeric forms **74** and **75** <1998J(P2)1889>.



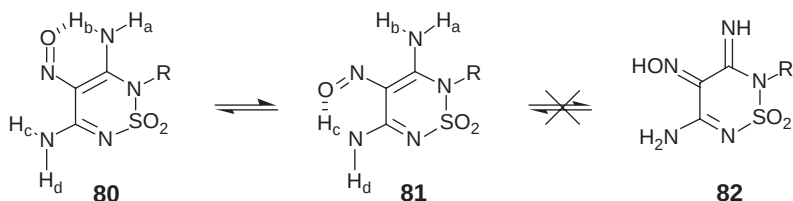
Compound **76** represents yet another interesting case of annular tautomerism. In principle, compound **76** can exist as four tautomers. Comparison of the UV spectrum of **76** with that of **77** indicated that the former exists in aqueous solution as the tautomer shown <1998H(48)1833>.



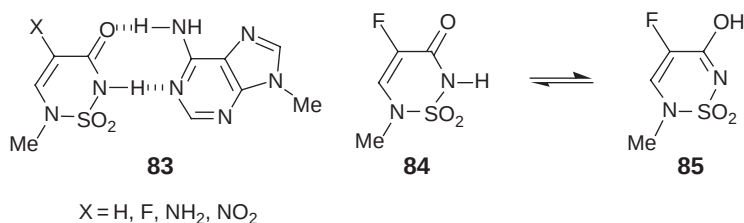
Thiadiazines **78** ($R^1 = \text{Me, Bn}$) showed an unusual NH/CH tautomerism in dichloromethane or chloroform solution. The tautomerism is indicated by the additional appearance of two doublets for the corresponding two geminal protons attached to C-4 in the ^1H NMR spectrum (tautomer **79**). The ^{13}C NMR spectrum displays the correlated CH_2 signal around 40 ppm; however, at lower temperatures, the NH form **78** is preferred in solution. In the solid state, too, only the NH tautomer **78** is present. X-Ray analysis of **78** ($R = \text{C}_5\text{H}_{11}$, $R^1 = \text{Me}$) showed that this tautomer is stabilized by intermolecular hydrogen bonding <2003JOC3817>.



In solution, the 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazine 2,2-dioxides **80** present a duplication of ^{15}N NMR signals (267 and 356 ppm), indicating the presence of two conformations (**80** and **81**) of the nitroso group rather than the existence of the 4-hydroxyimino tautomers **82** (expected δ 25–45 ppm). Four additional signals at ca. 280 ppm indicate the presence of four NH_2 groups, which eliminates a possible amino/imino tautomerism <1996J(P2)293>.

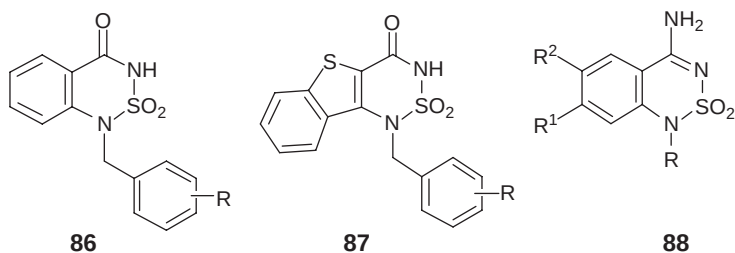


The hydrogen bond complex between adenine (**A**) and hydrogen-bond-equivalent 3-oxo-1,2,6-thiadiazine 1,1-dioxide derivatives **83** was about $1.5 \text{ kcal mol}^{-1}$ more stable than the hydrogen bond complex between uracil derivatives and **A**. The imide tautomer **84** is more stable than the enol tautomer **85**. Thus, **84** is a potent hydrogen bond equivalent of uracil <2003JMD329>.

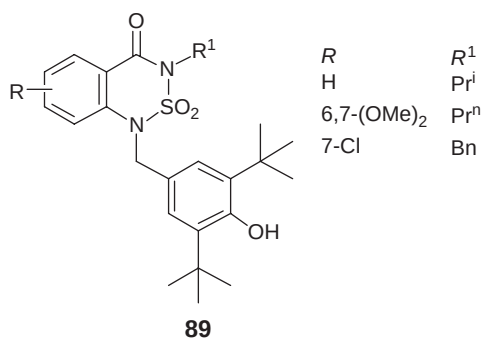


9.07.4.3 QSAR

A CoMFA study was conducted on a series of fused thiadiazine derivatives (**86** and **87**) with PDE 7 inhibitory activity in order to determine alternative molecular regions that could be modified to improve both activity on PDE 7 and selectivity versus PDE 4 and PDE 3. The main conclusion of this three-dimensional quantitative structure–activity relationship (3-D QSAR) study revealed the importance of hydrogen bond interactions for phosphodiesterase activity <2001EJM333, 2000JMC3218>. This is consistent with the lack of activity shown by disubstituted compounds **88** <2000JMC683>.



A model was established that correctly correlated antiplatelet activity of **89** with the partial atomic charges calculated by a local density functional *ab initio* method. As a result, the experimental platelet aggregation inhibitory activity was improved 300-fold <1996JMB470>. Flex X calculations as implemented in Sybyl 6.8 indicated compounds **89** could bind to the PDE 4D catalytic site occupying part of the pocket where Zardaverine, the co-crystallized ligand, binds <2005BMC1393>.



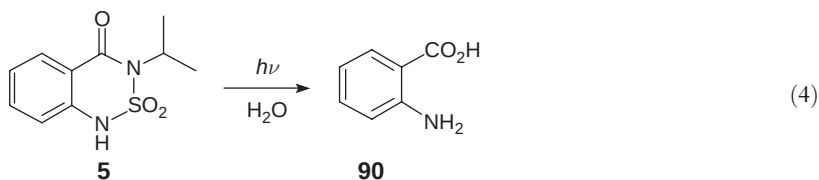
9.07.5 Reactivity of Fully Conjugated Rings

Although there is some theoretical evidence for heteroaromaticity with 2,1,3-benzothiadiazines, none of the monocyclic systems covered in this chapter possesses aromatic character. Thus, the chemistry of these systems and their benzo analogs is discussed in the following section.

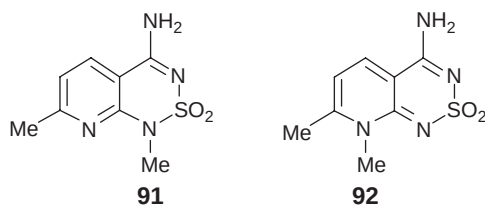
9.07.6 Reactivity of Nonconjugated Rings

9.07.6.1 Thermal and Photochemical Unimolecular Reactions

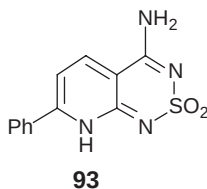
Photolysis of an aqueous solution of Bentazone (3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide, **5**) with a solar simulator affords 2-aminobenzoic acid **90**. The extinction coefficient ϵ at 300 nm was 1210 with a quantum yield of 2.0×10^{-4} (365 nm) (Equation 4) <2001FEB554>.



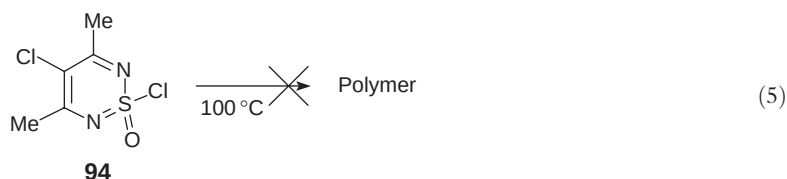
Aminopyrido[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides **91** and **92** represent a new family of laser dyes that are reasonably efficient and stable. The most outstanding characteristic of these compounds is the simultaneous lasing of the neutral and protonated species of **91** in acetonitrile <1995JPH35>.



The temporal and spectral characteristics and lasing efficiency observed for 4-amino-7-phenyl-8*H*-pyrazine[2,3-*c*]-[1,2,6]thiadiazine 2,2-dioxide **93** in acetonitrile was reproduced in a model developed to describe the amplification process of radiation in dye solutions of molecular acid-base related species. It appeared that the acid-base processes did not introduce losses during the amplification events, but redistributed the excitation energy <1995OQE1027>.

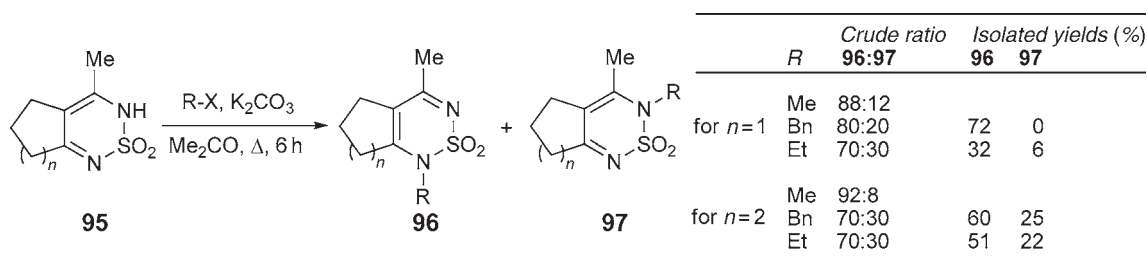


Ring-opening polymerization was attempted by heating **94** at 100 °C in a sealed, evacuated tube. This resulted in extensive charring (Equation 5) <1998ZNB532>.



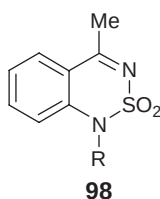
9.07.6.2 Electrophilic Attack at Nitrogen

Reaction of alkyl and benzyl halides with bicyclic thiadiazines **95** ($n = 1$) and **95** ($n = 2$) gave mixtures of isomers **96** and **97** (32–72% isolated yield at N-1 and 0–25% at N-3), whose ratio resulted from attack of the reagent on the less-hindered nitrogen. The isomer ratio was determined by ^1H NMR analysis of the crude reaction mixture (Scheme 1) <1995BMC179>.

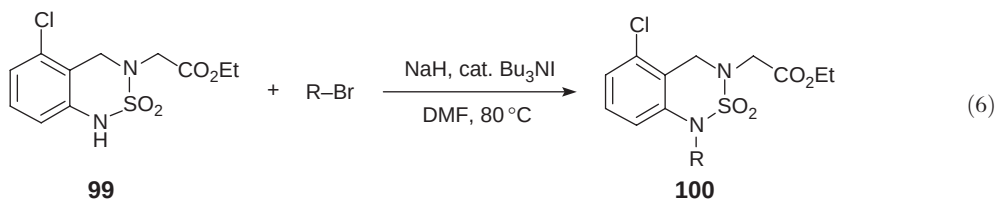


Scheme 1

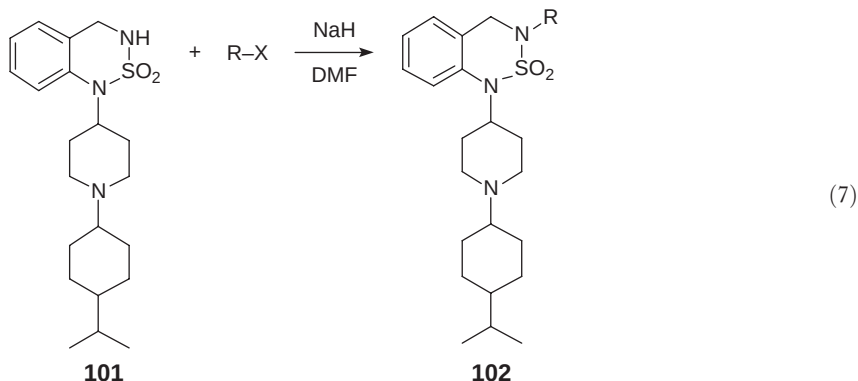
Surprisingly, benzylation of 4-methyl-2,1,3-benzothiazine 2,2-dioxide (**98**; $R = \text{H}$) gave only the 1-benzyl isomer **98** ($R = \text{Bn}$, 50%) <1995BMC179>.



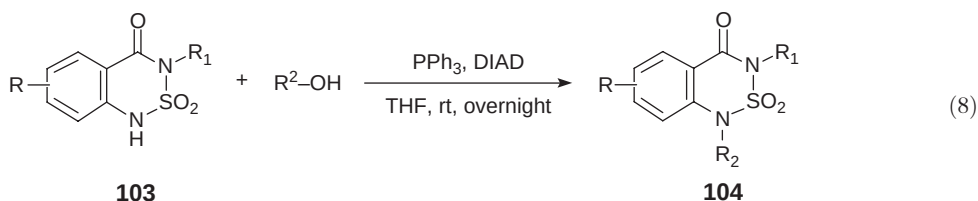
Alkylation of 5-chloro-1,4-dihydro-2*H*- λ^6 -2,1,3-benzothiadiazin-3-acetic acid 2,2-dioxide **99** with alkyl bromides using sodium hydride in dimethylformamide gave the corresponding 1-alkylated products **100** (Equation 6) <2001JMC1847>.



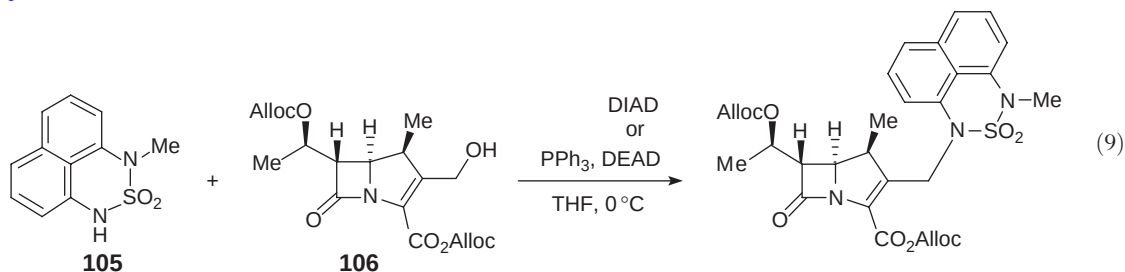
Alkylation of **101** in the other direction when the N-1 position is blocked gave **102** (Equation 7) <2004BML5045>.



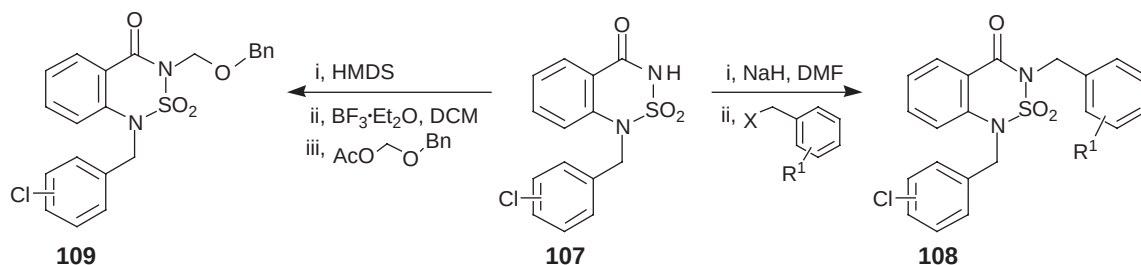
By alkylation of **103** with the appropriate alcohol, via Mitsunobu reaction, the N¹,N³-disubstituted derivatives **104** were obtained (12–74%, Equation 8) <2005BMC1393, 2004JHC747>.



It was reported also that Mitsunobu alkylation of **105** with carbapenam derivative **106** could be effected (Equation 9) <1999BML673>.



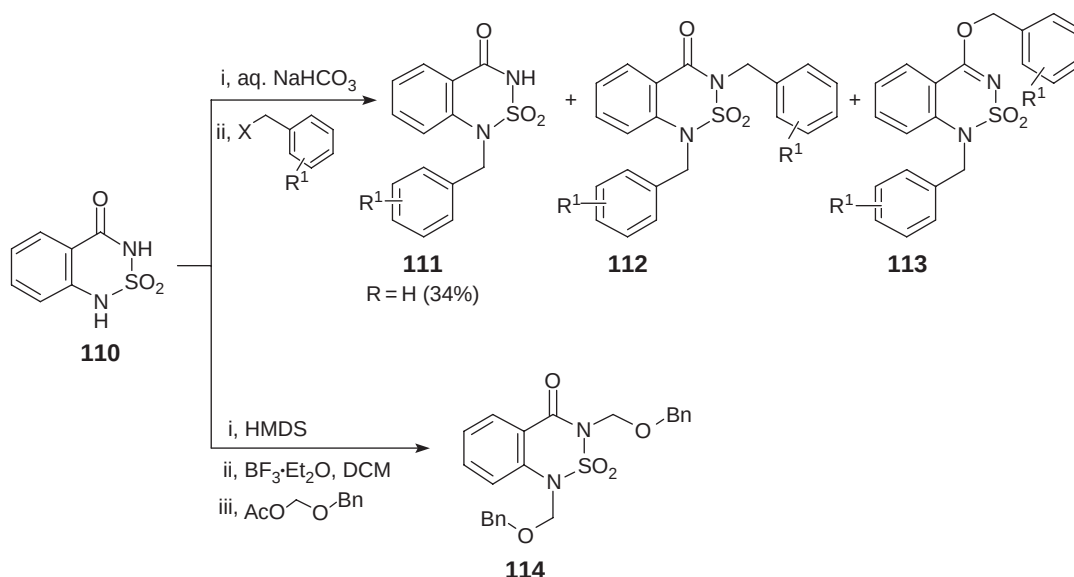
The 1-benzyl-2,1,3-benzothiadiazin-4-one 2,2-dioxide **107** was benzylated further to **108** with an appropriate benzyl halide using sodium hydride in dimethylformamide (Scheme 2) <1999BML3133>. Some modified acyclonucleosides **109** were obtained using the silylation procedure of Vorbrüggen (Scheme 2) <1974JOC3654>.



Scheme 2

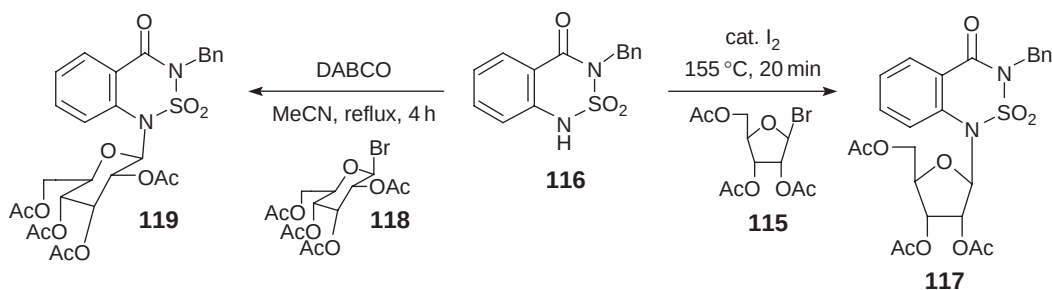
While alkylation of an already monoalkylated 2,1,3-benzothiadiazin-4-one 2,2-dioxide is straightforward, alkylation of the unalkylated parent **110** is more complex. Considering the different acidity of the two nitrogen atoms (pK_a 0.69, 7.95) <1999T12405>, the first chlorophenylmethyl fragment can be introduced in aqueous bicarbonate to give **111**

although some O,N- **113** and N¹,N²-dialkylation **112** products also can be obtained. Contrast the first alkylation using potassium carbonate in acetone with sodium hydride in dimethylformamide for the second alkylation <1999T12405, 1999JMC1145, 2003ACC107>. Using the silylation procedure described above, the bis-acylonucleoside **114** was obtained (Scheme 3) <1999BML3133>.



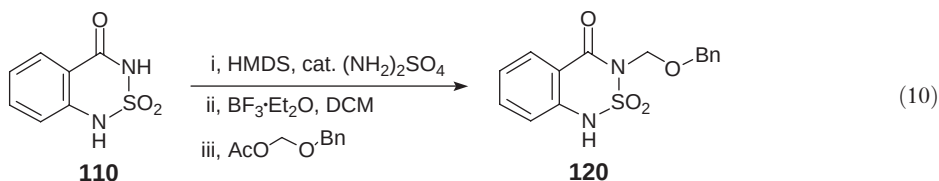
Scheme 3

Condensation of peracetylated D-ribofuranosyl bromide **115** and benzothiadiazine **116** by a direct fusion method gave the expected pseudonucleoside **117**. Similarly, peraceto bromoglucose **118** and **116** in refluxing acetonitrile in the presence of 2 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the β -anomer of the N-glucoside **119** (23%) (Scheme 4) <1996T993>.

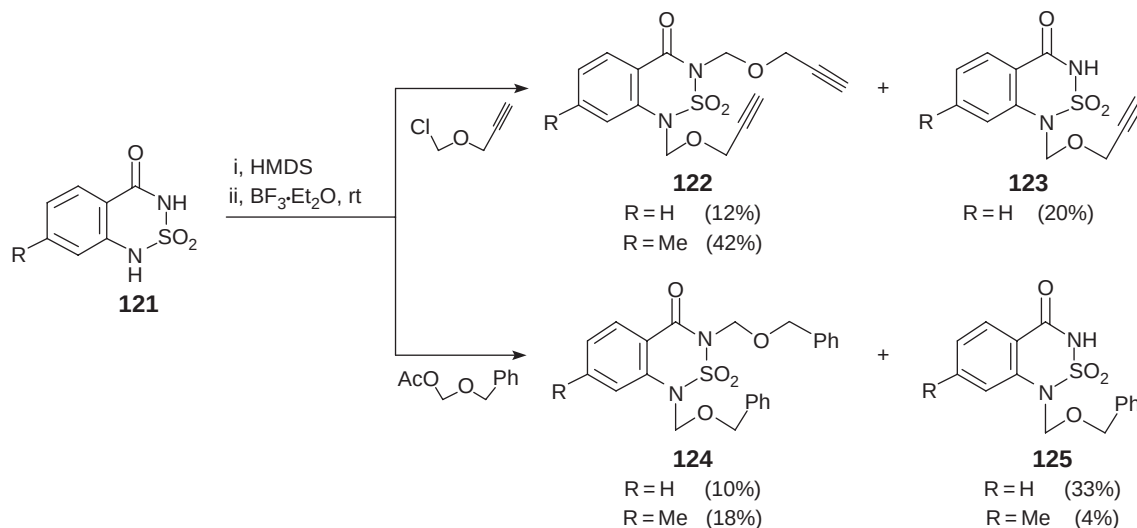


Scheme 4

The first acyclonucleosides derived from benzothiadiazinone dioxides were obtained using the Vorbrüggen silylation procedure. In all conditions tried, acycloglycosylation of **110** took place at N-3 to afford **120** (Equation 10) <1997BML1031>.

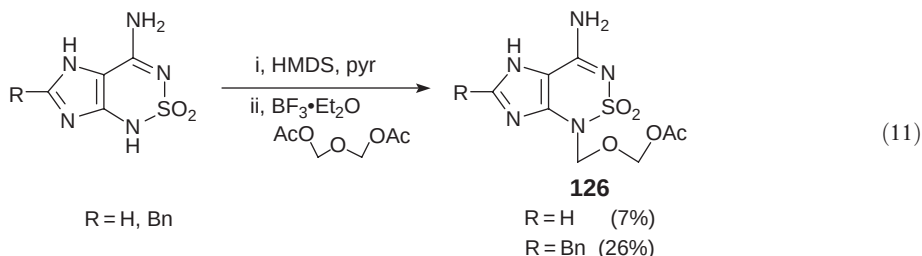


Employing this silylation procedure, thiadiazinones **121** ($R = H, Me$) reacted with either (propargyloxy)methyl chloride or acetoxymethyl benzyl ether in dichloromethane using boron trifluoride as catalyst to afford mixtures of N^1 -mono- and N^1, N^2 -disubstituted products **122–125** (Scheme 5) <1997NN265>.

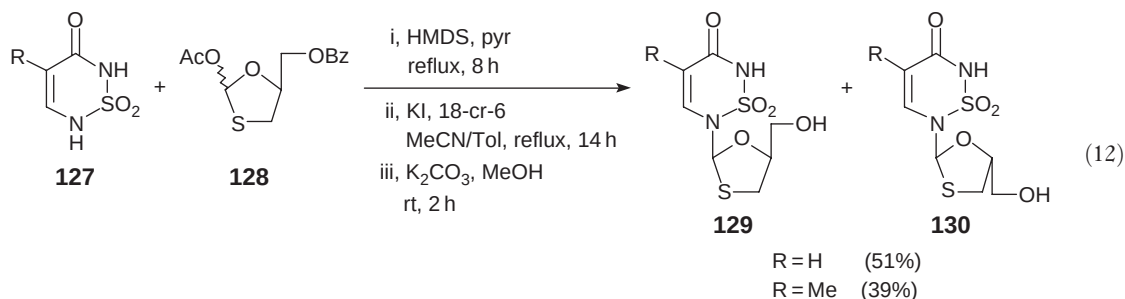


Scheme 5

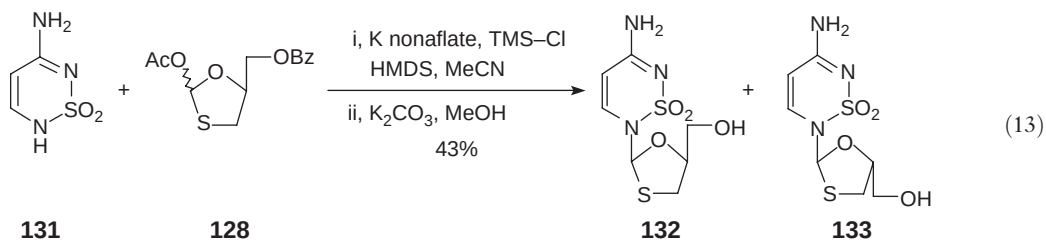
Similar modest yields were obtained in the preparation of acyclonucleosides **126** (Equation 11) <1999BMC1617>.



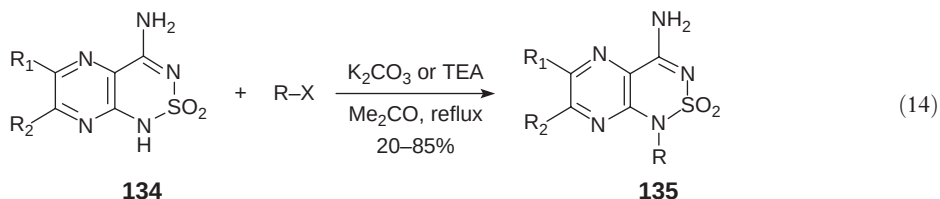
Persilylated derivatives of **127** ($R = H$), when treated with acetoxy ketal **128** followed by addition of potassium iodide and 18-crown-6 in acetonitrile at reflux, gave a 1:1 mixture of N -6-*cis*- **129** and *trans*-nucleosides **130** in 51% yield. Similarly, the thymine analogs were prepared (Equation 12) <1995H(41)87>.



In the case of 3-amino-1,2,6-thiadiazine 1,1-dioxide **131**, glycosylation was achieved using a mixture of potassium nonaflate, hexamethyldisilylazide, and trimethylsilyl chloride to obtain analogs **132** and **133** (Equation 13) <1995H(41)87>. Assessment of the relative stereochemistry was based on the ^1H NMR shifts and multiplicity of the anomeric protons that appear as a doublet in the *trans*-isomer about 0.3 ppm downfield from the doublet of doublets for the *cis*-isomer.



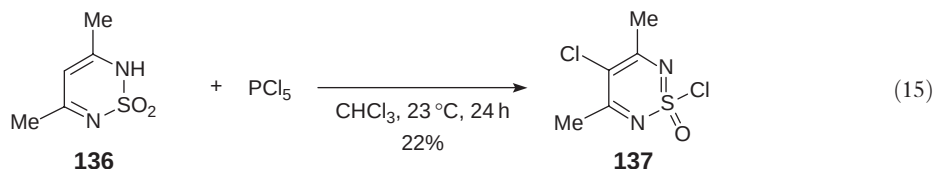
Different alkyl derivatives **135** of the pyrazino[2,3-*c*][1,2-*b*]thiadiazines **134** were prepared using the corresponding alkyl halides in acetone with either potassium carbonate or triethylamine <1999JMC1698, 1999JMC3279, 2000JMC4219> or with alkyl sulfates in water <1999JMC3279> (Equation 14).



9.07.6.3 Electrophilic Attack at Carbon

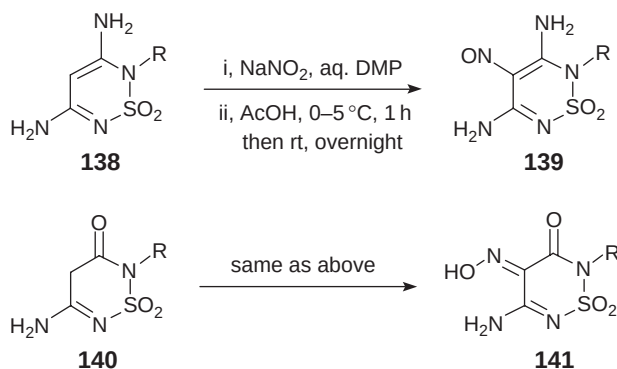
9.07.6.3.1 Halogenation

The sulfamuric chloride **137** was obtained as colorless crystals by reaction of thiadiazine **136** with phosphorus pentachloride in chloroform (Equation 15) <1998ZNB532>.



9.07.6.3.2 Nitrosation

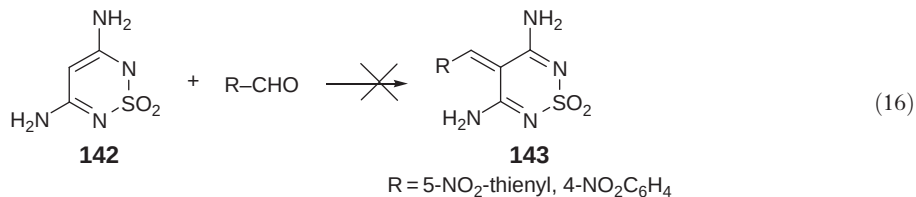
Nitrosation of 3,5-diamino-2*H*-1,2,6-thiadiazine 1,1-dioxides **138** and 5-amino-3-oxo-3,4-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides **140** provided the 4-nitroso derivatives **139** (58–96%) and 4-hydroxyimino compounds **141** (50–94%), respectively (Scheme 6) <1996J(P2)293>.



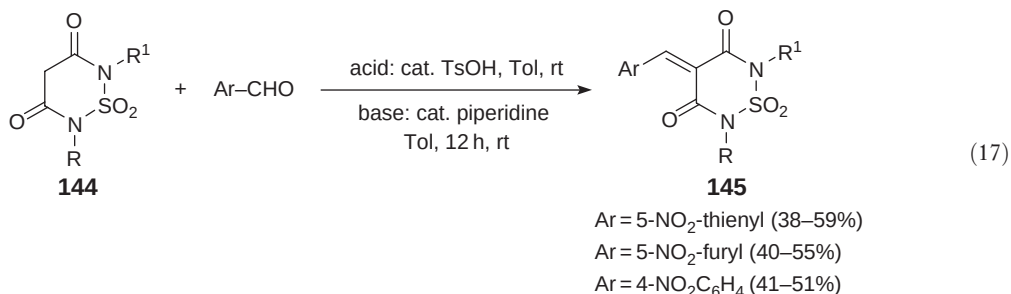
Scheme 6

9.07.6.3.3 Reaction with aldehydes

Attempts to synthesize analogs of **143** ($R = 5\text{-NO}_2\text{-2-furyl}$) following the reported procedure <1992AP509> were unsuccessful. Neither of the nitro aldehydes used reacted with **142**, starting materials being recovered in all cases (Equation 16) <1999AF759>.

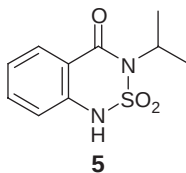


The putatively more reactive **144** ($R^1 = \text{Bn, PhCH}_2\text{CH}_2, \text{Bu, hexyl, cyclohexyl}$) condensed successfully with nitro aldehydes to afford **145** using either an acid- (38–55%) or base-mediated (41–59%) protocol (Equation 17) <1999AF759>.



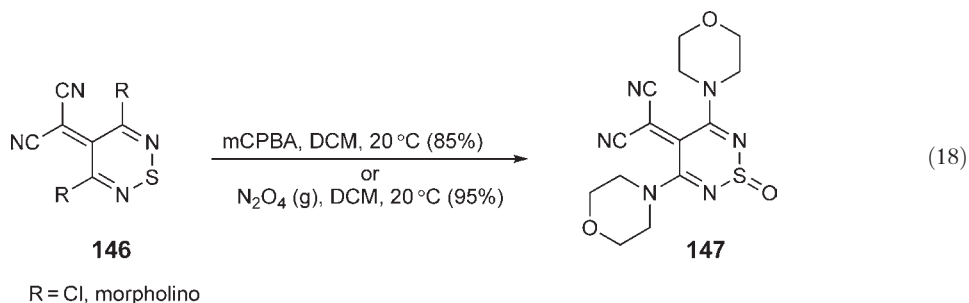
9.07.6.3.4 Oxidation

The kinetics of ozonization of the herbicide Bentazone **5** were studied. A consumption of 2 moles of ozone per mole of herbicide degraded was determined for the direct reaction. An expression for the kinetic rate constants was proposed <1996JSH519>.



9.07.6.4 Electrophilic Attack at Sulfur

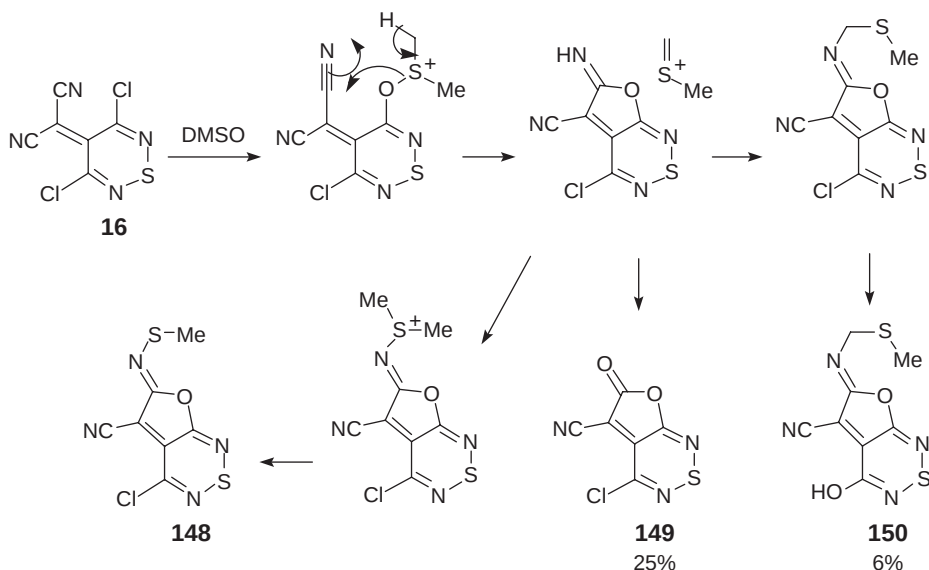
The oxidation of thiadiazine **146** ($R = \text{Cl}$) with *m*-chloroperoxybenzoic acid or with dinitrogen tetroxide was unsuccessful, neither sulfoxide nor starting material being recovered. However, oxidation of the 3,5-dimorpholinothiadiazone **146** ($R = 1\text{-morpholino}$) with either oxidant gave excellent yields of sulfoxide **147** (Equation 18) <2000J(P1)1081>.



9.07.6.5 Nucleophilic Attack at Carbon

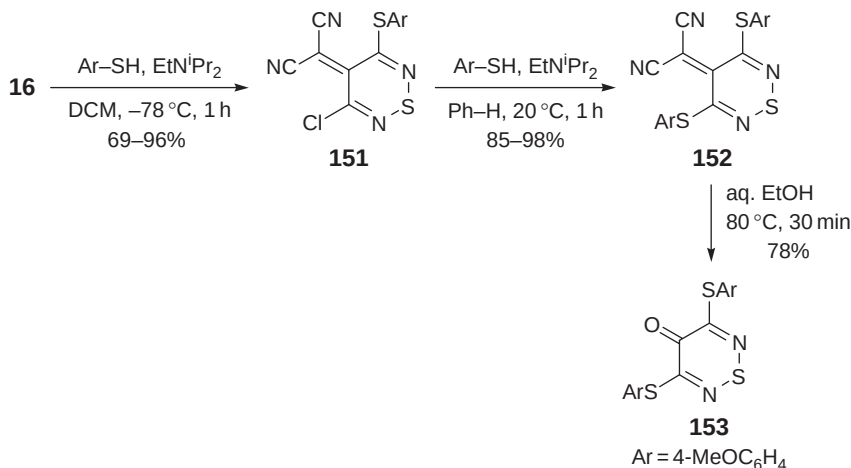
9.07.6.5.1 By oxygen and sulfur nucleophiles

Thiadiazine **16** reacted with dimethyl sulfoxide at room temperature to give a separable mixture of **148**, **149**, and **150**. Introduction of the oxygen atom presumably occurred through reaction with dimethyl sulfoxide acting as a nucleophile and displacing a chlorine in **16**. A mechanistic rationale involving such an attack was proposed and is outlined in [Scheme 7](#) <2000J(P1)1081>.



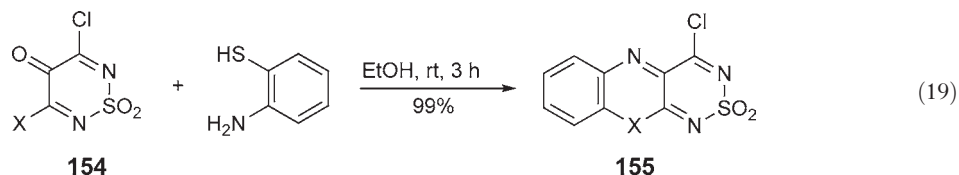
Scheme 7

Dichlorothiadiazine **16** reacted with thiophenols in the presence of tertiary amines, preferably diisopropylethylamine (Hünig's base), to afford mono- and disubstituted derivatives **151** and **152**. Monosubstitution was achieved at -78°C while the second chloride was displaced at 20°C . In the absence of base, no reaction was observed ([Scheme 8](#)) <2000J(P1)1081>. Attempted crystallization of **152** (Ar = 4-MeOC₆H₄) from aqueous ethanol gave the 1,2,6-thiadiazin-4-one **153** in good yield ([Scheme 8](#)) <2000J(P1)1081>.

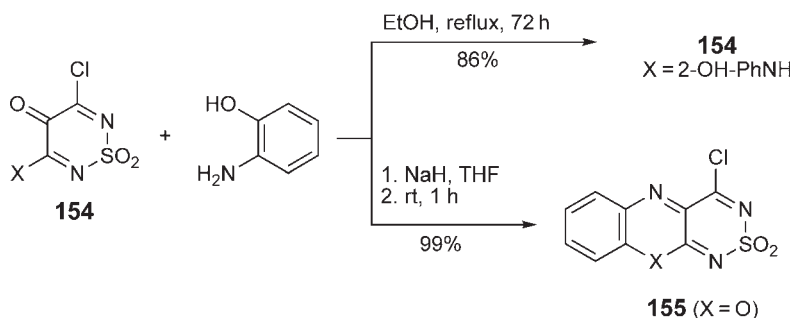


Scheme 8

Thiadiazine **154** (X=Cl) reacted with 2-aminothiophenol to afford 4-chloro[1,2,6]thiadiazino[3,4-*b*][1,4]benzothiazine **155** (X=S) (Equation 19) <2000J(P1)2601>.

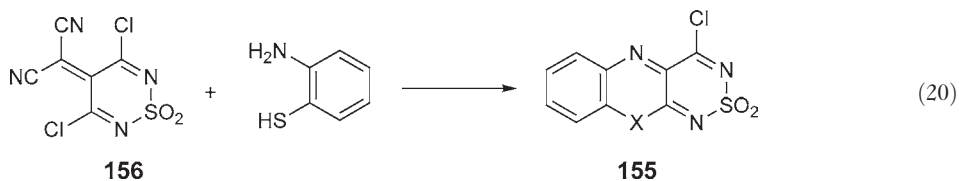


By contrast, 2-aminophenol reacted slowly with **154** (X=Cl) in refluxing ethanol to afford **154** (X=2-(OH)-PhNH) (86%) where the chloro group was displaced by the amine. However, **154** (X=Cl) reacted rapidly and completely with the sodium salt of aminophenol to give **155** (X=O) (Scheme 9) <2000J(P1)2601>.

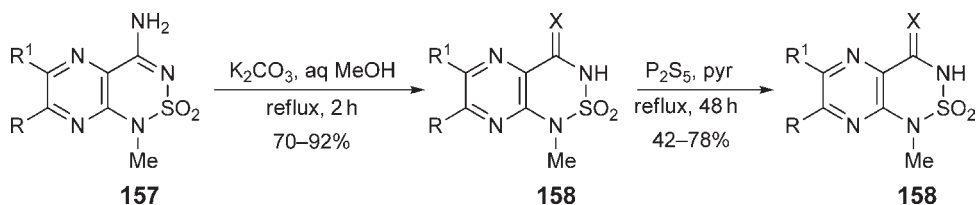


Scheme 9

Similarly, **156** reacted with 2-aminothiophenol to afford **155** (X=S) (87%). Presumably, the reaction is the same as in Equation (19) but with expulsion of malonitrile (Equation 20) <2000J(P1)2601>.

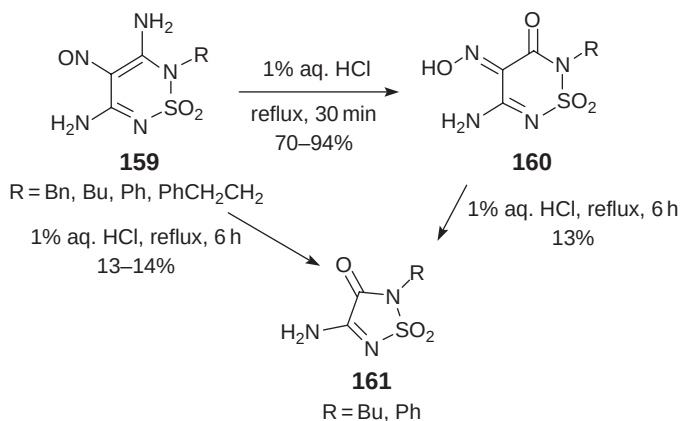


Hydrolysis of the 4-amino group provided entry to the corresponding 4-oxo derivatives and, so, **157** was converted readily to the 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-ones **158** (X=O) by reaction with potassium carbonate in aqueous methanol. The parent system was prepared previously by reaction of 4,5-diamino-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide with 1,2-dicarbonyl compounds <1984JHC861>, but the starting diamine was difficult to prepare, so this is a more versatile method for preparation of the 4-oxo compounds. The 4-oxo compounds **158** (X=O) were converted to the corresponding 4-thioxo derivatives **158** (X=S) by reaction with phosphorus pentasulfide (Scheme 10) <2003HCA139>.



Scheme 10

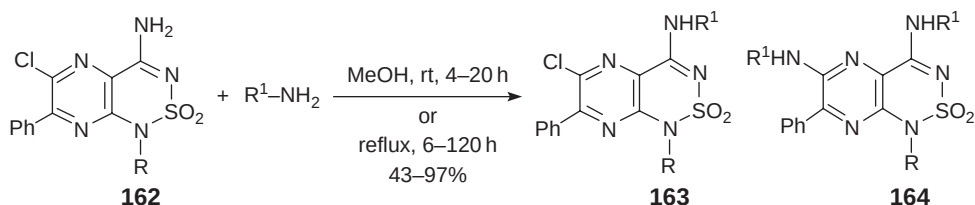
Mild acid hydrolysis of **159** gave the oxo analog **160**; however, more vigorous conditions led to ring contraction products **161** (Scheme 11) <1996J(P2)293>.



Scheme 11

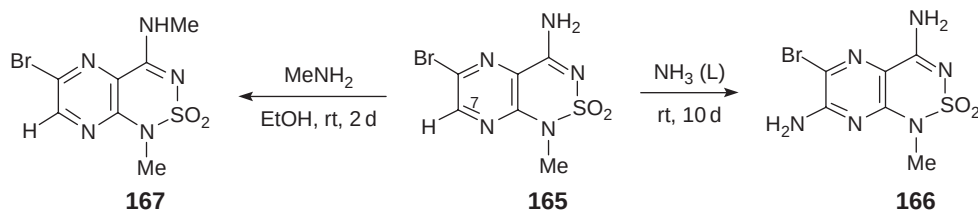
9.07.6.5.2 By nitrogen nucleophiles

A transamination reaction was developed to prepare 4-monosubstituted amino pyrazino[2,3-*c*][1,2,6]thiadiazines. Thus, reaction of **162** with a variety of amines in alcoholic solvents gave the corresponding amines **163**. This method can also be used with secondary amines such as pyrrolidine (50% yield) (Scheme 12) <2000JMC4219, 2003HCA139>. When reacting an excess of methylamine with **162** (R = Et), the 4,6-bis-methylamino compound **164** (R = Et, R¹ = Me) was obtained. Here, nucleophilic chlorine displacement occurred in addition to the desired displacement reaction.



Scheme 12

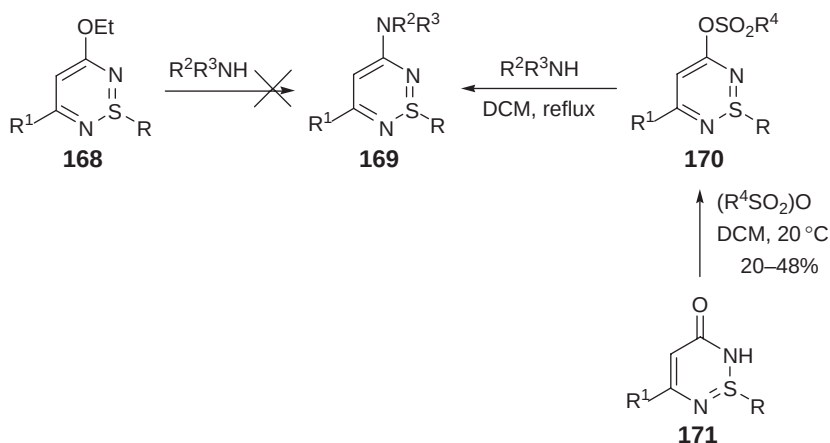
There was different reactivity shown if the C-7 position was unsubstituted. Thus, reaction of **165** with ammonia gave the addition/oxidation product **166**, whereas, with methylamine, only the transamination product **167** was obtained (Scheme 13) <2003HCA139>.



Scheme 13

Reaction of imidates **168** with different amines using various reaction conditions resulted only in isolation of the starting material. If, instead, the sulfonates **170**, prepared from λ⁴-thiazine **171** with methanol and *p*-toluenesulfonic

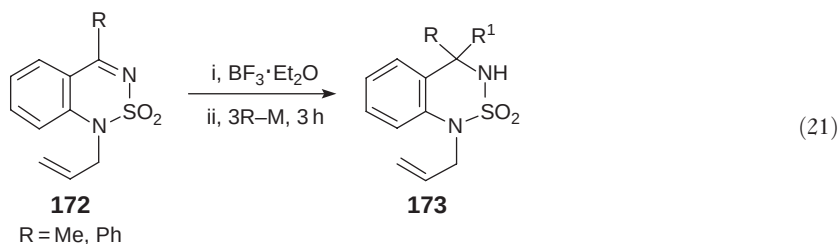
acid anhydrides in dichloromethane at 20 °C, were reacted with amines, the desired amino compounds **169** were obtained. In the case where $R^1 = \text{Bn}$, as compared to CF_3 , higher temperatures and longer reaction times were required and lower yields were obtained, confirming that electron-withdrawing substituents facilitate nucleophilic attack at C-3 (**Scheme 14**) <2003JOC3817> (see [Section 9.07.8.5](#)).



Scheme 14

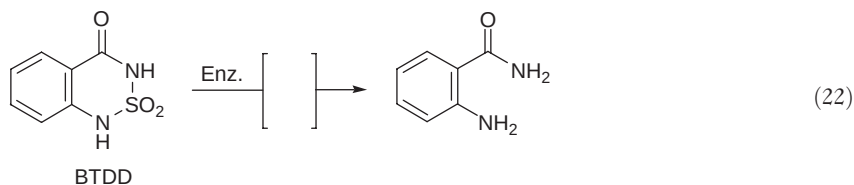
9.07.6.5.3 By carbon nucleophiles

Reaction of **172** with ethylmagnesium bromide did not give the desired addition product, only starting material being recovered. However, use of zinc bromide or ytterbium triflate allowed formation of the addition product **173** ($R = \text{Et}$, $R^1 = \text{Me}$). The best results (35%) were obtained by using boron trifluoride etherate as the Lewis acid. The moderate yield that resulted from the Grignard reagents could be improved using more nucleophilic lithium reagents (65%). Lithium anions from ethyl acetate, *N,N*-dimethyl acetamide, or methyl *p*-toluenesulfoxides in the presence of boron trifluoride etherate gave the corresponding addition products. Reagents such as Me_2CuLi , AlEt_2CN , TMS-CN , or KCN did not react even at room temperature and extended reaction times. These results indicated that ketimine addition did not occur when the nucleophilicity of the organometallic species was low ([Equation 21](#)) <2000TL9825, 2000BML193>.



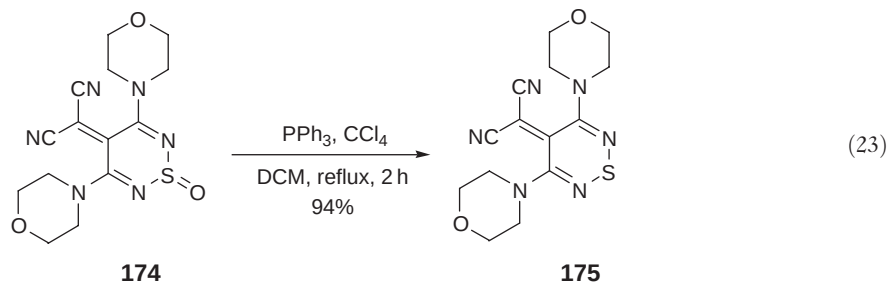
9.07.6.6 Nucleophilic Attack at Sulfur

Pure cultures of aerobic bacteria were found that utilize sulfamate or 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (BTDD) as the sole source for growth and thus cleave an N-SO₂ bond ([Equation 22](#)) <1999FML107>.



9.07.6.7 Reduction

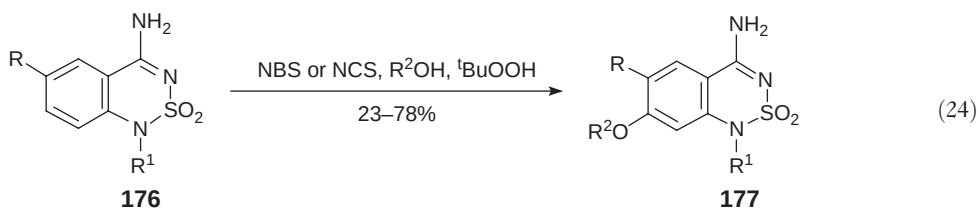
The sulfoxide **174** was reduced with triphenylphosphine and carbon tetrachloride to the sulfide **175** (Equation 23) <2000J(P1)1081>.



9.07.7 Reactivity of Substituents Attached to Ring Carbon Atoms

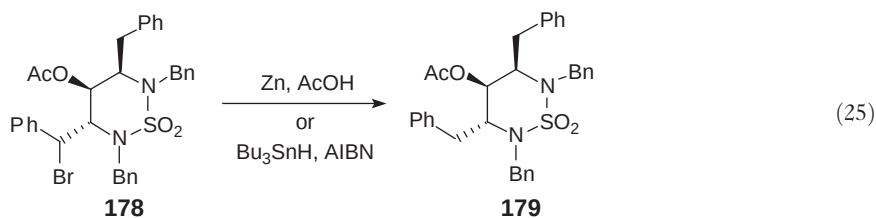
9.07.7.1 Aryl Groups

An alkoxylation at the C-7 position of compound **176** (to yield **177**) occurred using *N*-bromosuccinimide or *N*-chlorosuccinimide in an alcohol solvent containing a catalytic amount of *tert*-butyl peroxide. The formation of **177** does not occur through a conventional mechanism; neither direct addition of alcohol to C-7 or substitution of a C-7 halo compound is operative, but the reaction is mediated by the presence of free radicals (Equation 24) <2002EJO2109>.

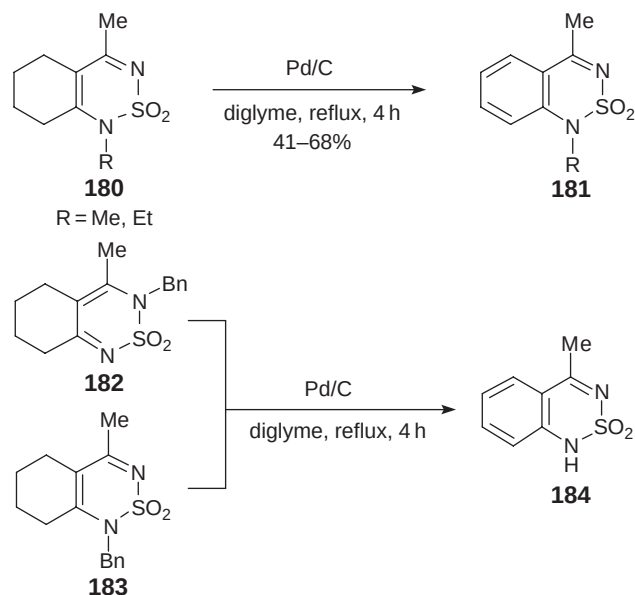


9.07.7.2 Alkyl Groups

Reduction of **178** with zinc dust gave **179** as the major product, but the reduction was not clean since an unidentified olefinic by-product was obtained under a variety of conditions (Equation 25) <1998JOC4755>.



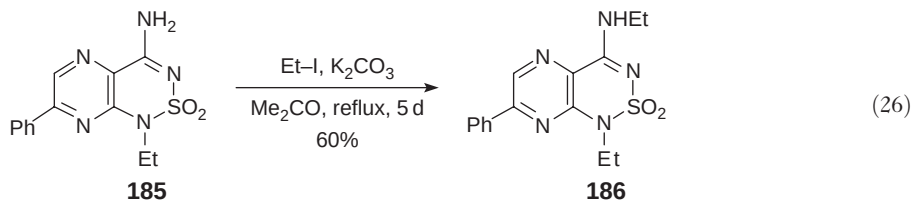
Aromatization of some bicyclic thiadiazines by dehydrogenation over palladium at high temperature was effected. Thus, compounds **181** were obtained in modest yields (41–68%) from **180**. When nitrogens were benzylated as in **182** and **183**, aromatization was accomplished with concomitant hydrogenolysis of the benzyl groups affording **184** (Scheme 15) <1995BMC179>.



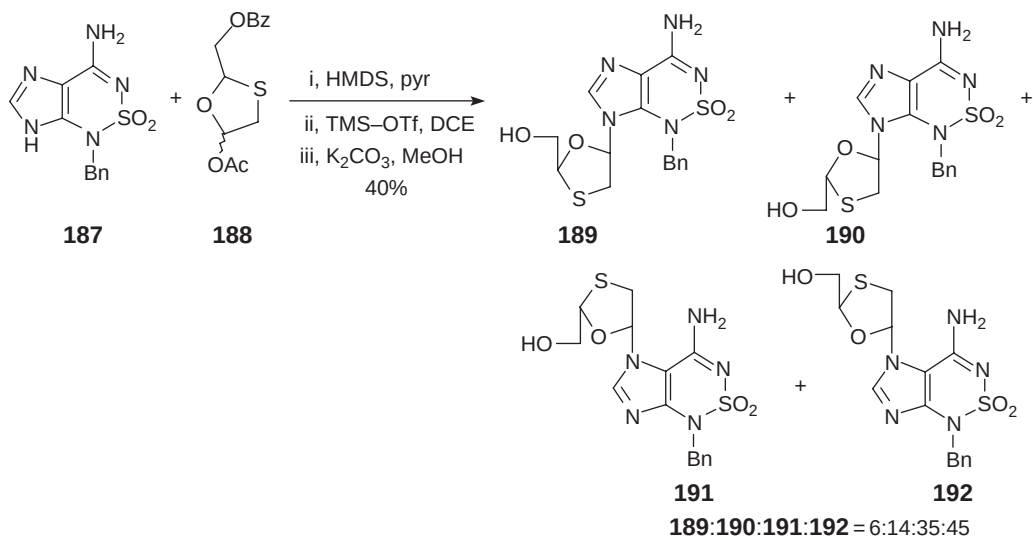
Scheme 15

9.07.7.3 Amino Groups

Reaction of 4-amino compound **185** with ethyl iodide and potassium carbonate gave the 4-ethylamino compound **186**. However, it was difficult to prevent formation of mixtures of mono- and dialkyl products (Equation 26) <2000JMC4219>.

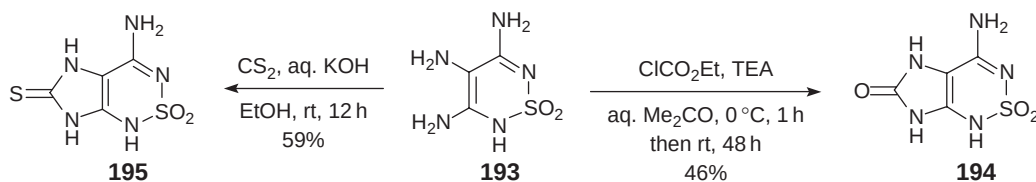


Glycosylation of **187** with acetal **188** under Vorbrüggen's conditions afforded the stereo- and regioisomers **189–192** (Scheme 16) <1995H(41)87>.



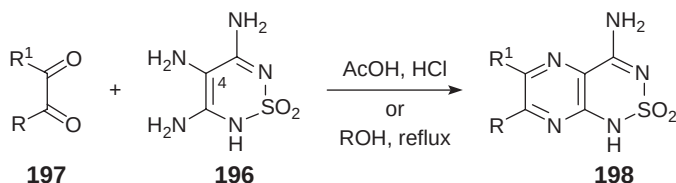
Scheme 16

Cyclocondensation reactions of 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide **193** with various acceptors allowed formation of bicyclic compounds. In the first instance, condensations with methyl chloroformate or carbon disulfide provided 6-oxo **194** and 6-thio **195** derivatives of 4-amino-1*H*,5*H*-imidazo[4,5-*c*][1,2,6]thiadiazine 2,2-dioxide, respectively (**Scheme 17**) <1999BMC1617>.



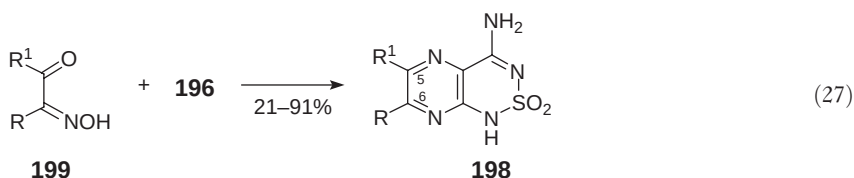
Scheme 17

Reaction of **196** with symmetric 1,2-dicarbonyl compounds **197** ($\text{R}=\text{R}^1$) afforded the corresponding 6,7-disubstituted compounds **198** ($\text{R}=\text{R}^1$, 45%). When the dicarbonyl compound was not symmetric (**197**, $\text{R}\neq\text{R}^1$), in principle, two regioisomers were possible. The C-4 amino group reacted with the more reactive carbonyl and, thus, phenylglyoxal and ethyl glyoxal gave the corresponding 7-phenyl ($\text{R}=\text{Ph}$, 73%) and 7-ethyl ($\text{R}=\text{Et}$, 42%) derivatives, respectively, and phenyl-1,2-propanedione (**197**: $\text{R}=\text{Ph}$, $\text{R}^1=\text{Me}$), 2,3-heptanedione (**197**: $\text{R}=\text{Bu}$, $\text{R}^1=\text{Me}$), and 4-methyl-2,3-pentanedione (**197**: $\text{R}=\text{Pr}$, $\text{R}^1=\text{Me}$) gave the corresponding 6-methyl-7-substituted derivatives **198** ($\text{R}^1=\text{Me}$, $\text{R}=\text{Ph}$ (71%), Bu (73%) and Pr (53%), respectively) (**Scheme 18**) <1999JMC1698, 1999JMC3279, 2000JMC4219>.



Scheme 18

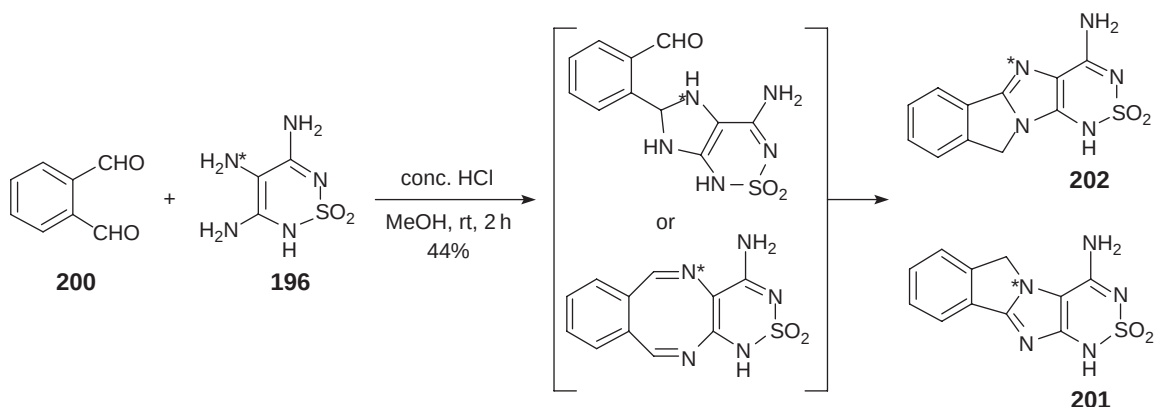
From α -oximino ketones **199**, it was possible to obtain selectively the C-6- or C-7-substituted derivatives, depending on which substituent was attached to the carbonyl or the oximino function (**Equation 27**) <1999JMC1698, 1999JMC3279, 2000JMC4219>.



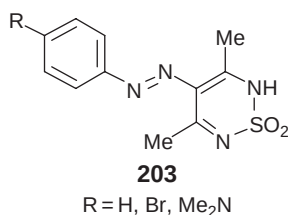
In principle, both thiadiazinoimidazo[2,1-*a*]isoindoles **201** and **202** could arise from the reaction of *o*-phthaldehyde **200** with **196**. However, only one of these compounds was isolated and the ^1H and ^{13}C NMR spectra were compatible with both structures. The product structure was elucidated by using ^{15}N -enriched **196** unequivocally labeled on the 4-amino group (prepared by reaction of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide with 5% enriched $\text{Na}^{15}\text{NO}_2$ in acetic acid followed by dithionite reduction). The structure was then shown by ^{15}N NMR to be **201** (**Scheme 19**) <1998H(48)1833>.

9.07.7.4 Other Nitrogen-Linked Substituents

Besides the main reduction wave, no other wave was obtained for 3,5-dimethyl-4-(4*R*-phenylazo)-2*H*-1,2,6-thiazine 1,1-dioxide (**203**: $\text{R}=\text{H}$). The reductive polarographic behavior of **203** in aqueous Bratton–Robinson buffers, in the pH range 2.5–11.4, takes place in a single two-electron transfer, giving an irreversible wave corresponding to reduction of the azo group <1998BEC180>.

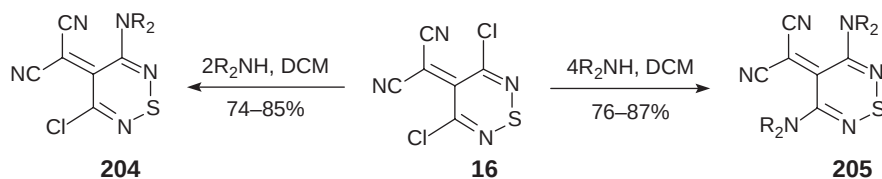


Scheme 19



9.07.7.5 Halogen Atoms

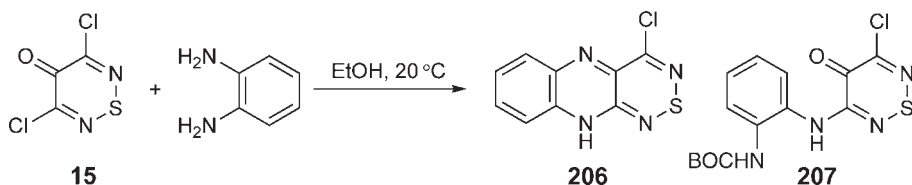
Both chlorine atoms on **16** were replaced smoothly to give the red, monoamino derivatives **204** and the blue, diamino derivatives **205**. Nonsterically hindered amines displaced both chlorines readily; piperidine displaced the first chlorine at -78°C and the second at -30°C . Bulky amines gave lower yields and required more severe conditions for complete reaction. A limit was reached with diisopropylamine, where only the monoamine derivative could be obtained in a maximum of 30% yield (dichloromethane at reflux for 3 h with 6 equiv of amine) (Scheme 20) <2000J(P1)1081>.



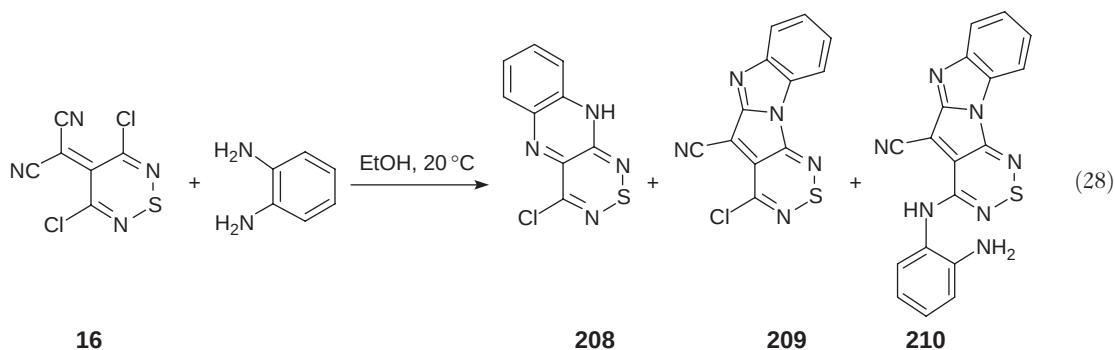
Scheme 20

Reaction of **15** with 1,2-diaminobenzene gave **206** (96%). The first step was shown to be nucleophilic displacement of chlorine by reaction of **15** with the mono-*t*-butoxycarbonyl (mono-BOC) analog to afford **207** (76%) that upon deprotection gave **206** (72%) (Scheme 21) <2000J(P1)2601>.

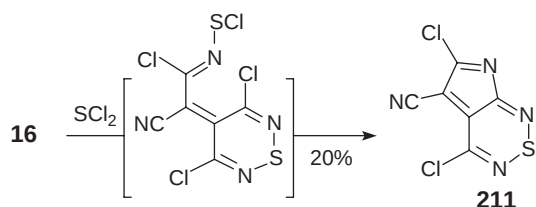
The reaction of 1,2-diaminobenzene with **16** was more complex. The major products **208** (42%) and **209** (19%) were obtained along with a small amount (1%) of **210** (Equation 28) <2000J(P1)2601>.



Scheme 21



Treatment of **16** with sulfur dichloride produced 4,6-dichloro-5-cyanopyrazolo[3,2-*c*][1,2,6]thiadiazine (**211**, 20%) (Scheme 22) <2000J(P1)1089>.



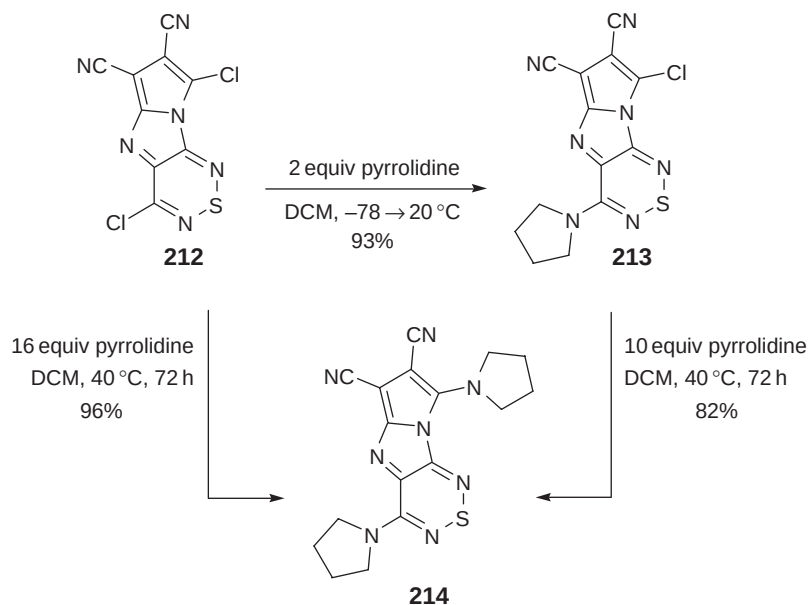
Scheme 22

Both chlorine atoms in pyrroloimidazothiadiazine **212** were displaced sequentially by pyrrolidine. With 2 equiv of pyrrolidine, **213** was formed and then further transformed to **214** with 10 equiv of pyrrolidine. The latter compound was obtainable directly by reaction of **212** with 16 equiv of pyrrolidine (Scheme 23) <2000J(P1)1089>.

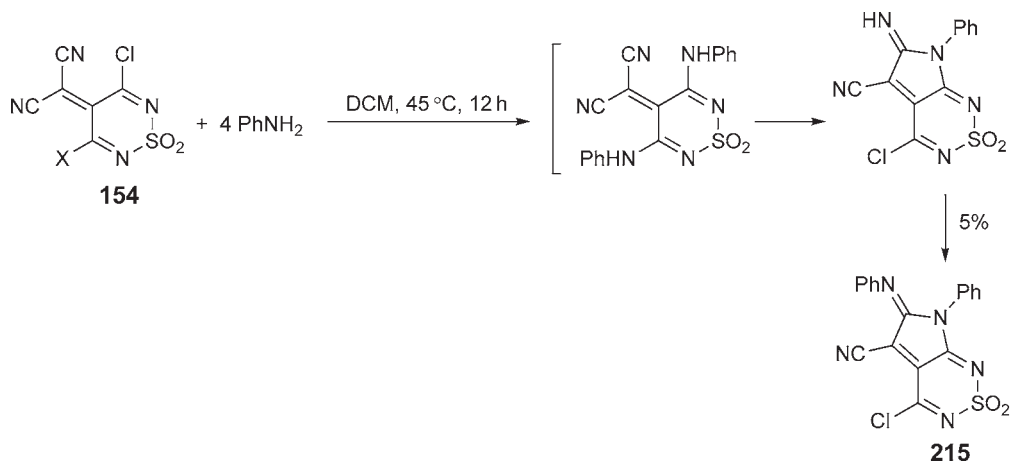
Attempts to displace both chlorine atoms in **154** ($\text{X}=\text{Cl}$) with primary amines or ammonia led to complex mixtures. Reaction with aniline gave a low yield of **215** which was tentatively assigned the structure shown based on spectrographic grounds (Scheme 24) <2000J(P1)1081>.

9.07.8 Reactivity of Substituents Attached to Ring Heteroatoms

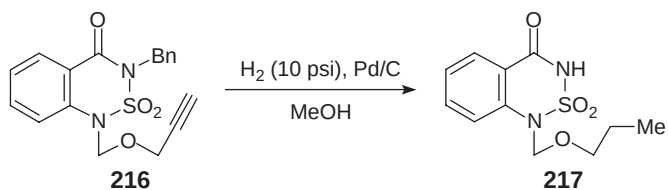
Catalytic debenzoylation of 3-benzyl-1-substituted acyclic nucleoside **216** was effected (Equation 29) <1997BML1031, 1999JMC1145>. As might be expected in the case of **216**, reduction of the acetylene occurred concomitantly with debenzoylation (90% yield) <1999JMC1145>.



Scheme 23



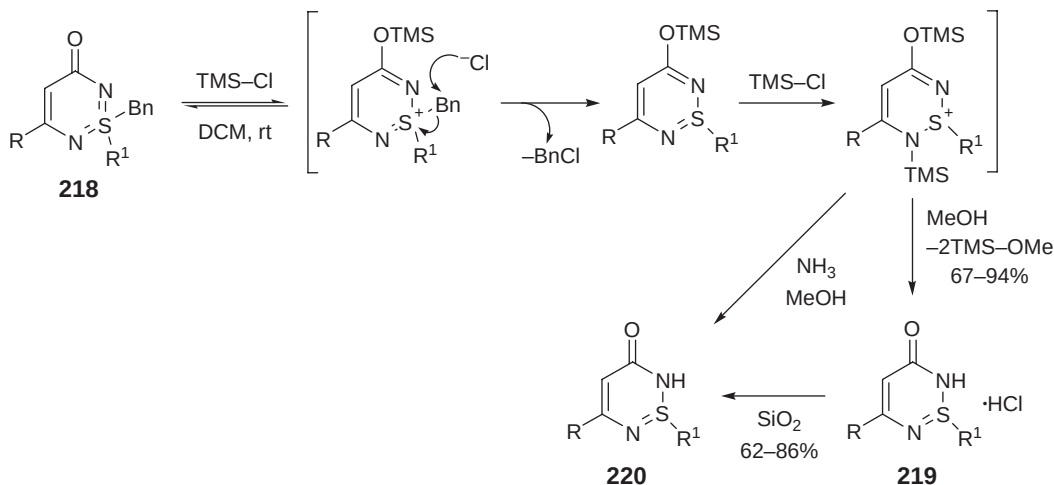
Scheme 24



(29)

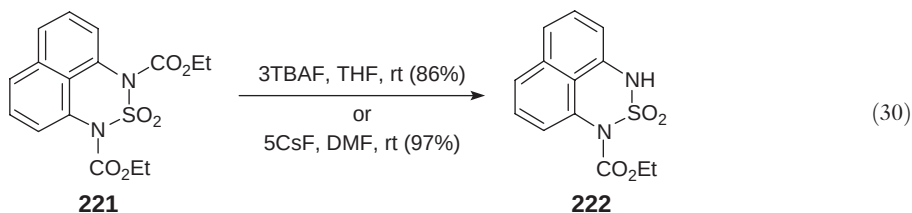
Attempts to S-debenzylate 1 λ^6 ,2,6-thiadiazines **218** with catalytic tosic acid in ethanol at reflux, a method that was useful in the synthesis of the related 1 λ^4 ,2,4,6-thiatriazines <1988ZNB763, 1994PS315, 1988CB383> was unsuccessful <2003JOC3817>.

Reaction of **218** with 2 equiv of trimethylsilyl chloride in dry dichloromethane at room temperature, followed by addition of methanol, provided the corresponding hydrochlorides **219** in good yield. These latter may be considered as a new type of cyclic *S*, *S*-diamino sulfonium salt. If, in the desilylation step, a methanolic ammonia solution were used, the deprotonated thiadiazines **220** were obtained. The latter compounds were obtained also by column chromatography of **219** (Scheme 25) <2003JOC3817>.



Scheme 25

A mild, efficient method for the selective differentiation of a diacylated sulfamide was discovered. By treatment of **221** with fluoride ion, good yields of the monoprotected derivative **222** were obtained (Equation 30) <2001OL4247>.



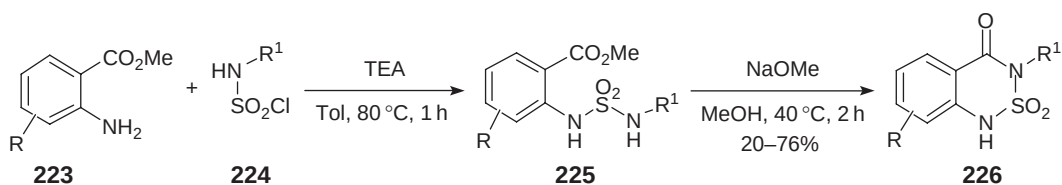
9.07.9 Ring Synthesis from Acyclic Compounds Classified by Numbers of Ring Atoms Contributed by Each Component

9.07.9.1 By Formation of One Bond

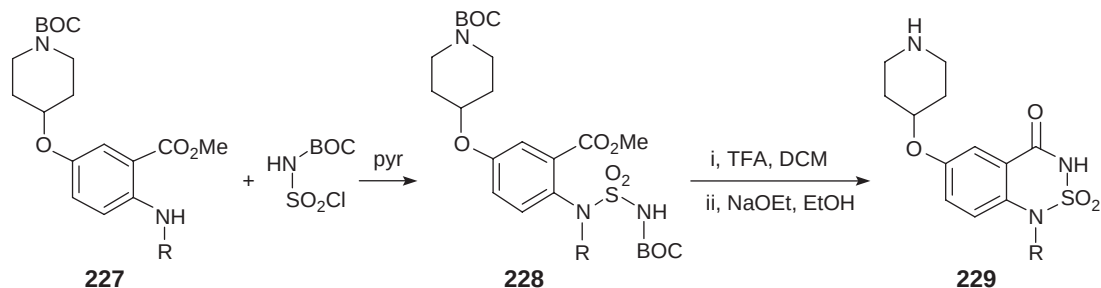
9.07.9.1.1 Between carbon and nitrogen

Treatment of the substituted methyl anthranilates **223** with sulfamyl chlorides **224** by the method of Cohen and Klarberg <1962JACS1994> gave N-3-substituted 2,1,3-benzothiadiazin-4-ones **226** (Scheme 26) <2004JHC747>. Generally, the intermediate *N*-arylsulfamides (e.g., **225**) were cyclized *in situ* with aqueous sodium hydroxide <2005BMC1393, 2000JMC3218, 2000JMC683>. The use of sodium methoxide rather than 6N sodium hydroxide for the cyclization improved yields <2004JHC747>.

The anthranilic acid derivatives **227** were reacted with *tert*-butyl chlorosulfonylcarbamate <2002BMC1509> in pyridine to afford sulfamides **228**. Conversion of the latter to the corresponding benzothiadiazin-4-ones **229** was effected by trifluoroacetic acid deprotection followed by cyclization with ethanolic sodium ethoxide (Scheme 27) <2003BMC367>.

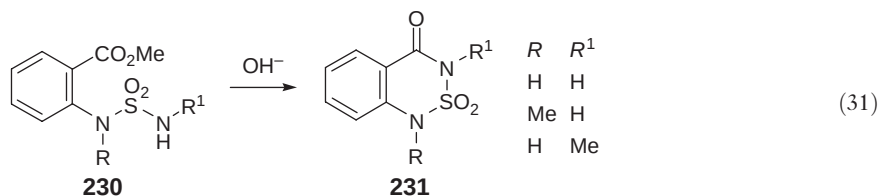


Scheme 26



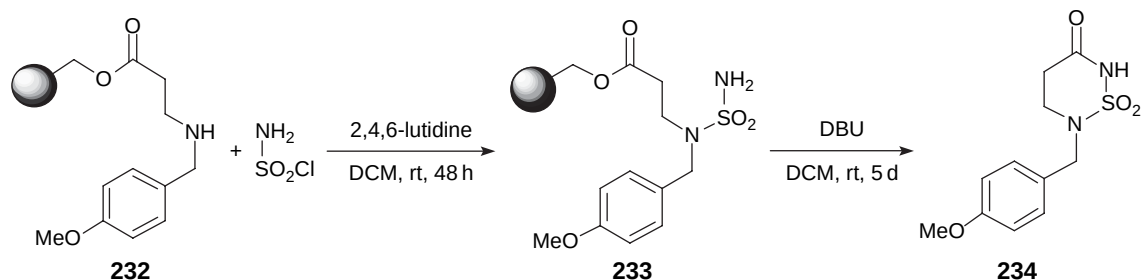
Scheme 27

The reaction kinetics of the base-catalyzed cyclizations of benzenesulfamides **230** ($R = R^1 = H$) <1995CCCC79> and methylated benzenesulfamides ($R = Me$, $R^1 = H$; $R = H$, $R^1 = Me$) <1996MOL170> to the corresponding 2,1,3-benzothiadiazin-4(3*H*)-one 1,1-dioxides **231** were determined (Equation 31).



(31)

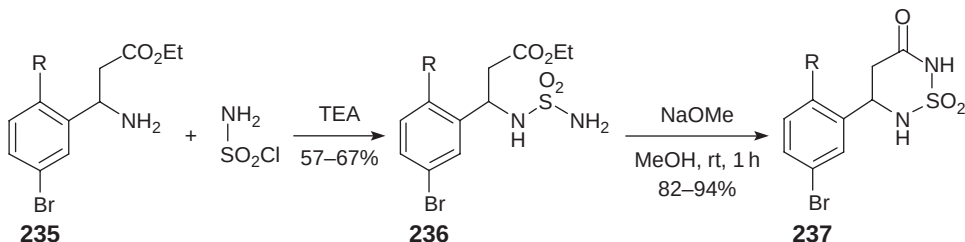
A solid-phase variant of the above synthesis utilized previously prepared MBHA-AB resin-bound **232** in reaction with sulfamyl chloride. The crude product from treatment of **233** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 48 h was analyzed by liquid chromatography–mass spectrometry (LC–MS), which indicated the presence of the desired product **234** as the major component (56%) of the mixture. A significant amount (26%) of unidentified material ($m/z = 237$) was also present. As the focus of this work was preparation of sulfahydantoins, the effort to optimize the synthesis of **234** was not undertaken (Scheme 28) <2001JCO290>.



Scheme 28

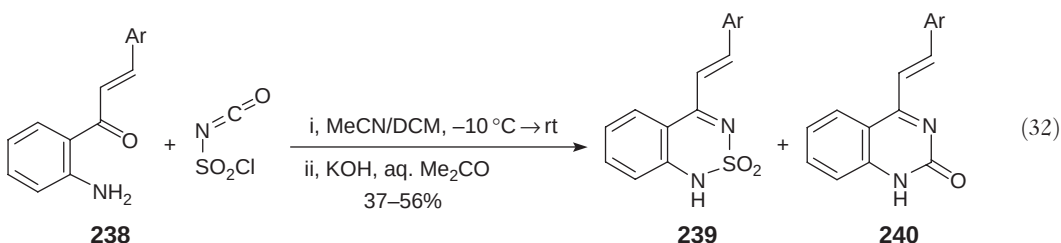
β -Amino esters **235** were reacted with sulfamyl chloride prepared from chlorosulfonyl isocyanate and water in tetrahydrofuran. The procedure gave improved yields of **236** compared to the formic acid procedure

<1989JOC3077>. The sulfamoylated products **236** underwent smooth cyclization with sodium methoxide in methanol to afford the substituted ring system **237** (Scheme 29) <2005SL834>.

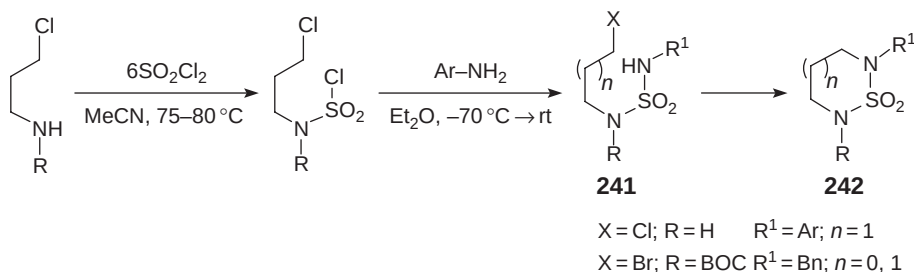


Scheme 29

Reaction of 2-aminochalcones **238** with chlorosulfonyl isocyanate (CSI) gave a mixture of 1*H*-2,1,3-benzothiazine 2,2-dioxides **239** and 2(1*H*)-quinazolinones **240** (Equation 32) <1995SC1933>.



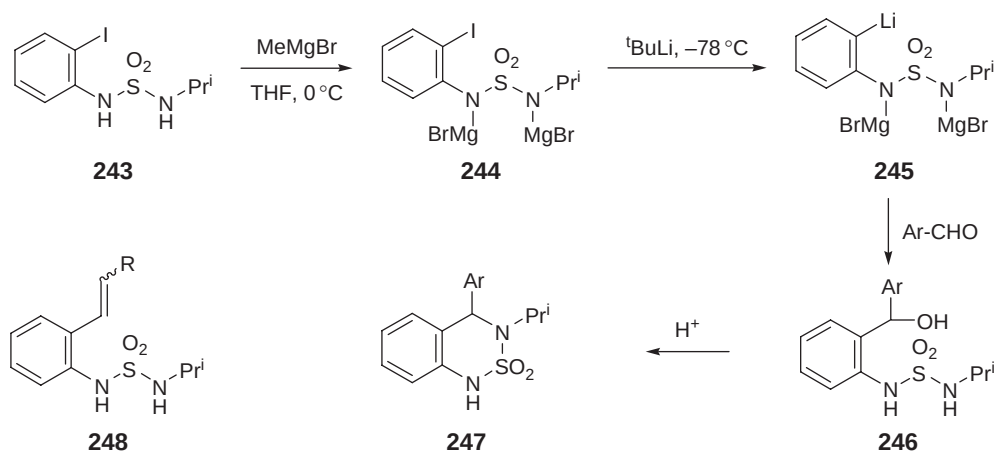
A simple, efficient synthesis of *N*-aryl-1,2,6-thiadiazine 1,1-dioxides **242** using 3-chloropropylamine, sulfuryl chloride, and aryl amines was developed. When an acetonitrile solution of 3-chloropropylamine and 6 equiv of sulfuryl chloride was heated at 75–80 °C for 18 h, mono(3-chloropropyl)sulfamyl chloride was obtained. After 4 h at room temperature, an ethereal solution of the arylamine and triethylamine gave 3-chloropropyl phenylsulfamide **241**. Treatment of the latter with 1 equiv of potassium carbonate in dimethyl sulfoxide gave **242** (68–82% yield) (Scheme 30) <2003TL5483>. Another general synthesis of **242** was developed <2003T6051>, which started with a regiospecific, heterogeneous alkylation of *N*-BOC *N*¹-benzylsulfamide with 1,ω-dibromoalkane using potassium carbonate in acetone to afford **241**. In the case of *n* = 0 or 1, cyclized products **242** were obtained directly (80–85% yield) under these experimental conditions.



Scheme 30

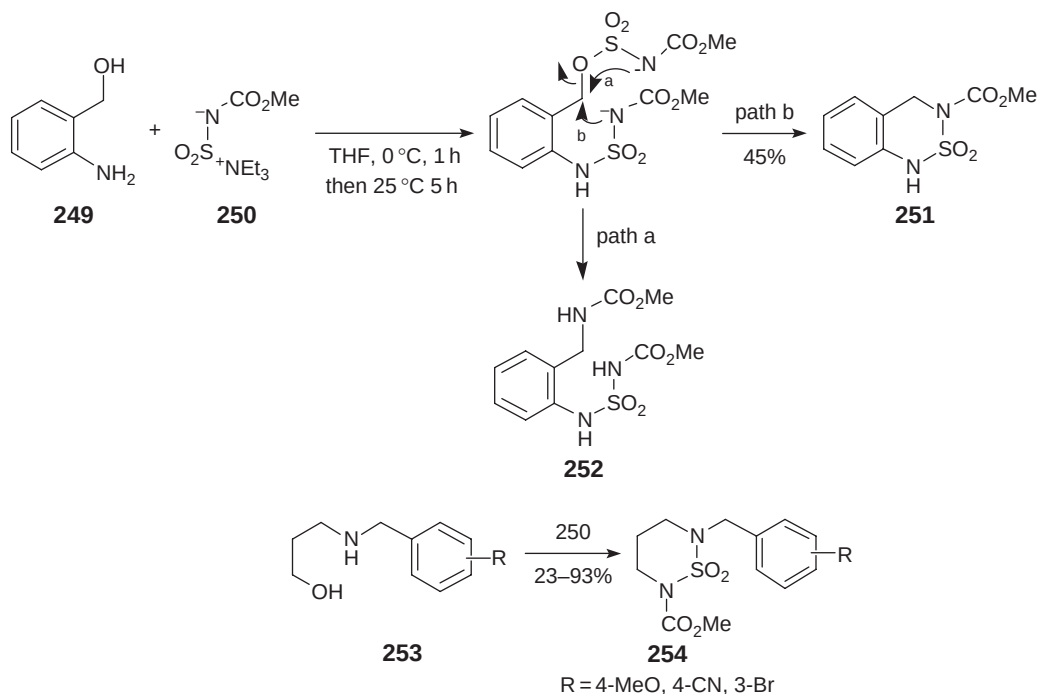
4-Substituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **247** were prepared efficiently in two steps from *ortho*-iodosulfamides **243**. The key step, condensation of trianion **245** with aldehydes, was initiated by removal of the sulfamide protons using methyl Grignard as a base that would not interfere with the halogen. For the metal–halogen exchange, *tert*-butyllithium was used because of its high iodine affinity even in the presence of sensitive groups.

Addition of aldehyde gave the desired alcohol **246** in 62–88% yield. (Ketones generally were not effective in this reaction.) The final step was effected with methanesulfonic acid. When aliphatic aldehydes were used, the alkene by-product **248** was isolated (18–70% yield; [Scheme 31](#)) [<2000TL9819>](#).



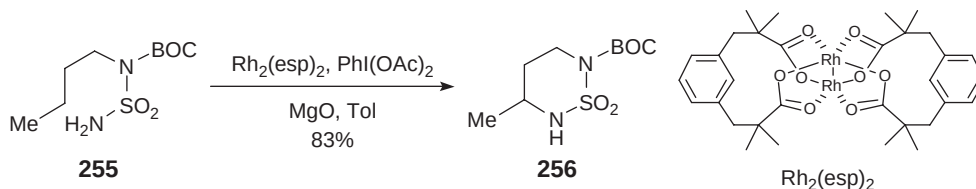
Scheme 31

Reaction of **249** with Burgess reagent **250** gave the desired product **251** in 45% yield. Other conditions examined provided no improvement and led to significant amounts of **252**. When less-activated alcohols such as **253** were used, this side reaction was suppressed and good yields of the cyclic sulfamides **254** were obtained ([Scheme 32](#)) [<2002AGE3866, 2004CEJ5581>](#).



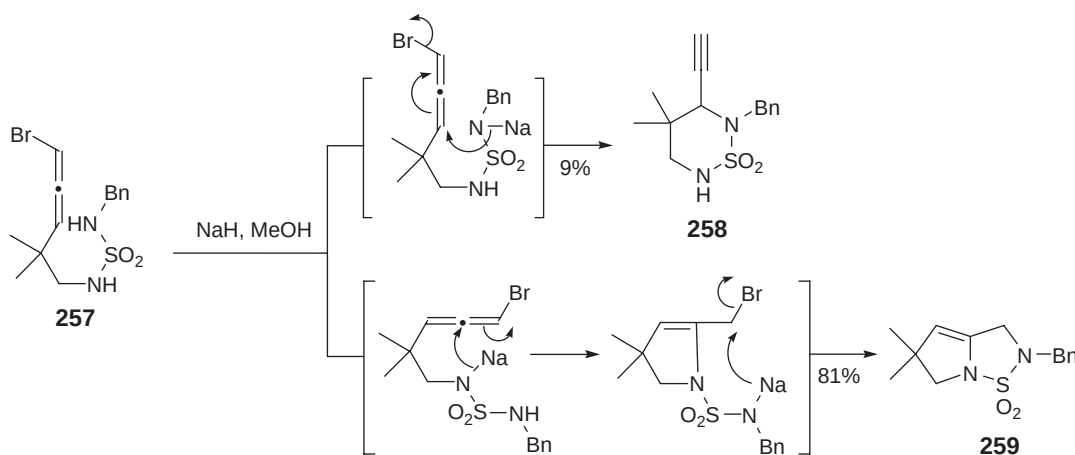
Scheme 32

$\alpha,\alpha,\alpha',\alpha'$ -Tetramethyl-1,3-benzenedipropionate ($\text{Rh}_2(\text{esp})_2$) proved to be an effective and general catalyst for C–H amination. For example, sulfamide **255** was cyclized using 1 mol% of the catalyst to give **256**. Analogous reactions using $\text{Rh}_2(\text{oct})_4$ or $\text{Rh}_2(\text{O}_2\text{CCPh}_3)_4$ afforded product yields below 40% (Scheme 33) (oct = octanoate) <2004JA15378>.



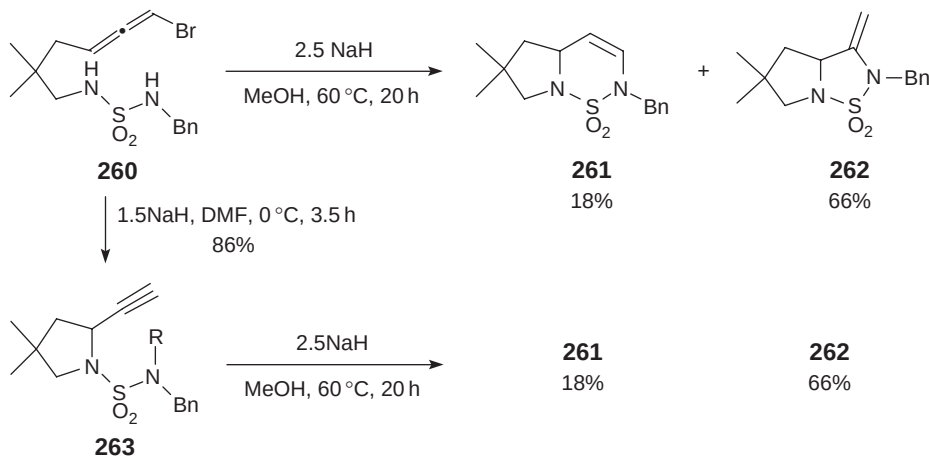
Scheme 33

Cyclization of bromoallene **257** with sodium hydride in methanol afforded thiadiazine **258** as a minor product along with **259** (Scheme 34). A proposed mechanism is shown <2005AGE1513>.



Scheme 34

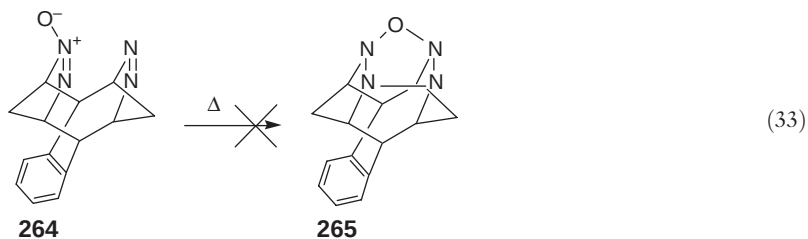
A similar reaction of bromoallene **260** having a three-atom tether gave a mixture of **261** and **262**. The possible intermediacy of **263** ($\text{R} = \text{Na}$) was supported by submitting **263** ($\text{R} = \text{H}$) to the reaction conditions and isolating **261** and **262** in the same yields (Scheme 35) <2005AGE1513>.



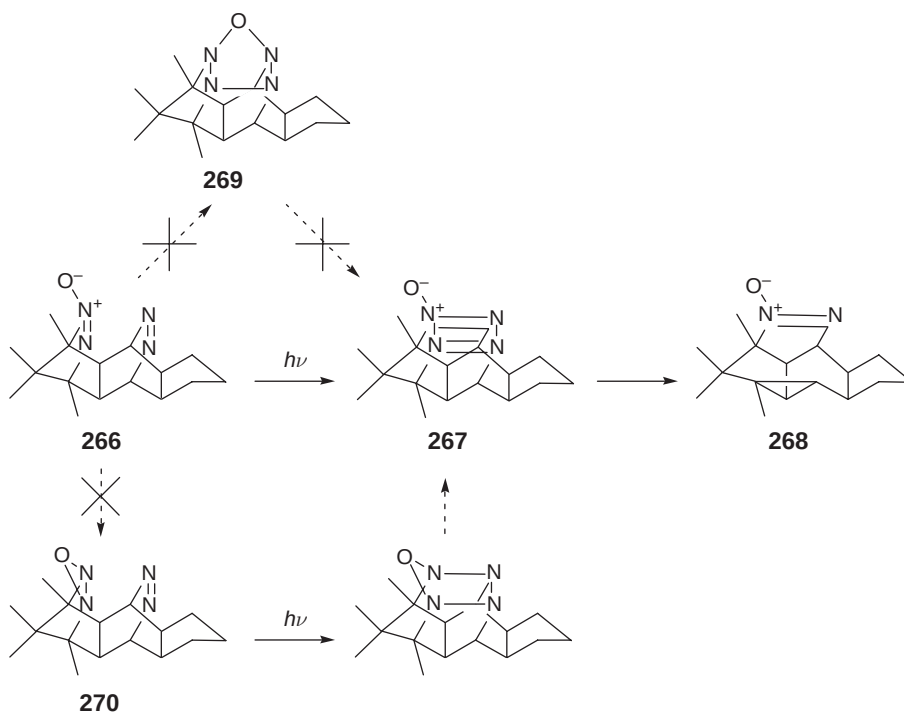
Scheme 35

9.07.9.1.2 Between nitrogen and oxygen

On heating **264** to its decomposition temperature (differently from ene/diazine oxides), [3+2] cycloaddition to oxatetrazolidine **265** was not found (Equation 33) <1998TL2303>.



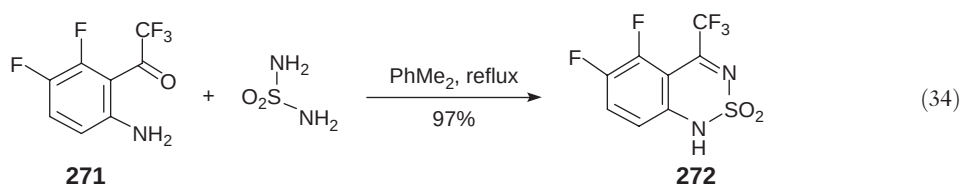
In discussing possible reaction pathways in the photochemistry of **266** to **267** and **268**, the [3+2] cycloaddition to oxatetraoxazolidine **269**, $[2\pi+2\sigma]$ cycloaddition to **270**, and [3+2] cycloreversion were considered and discarded (Scheme 36) <2000EJO787>.



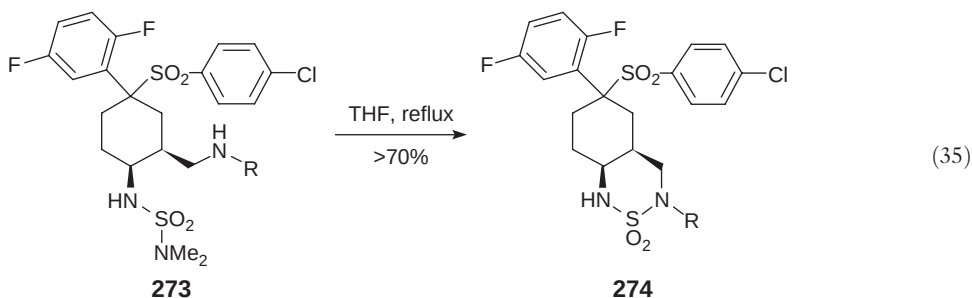
Scheme 36

9.07.9.1.3 Between nitrogen and sulfur

Condensation of sulfamide with *ortho*-amino trifluoromethyl ketone **271** afforded 2,1,3-benzothiazine 2,2-dioxide **272** (Equation 34) <2000BML193>.



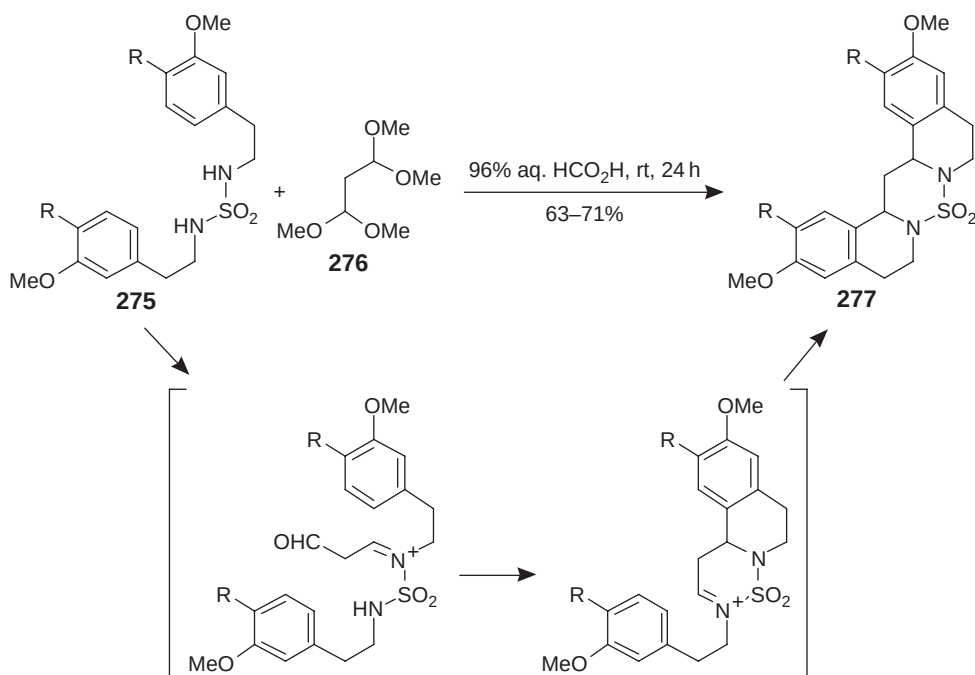
By heating in tetrahydrofuran, the amino sulfamide **273** underwent facile cyclization to sulfamide **274**, with extrusion of dimethylamine (Equation 35) <2006BML3073>.



9.07.9.2 Formation of Two Bonds

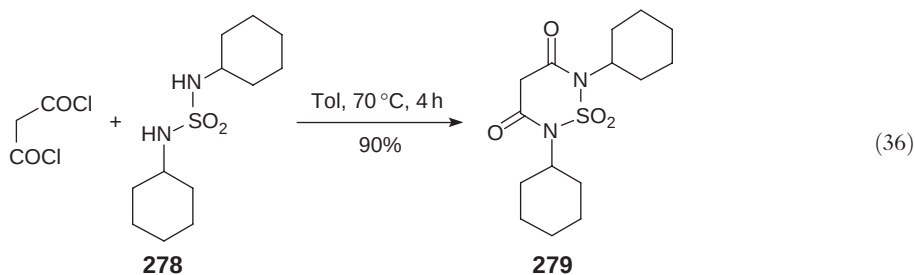
9.07.9.2.1 [3+3] Fragments

Treatment of *N,N*¹-bis(2-arylethyl)sulfamides **275** with diacetal **276** in formic acid gave the fused ring compounds **277** as the major products. Formation of **277** was proposed to proceed by the stepwise pathway shown (Scheme 37) <2003BKC129>.

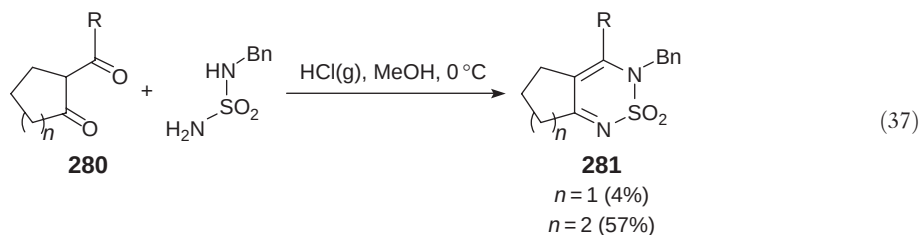


Scheme 37

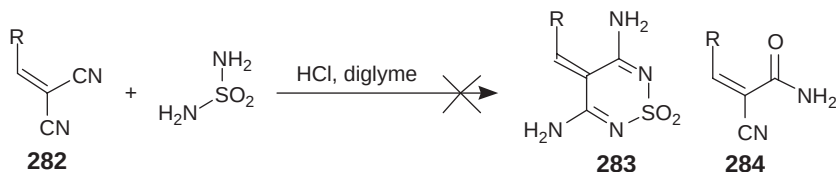
2,6-Dicyclohexyl-2*H*-1,2,6-thiadiazine-3,5(4*H*,6*H*)-dione 1,1-dioxide **279** was synthesized by reaction of dicyclohexylsulfamide **278** with malonyl dichloride (Equation 36) <1999AF759>.



Condensation of 2-acylcyclopentanones **280** ($n=1$) and 2-acylcyclohexanone (**280**: $n=2$) with benzylsulfamide gave bicycles **281** (Equation 37) <1995BMC179>.

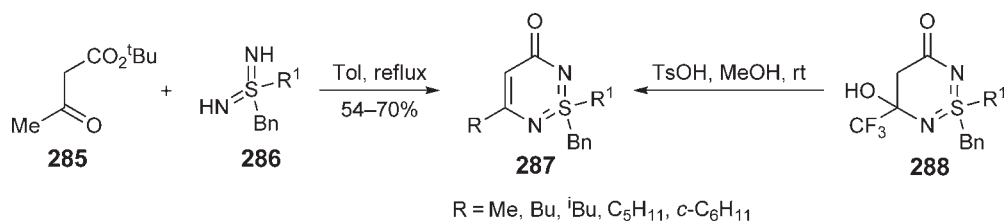


Cyclocondensation of sulfamide and arylidenemalononitriles **282** in hydrochloric acid-saturated diglyme, following a described procedure <1988J(P1)1271>, failed to give the desired **283**; only cyano acetamides **284** were obtained (Scheme 38) <1999AF759>.



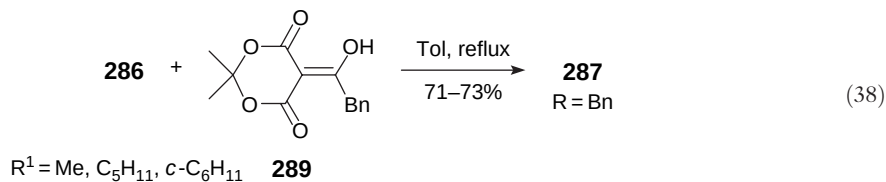
Scheme 38

Reaction of *tert*-butyl acetoacetate **285** with **286** ($\text{R}^1 = \text{Me}, n\text{-Bu}, i\text{-Bu}$) in refluxing toluene led directly to the dehydrated thiadiazines **287** in good yields. With the related isopropyl trifluoroacetoacetate, the 5-hydroxythiadiazines **288** were formed (54–78% yield) as inseparable, diastereomeric mixtures. The desired thiadiazines **287** ($\text{R}^1 = n\text{-C}_5\text{H}_{11}, c\text{-C}_6\text{H}_{11}$; $\text{R} = \text{CF}_3$) were obtained (67–72% yield) by dehydration using catalytic tosic acid in methanol at room temperature (Scheme 39) <2003JOC3817>.

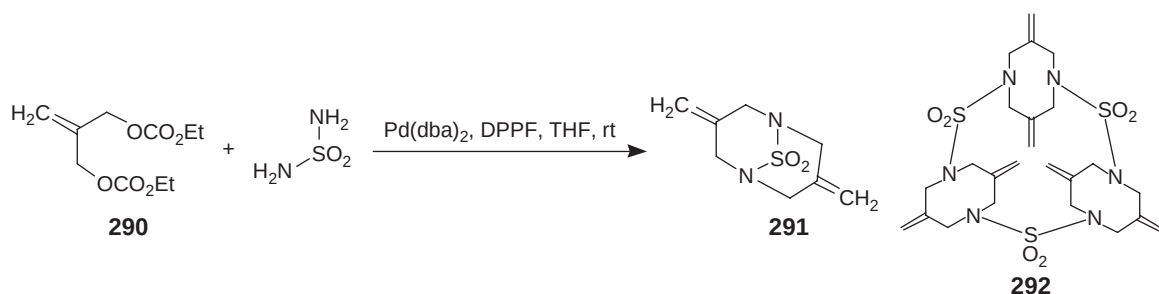


Scheme 39

Reaction of **286** with 5-acyl-Meldrum's acid **289** directly gave **287** ($\text{R} = \text{Bn}$) having a benzyl group at C-5 (Equation 38) <2003JOC3817>.



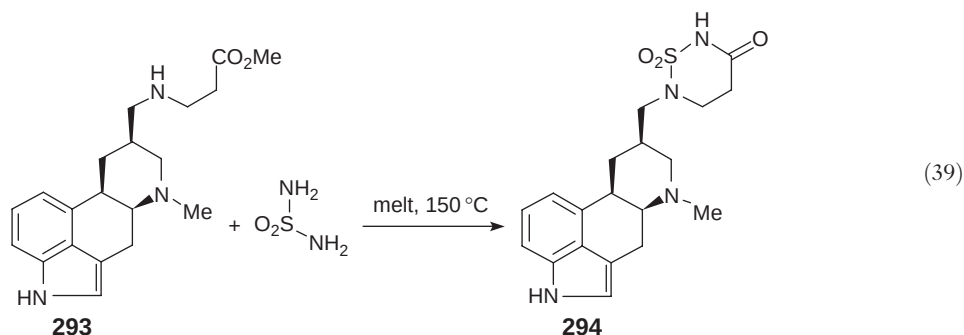
The reaction of biscarbonate **290** with sulfamide afforded bicyclic thiadiazine **291** (68% yield) along with traces (5%) of compound **292**. All other catalytic systems tested in this reaction, viz. $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{dppe})_2$, $\text{PdCl}_2(\text{dppf})$, $\text{Pd}(\text{OAc})_2/\text{PPh}_3$, $\text{PdCl}_2(\text{dppf})/\text{DIBAL}$, $\text{PdCl}_2(\text{dppf})/\text{dppf}/\text{BuLi}$, $\text{Pd}(\text{OAc})_2/\text{dppf}$, failed to give **291** (dppe = bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene; DIBAL = diisobutylaluminium) (Scheme 40) <1998T14885>.



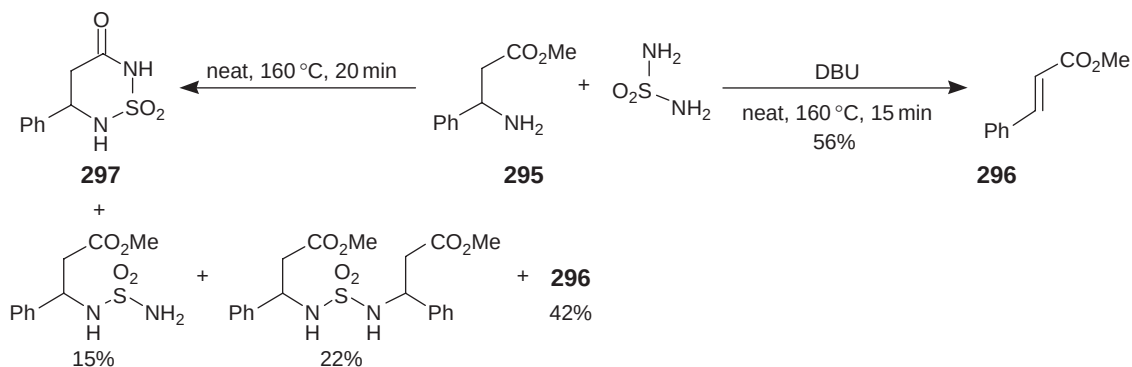
Scheme 40

9.07.9.2.2 [4+2] Fragments

N-[(6-methylergolin-8 β -yl)methyl]- β -alanine methyl ester **293** was melted with sulfamide to afford analog **294** (Equation 39) <1998FA293>.



By contrast, heating **295** with sulfamide and DBU afforded only cinnamate **296**. In the absence of DBU, a 'low yield' of the desired thiadiazine **297** was formed (Scheme 41) <2005SL834>.

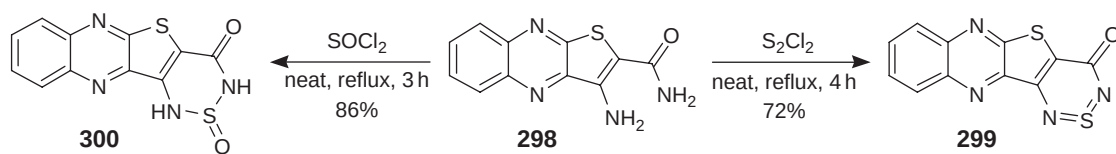


Scheme 41

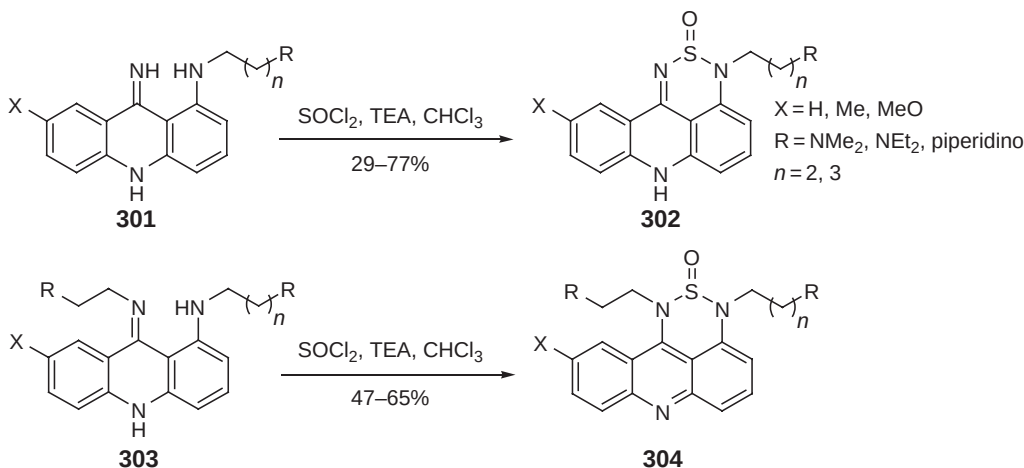
9.07.9.2.3 [5+1] Fragments

Treatment of **298** with sulfur monochloride gave thiadiazino[4',5':4,5]thieno[2,3-*b*]quinoxaline **299**. Similar treatment of **298** with thionyl chloride produced the corresponding sulfoxide **300** (Scheme 42) <1997PS49>.

The cyclization of **301** or **303** with thionyl chloride yielded the target [1,2,6]thiadiazino[3,4,5-*k*,*l*]acridines **302** and **304**, respectively (Scheme 43) <2003BMC399>.

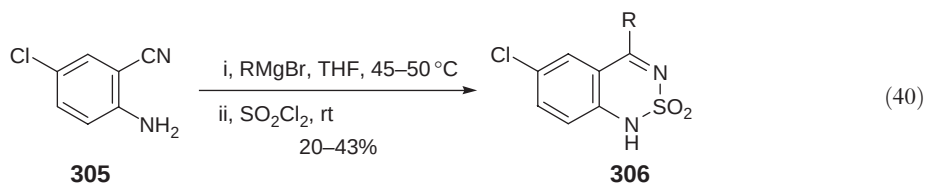


Scheme 42

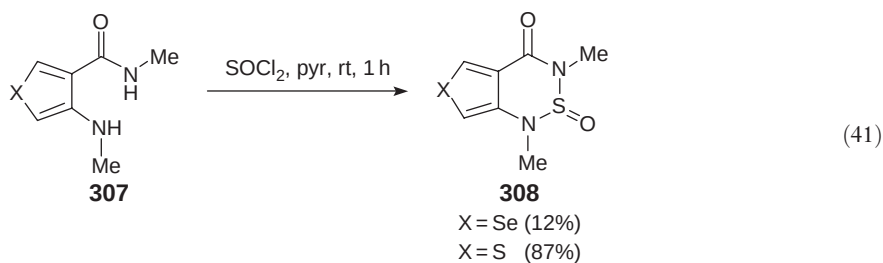


Scheme 43

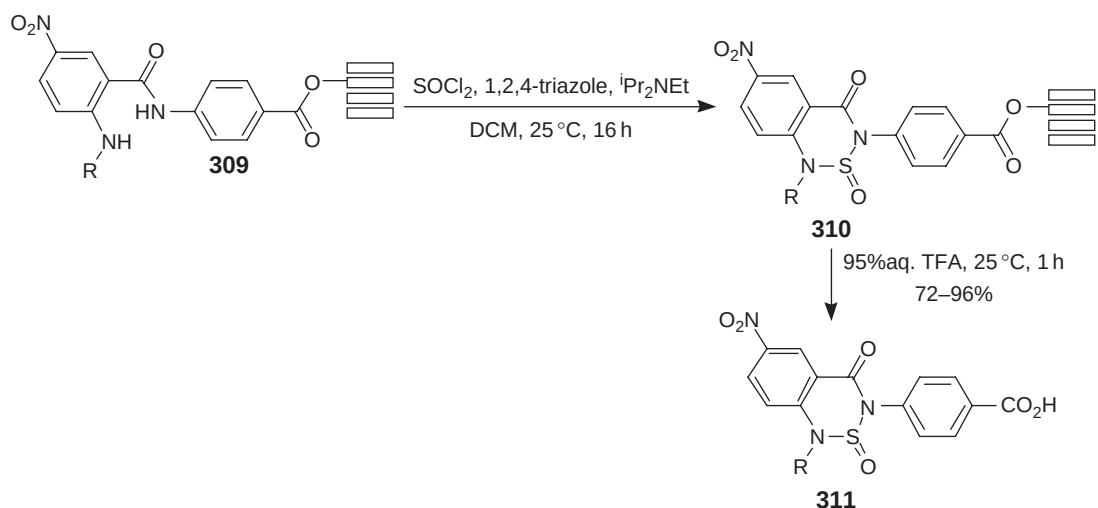
In a similar reaction, imino amines were generated by Grignard addition to anthranilonitrile **305** followed by reaction with sulfuryl chloride to afford the 1*H*-2,1,3-benzothiadiazine 2,2-dioxides **306** in modest yields (Equation 40) <2000BML193>.



The synthesis of 6,7-dihydro-4,6-dimethyl-5,7-dioxo-4-methyl-4*H*-[1,2,5]seleno (or thia) diazolo[3,4-*c*][1,2,6]thiadiazine 5-oxides **308** was accomplished by reaction of amino amides **307** with thionyl chloride (Equation 41) <2000JHC1269>.

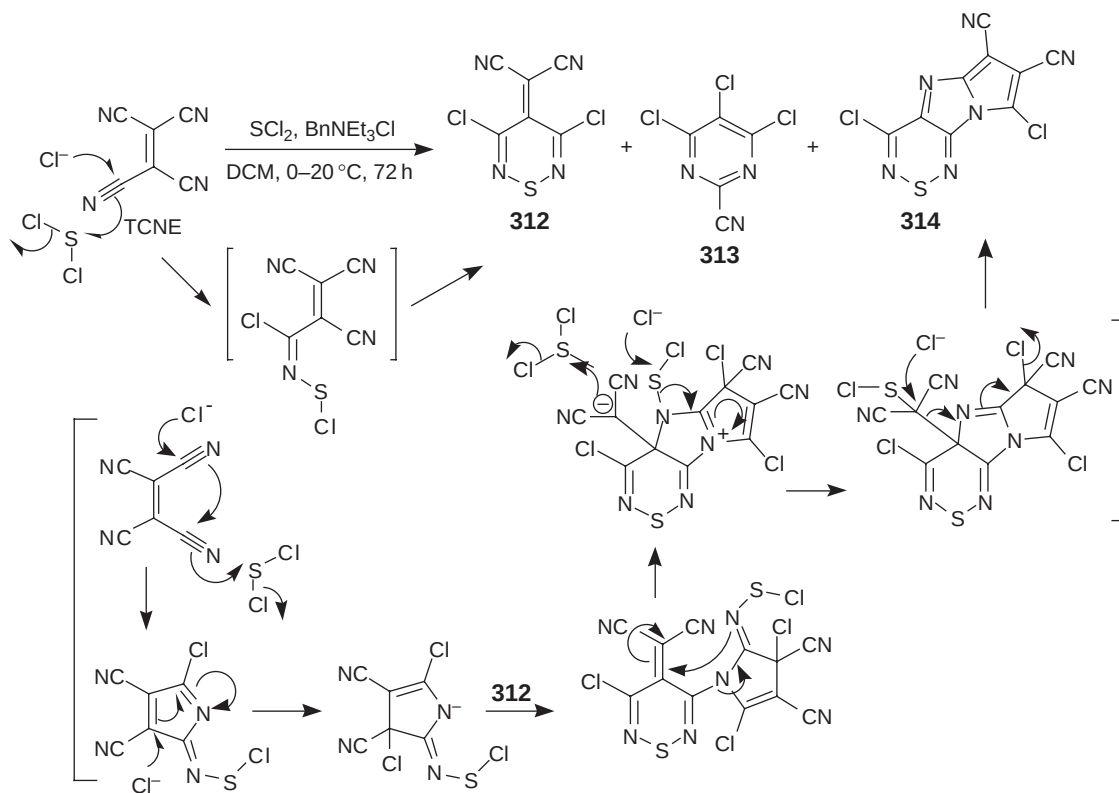


Solid-phase syntheses of 2,1,3-benzothiadiazine-4-one 2-oxides were effected on SynPhase™ Lantern. Attempts to cyclize **309** with thionyl chloride under a variety of conditions gave compound **310** together with unknown by-products. If the thionyl chloride were converted to a less reactive reagent (prior reaction with tetrazole, 1,2,4-triazole, imidazole) before the addition to the Lantern, the product **311** was obtained in high purity (Scheme 44) <2003BKC389>.



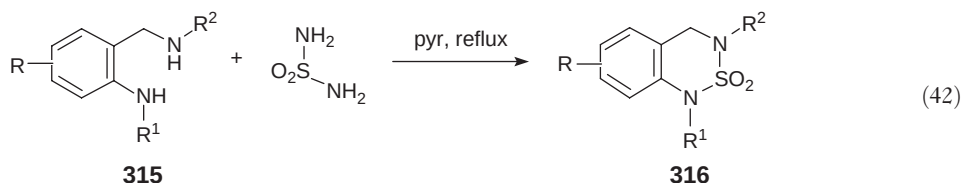
Scheme 44

Treatment of tetracyanoethene (TCNE) with 2 equiv of sulfur dichloride gave **312** (40–60% yield) together with two minor products **313** (5%) and **314** (0–5%). The reaction was slow, requiring 72 h at 20°C . Heating the mixture improved the yield of **314** at the expense of **312**. Using freshly distilled sulfur dichloride added dropwise at low temperature gave the highest yield of **312** (60%). The presence of catalytic amounts (1–5%) of chloride ion was essential for the reaction (Scheme 45) <2000J(P1)1089, 2000CC303>.



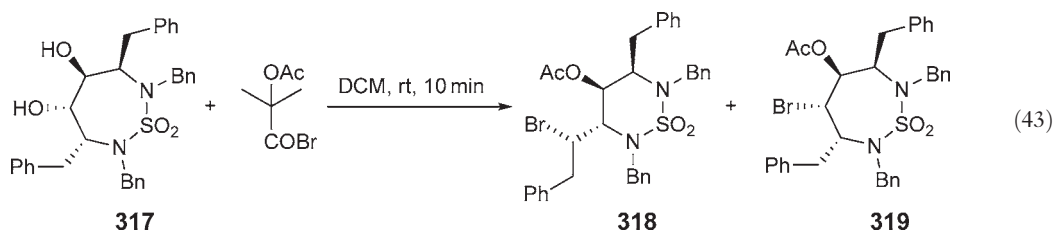
Scheme 45

The thiadiazine ring of **316** was constructed from diamine **315** by treatment with sulfamide in pyridine under reflux (Equation 42) <2004BML5045, 2003BMC367, 2001JMC1847>.



9.07.10 Ring Syntheses by Transformation of Another Ring

Rearrangement of **317** produced a mixture of products from which the six- and seven-membered ring bromo acetates **318** (37.5%) and **319** (15%) were isolated (Equation 43) <1998JOC4755>.



9.07.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes

9.07.11.1 1,2,6-Oxadiazines and 2,1,3-Benzoxadiazines

There are no general methods for the preparation of 1,2,6-oxadiazines, and 2,1,3-benzoxadiazines appear to be unknown. Mention of the 1,2,6-oxadiazine system was made in regard to diazine/diazine oxide thermolysis (Section 9.07.9.1.3), but the ring system was not prepared.

9.07.11.2 1,2,6-Thiadiazines

There are several methods available for the synthesis of 1,2,6-thiadiazine 1,1-dioxides. A common method is a two-step procedure condensing a β -amino ketone or ester with sulfamyl chloride (prepared from chlorosulfonyl isocyanate and water in tetrahydrofuran) followed by cyclization with potassium hydroxide or preferably with sodium methoxide. The synthesis works with substituted sulfamyl chlorides and with CSI (Section 9.07.9.1.1). A solid-phase variant of this reaction was effected.

Heating β -amino esters with sulfamide affords 1,2,6-thiadiazin-3-ones (Section 9.07.9.1.3); however, with a phenyl group attached to the amino carbon, the reaction does not give the desired product.

1,3-Dicarbonyl-containing compounds, such as malondialdehyde, malonyl dichloride, or 1,3-diketones, successfully react with sulfamides to afford the corresponding 1,2,6-thiadiazine 1,1-dioxides (Section 9.07.9.2.1).

Good yields of the saturated ring system were prepared by reaction of Burgess reagent with 3-hydroxypropylamines (Section 9.07.9.1.1). An interesting synthesis of the saturated ring system utilized $\text{Rh}_2(\text{esp})_2$ as an effective catalyst for C–H amination of sulfamides (Section 9.07.9.1.1).

Reaction of tetracyanoethylene with sulfur dichloride affords modest yields of the novel 3,5-dichloro-4-dicyanomethylene-4*H*-1,2,6-thiadiazine (Section 9.07.9.2.2).

9.07.11.3 2,1,3-Benzothiadiazines

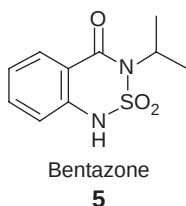
Cyclization of methyl anthranilates with sulfamyl chloride affords 2,1,3-benzothiadiazin-4-ones (Section 9.07.9.1.1). The less common 1*H*-2,1,3-benzothiadiazine 2,2-dioxides were obtained in modest yield by reaction of 2-hydroxymethyl anilines with Burgess reagent (Section 9.07.9.1.1). A two-step process starting from *ortho*-iodosulfamides, via generation of a trianion, condensation with an aldehyde, and subsequent acid-catalyzed cyclization, led efficiently to 4-substituted-3,4-dihydro-1*H*-2,1,3-benzothiazine 2,2-dioxides (Section 9.07.9.2.2).

Condensation of *ortho*-amino acetophenones with sulfamide affords 4-substituted-1*H*-2,1,3-benzothiadiazine 2,2-dioxides (Section 9.07.9.1.3). An interesting approach to the same class of compounds involves Grignard addition to anthranilonitrile followed by addition of sulfonyl chloride (Section 9.07.9.2.1). The 1*H*-1,2,6-benzothiadiazine 2,2-dioxide ring was constructed by treatment of an *ortho*-aminomethyl aniline with sulfamide in pyridine at reflux (Section 9.07.9.2.2).

Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides were prepared by condensation of 4,5,6-triamino-1,2,6-thiadiazine 1,1-dioxide with 1,2-diketones. Regioselectivity was achieved as the more reactive carbonyl reacted with the 4-amino group. Alternately, selectivity could be attained by use of α -oximino ketones (Section 9.07.7.2).

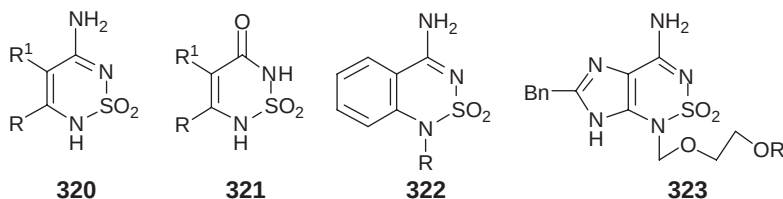
9.07.12 Important Compounds and Applications

Commercially, the most important compound containing the 1,2,6 thiadiazine system is Bentazone **5**, a well-known, highly active, and selective herbicide. It controls broadleaf and sage weeds and is important for weed control in soybeans, sweet potatoes, pepper, oats, and barley <1996JSH519>. The great preponderance of literature from this period has to do with the properties (biological, environmental, synergistic, etc.) of this material.

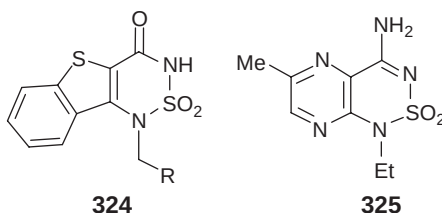


The aminosulfonylamino moiety (NSO₂N, sulfamide) is a component in a number of bioactive, heterocyclic compounds. These biological activities range from antiviral <1997BML1031, 1999BMC1617, 2003BMC2395, 1997NN265, 2004JHC747>, human immunodeficiency virus (HIV) <2000BML193, 2000JMC3218>, anticancer <2003BMC399>, anti-infective <2001JMC1847>, antitrypanosomal <1999AF7591> to antiasthma (<1997EUJ69, 2000JMC683, 2005BMC1393, 2000JMC4219>, antithrombotic <1999JMC1698, 1999JMC3279, 2003BMC367>, antihypertensive <1998FA293>, antidepressant <2001EUJ9, 2001EUJ19>, and antiopiate <2004BML5045>.

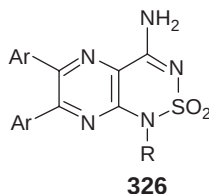
Thiadiazines **320** and **321** resemble cytosine and uracil <2003JMD329>, respectively, and were used as scaffolds to explore potential antiviral activity analogous to Acyclovir <1995BMC1527, 1997NN265>. The imidazo thiadiazine dioxides **322** and **323** were considered as new lead compounds for anti-cytomegalovirus (CMV) and anti-varicella-zoster virus (VZV) drug research <1995H(41)87, 1999BMC1617>. Benzothiadiazine dioxide-modified acyclonucleosides with marked activity against human CMV and VZV infection were discovered <1997BML1031, 1999JMC1145>, their optimization described <1999JMC1145, 1999BML3133, 2000JMC3218, 2004JHC747>, and the structural requirements for potency and toxicity defined <2000JMC3218, 2003BMC2395, 2003ACC107>. Benzothiadiazine dioxides are potent anti-HCMV drugs with a mechanism of action completely different from current clinical drugs, acting in the first stages of the viral replicative cycle <2000JMC3267, 2005BML1919>.



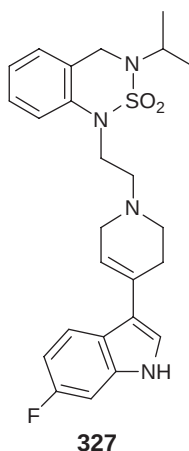
Compounds **324** represent novel heterocycles with PDE 7 inhibitory properties, a new objective for treatment of T-cell-dependent disorders. Additionally, the fact that some of these compounds also inhibit PDE 4 and PDE 3 implies that they could be considered as new leads in the development of drugs for asthma and other allergic airway pathologies <2000JMC683, 2005BMC1393>. PF-904 **325** is a nonselective phosphodiesterase inhibitor. Orally, it inhibits bronchoconstriction caused by a variety of spasmogens in the guinea pig and prevents airway hyperactivity to histamine after PAF exposure. These and other data suggest that PF-904 may be a useful antiasthma agent and it is in preclinical development for this indication <1997EUJ69, 2000JMC4219>.



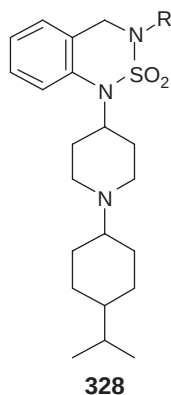
A new class of platelet aggregation inhibitors that are pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides having aryl substituents on the pyrazine ring **326** was described <1999JMC1698, 1999JMC3279>.



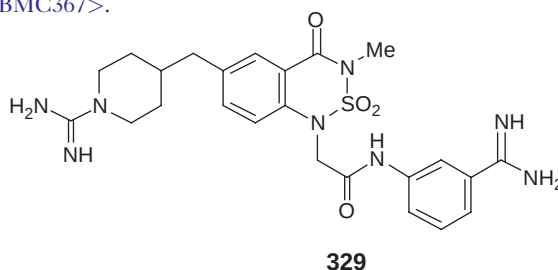
LY393558 **327** is a platelet inhibitor of the 5-HT transporter and agonist of the 5-HT_{1β/1D} receptors. It should be an effective antidepressant with potential for producing an early onset of efficacy <2001EUJ9, 2001EUJ19, 2005JEP539>.



Similar compounds **328** were found to be high-affinity, selective full agonists of the NOP opioid receptor (formerly named ORL-1). Unfortunately, these compounds had poor metabolic stability <2004BML5045>.

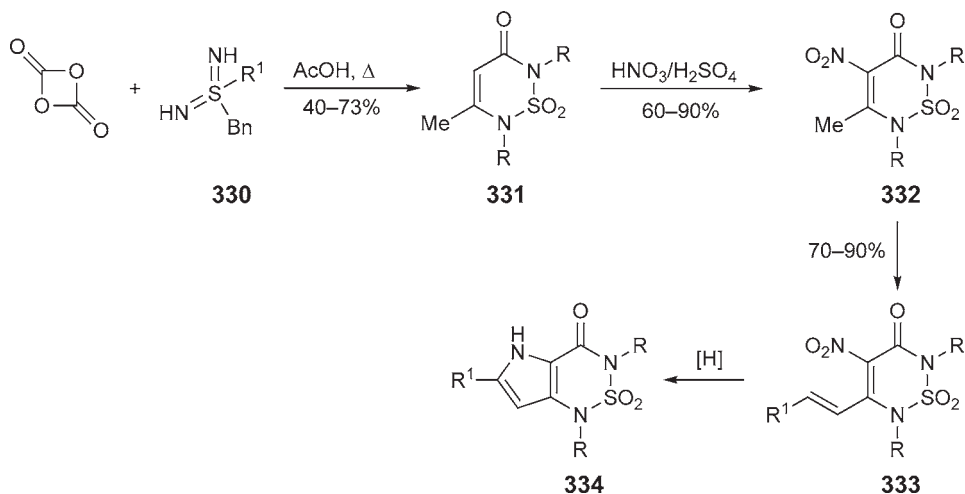


A novel series of Factor X_a (FX_a) inhibitors based on a benzothiadiazin-4-one template was synthesized. Compound **329** (YM-169920) showed excellent anticoagulant activity in mice and squirrel monkeys after oral administration *ex vivo* <2003BMC367>.



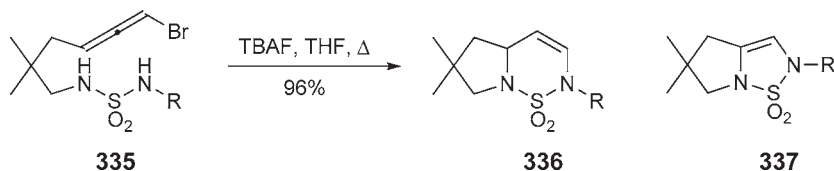
9.07.13 Further Developments

Thiadiazinones **331** were prepared by reaction of sulfamides **330** with diketene in refluxing acetic acid (Scheme 46). After nitration, the resulting nitro thiadiazinones **332** were condensed with dimethylformamide diethyl acetal to give the dimethylaminomethylene compounds **333** (R¹ = NMe₂). Piperazine catalyzed reaction of **332** with aldehydes afforded **333**. Reductive cyclization was effected with sodium dithionite in formic acid affording the novel 1,5-dihydropyrrolo[3,2-*c*]-[1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxides **334**. It is interesting to note that dithionite reduction of **333** (R¹ = NMe₂) gave **334** (R¹ = H) whereas palladium catalyzed hydrogenation gave primarily **334** (R = NMe₂) <2006TL5875>.



Scheme 46

Base induced tandem cyclization of bromo allene **335** (R = Ph) afforded the bicyclic sulfamide **336** (R = Ph) as the sole product. The *N*-methyl analog **335** (R = Me) under the same conditions gave bicycle **337** (R = Me) as the major product along with **336** (R = Me) in a ratio of 2.5:1 (Scheme 47) <2007CEJ1692>.



Scheme 47

References

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Biographical Sketch



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9.08

1,3,4-Oxadiazines and 1,3,4-Thiadiazines

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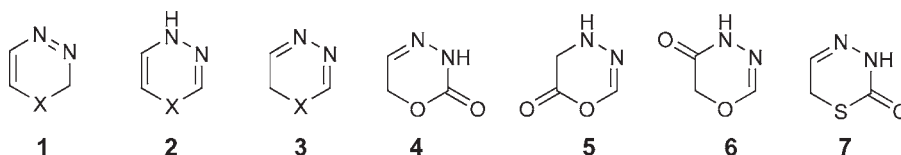
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9.08.1 Introduction

Of the different oxa- and thiadiazines, the 1-oxa- and 1-thia-3,4-diazines have been most extensively studied. The 1-oxa- and 1-thia-3,4-diazines may exist in different tautomeric forms. The compounds **1–3** shown are designated as *2H*-1,3,4-oxadiazines **1** (X = O), *4H*-1,3,4-oxadiazines **2** (X = O), *6H*-1,3,4-oxadiazines **3** (X = O), *2H*-1,3,4-thiadiazines **1** (X = S), *4H*-1,3,4-thiadiazines **2** (X = S), and *6H*-1,3,4-thiadiazines **3** (X = S). The *4H*-derivatives represent potentially antiaromatic 8π -systems. *3H,6H*-1,3,4-Oxadiazin-2-ones **4** and *4H,5H*-1,3,4-oxadiazin-6-ones **5** are lactones. *4H,6H*-1,3,4-Oxadiazin-5-ones **6** are δ -lactams. *3H,6H*-1,3,4-Oxadiazin-2-ones **4** and *3H,6H*-1,3,4-thiadiazin-2-ones **7** exhibit excellent cardiotonic activities (Section 9.08.11). 1-Oxa- and 1-thia-3,4-diazines have been the subject of numerous review articles <B-1959MI(IVc)1559, 1969ZC361, 1970QRS177, 1978MI135, 1979COC(4)1051, 1984CHEC(3)1039, 1988AHC(50)81, 1988MI38, 1991KGS435, 1991KGS1443, 1996CHEC-II(6)737, 1998H(49)557, 1998HOU(E9c)427, 1998HOU(E9c)483, 1998HOU(E9c)518>.



9.08.2 Experimental Structural Methods

9.08.2.1 Spectroscopic Studies

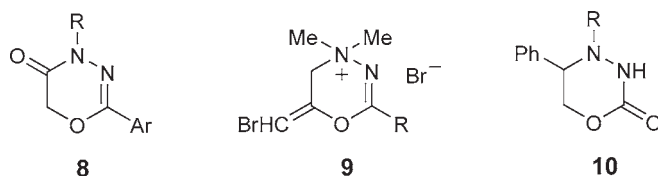
9.08.2.1.1 Ultraviolet and infrared spectra

The carbonyl stretching frequency for 1,3,4-oxadiazin-2-ones is seen at $1660\text{--}1710\text{ cm}^{-1}$ <2003CHE1057>. The main infrared (IR) absorption bands for some substituted *4H*-1,3,4-thiadiazines have been assigned <2003SL2392>. 2,5-Di(trifluoromethyl)-6,6-diaryl-6*H*-1,3,4-thiadiazines absorb at $261\text{--}279\text{ nm}$ <1998EJO2861>. 2-Alkylimino-3-alkyl-6*H*-1,3,4-thiadiazines exhibit absorption maxima at $227\text{--}243$ and $331\text{--}339\text{ nm}$, whereas for 2-dialkylamino-6*H*-1,3,4-thiadiazines λ_{max} occurs at 297 and 344 nm <2006UP1>.

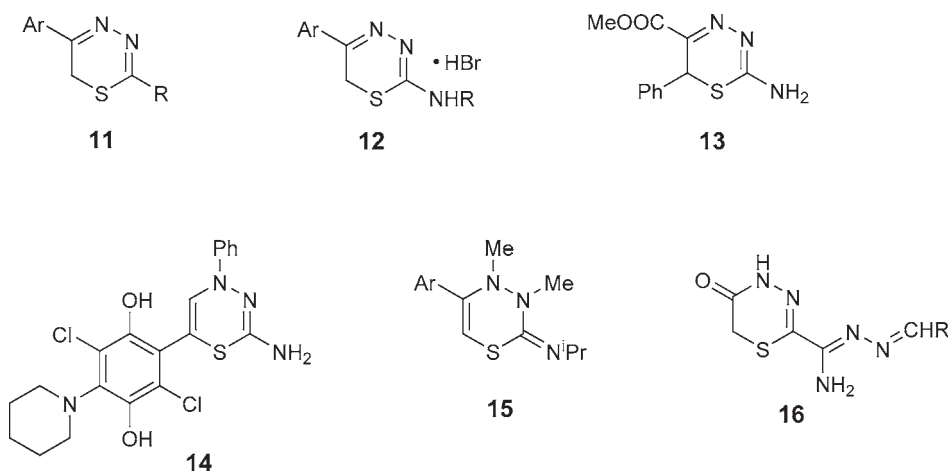
9.08.2.1.2 NMR spectra

9.08.2.1.2(i) Proton NMR spectra

5,6-Dihydro-5-oxo-4*H*-1,3,4-oxadiazine-4-propanenitriles **8** ($R = \text{CH}_2\text{CH}_2\text{CN}$) exhibit C-6 proton resonances at δ 4.78–4.85 (all δ values) in ppm <2002HCA559>. The C-5 methylene protons of 6-bromomethylidene-4,4-dimethyl-5*H*-1,3,4-oxadiazinium bromides **9** ($R = \text{Ar}$, HetAr) appear in the range 4.84–4.95 <2003RJO1561>. 5-Phenyl-2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **10** ($R = \text{H}$, Bn) exhibit C-6 methylene protons at δ 3.40–3.75 <2000S1170>.

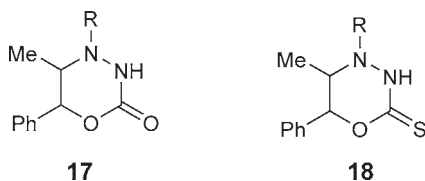


2-Amino-, 2-alkylamino-, and 2-morpholino-5-aryl-6*H*-1,3,4-thiadiazines <1998RJO417, 2004IJH283, 2006UP1, 2006UP2> **11** ($R = \text{NH}_2$, MeNH, EtNH, morpholino) have C-6 methylene proton resonances at 3.45–3.61, whereas 2-amino- and 2-alkylamino-5-aryl-6*H*-1,3,4-thiadiazine hydrobromides **12** exhibit C-6 methylene proton resonances at δ 4.27–4.36 <2001JME3231>. The C-6 proton signal of 2-amino-5-methoxycarbonyl-6-phenyl-6*H*-1,3,4-thiadiazine **13** is found at δ 5.46 <1996CHE1089>. The C-5 proton resonance of 2-amino-4-phenyl-4*H*-1,3,4-thiadiazine derivative **14** <2005H(65)1569> appears at δ 7.29, whereas 2-isopropylimino-3,4-dimethyl-5-aryl-4*H*-2,3-dihydro-1,3,4-thiadiazines **15** have C-6 proton resonances at δ 6.26–6.30 <2003SL2392>. 5,6-Dihydro-5-oxo-4*H*-1,3,4-thiadiazines **16** ($R = \text{aryl}$) exhibit C-6 proton resonances at δ 3.47–3.49 <1998SUL163>.



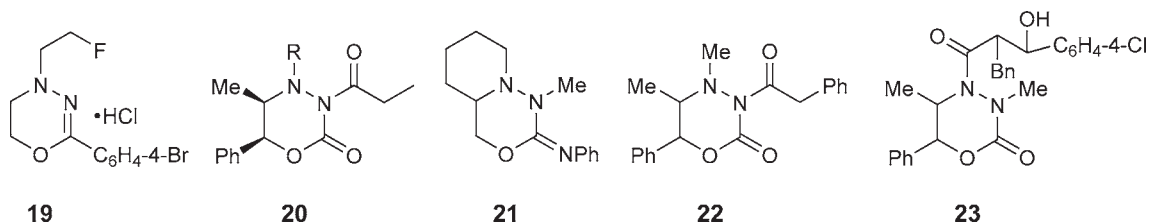
9.08.2.1.2(ii) Carbon-13 NMR

The carbon resonances for the 2-alkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **11** occur at δ 30.6–39.1 (C-6) and δ 149.4–149.6 (C-2) <2006UP2>. 5-Phenyl-2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **10** ($R = \text{H}$, Bn) exhibit carbon resonances at δ 55.6–59.6 (C-6) and δ 151.7–155.1 <2000S1170>. The carbon resonances for 2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **17** ($R = \text{Pr}^n$, Bu^t, Bn) are at δ 152–158.8 (C-2) <2002JHC823>. Carbon resonances at δ 180.1–182 (C-2) have been reported for 2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-thiones **18** <2002JHC1113>.

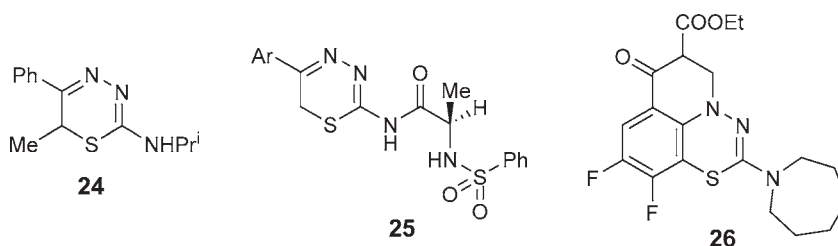


9.08.2.2 X-Ray Crystallography

The X-ray crystal structures for 2-(4-bromophenyl)-4-(2-fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride **19** <1995CJC853>, 3-*N*-propionyl-4-*N*-bornyl-5-methyl-4-phenyl-3,4,5,6-tetrahydro-1,3,4-oxadiazin-4-one **20** (R = *N*-bornyl) <2005TA1047>, 2-phenylimino-3-methyl-perhydropyrido[1,2-*b*][1,3,4]-oxadiazine **21** <1997H(45)927> and 4,5-dimethyl-6-phenyl-3-phenylacetyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one **22** <2001T9789> have been recorded. The X-ray crystal structure of 3,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-1,3,4-oxadiazin-2-one derivative **23** has been reported <2004JOC727>. The structure of **23** may be described as a twisted boat conformation.



The X-ray crystal structure has been determined for 2-isopropylamino-5-phenyl-6-methyl-6*H*-1,3,4-thiadiazine **24** <1993ACS302>. The structure of this compound may be described as a skew boat form. The bond lengths C(2)–NHP*r*ⁱ and C(2)–N(3) indicate that the amine tautomer is preferred in the solid state. Analogous results are observed for *N*-[5-aryl-6*H*-1,3,4-thiadiazin-2-yl]2-[(phenylsulfonyl)amino]propanamides **25** <2001AXC593>. The X-ray crystal structure of the 1,3,4-thiadiazino[6,5,4-*i,j*]quinoline derivative **26** has been reported <1998MC131>.

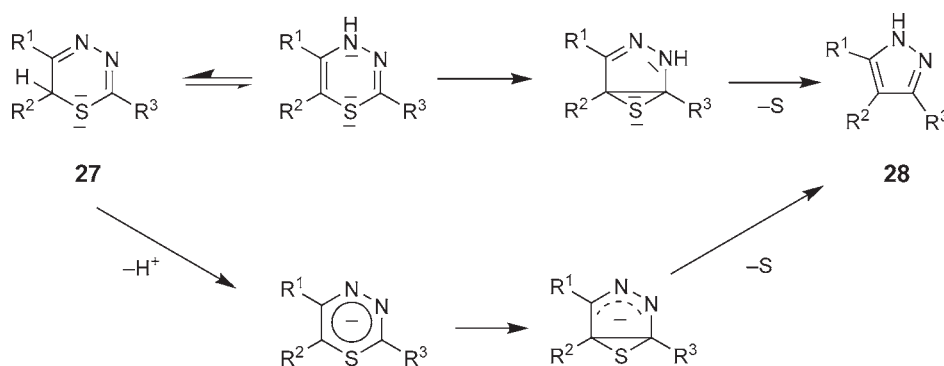


9.08.3 Thermodynamic Aspects

9.08.3.1 Antiaromaticity, Tautomerism, and Ring Conformation

The 4*H*-form of 1,3,4-thiadiazines **27** and the 1,3,4-thiadiazinyl anions are antiaromatic ring systems which extrude sulfur to give pyrazoles <1998HOU(E9c)483, 1992MI173>. The thermodynamically favored 6*H*-tautomer is in equilibrium with the energetically higher 4*H*-1,3,4-thiadiazine tautomer. The formation of the 4*H* species is the rate-limiting step of the reaction. A valence isomerization of this 8π-tautomer then follows to form a thia-σ-homopyrazole with an episulfide ring in the molecule. Finally, the opening of the three-membered ring follows with sulfur extrusion to form the pyrazoles **28** <2003SL2392>. 5-Aryl-1,3,4-thiadiazines with an unsubstituted 6-position can undergo ring contraction, with the sulfur atom being retained in the molecule as a sulfanyl group in the product pyrazole-4-thiols. The formation of 1,3,4-thiadiazinyl anions by reaction of butyllithium with 4*H*-1,3,4-thiadiazines has been reported <1998HOU(E9c)483, 1982ZC137, 1975TL33>. The thiadiazinyl anions are antiaromatic ring systems, which undergo sulfur extrusion to form the pyrazoles **28**. Analogous 1,3,4-selenadiazines can be converted to pyrazoles by selenium extrusion (Scheme 1).

The amino–imino tautomerism of 1,3,4-thiadiazines was investigated by ultraviolet (UV) spectroscopy and X-ray analysis <1993ACS302, 2001AXC593>. The conformational behavior of the (4*S*,4*aS*)-2-phenyl-4*H*-4*a*,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine was elucidated by means of nuclear magnetic resonance (NMR) spectroscopy and X-ray analysis <1999H(51)2575>.



Scheme 1

9.08.3.2 Kinetic Investigations and Determinations of Enthalpies and Entropies

Kinetic parameters for the chalcogen extrusion from 1,3,4-thiadiazines and 1,3,4-selenadiazines **29** to pyrazoles have been determined [<1993PHA732, 2006UP1>](#). It was found that the activation energy and enthalpy of activation are higher for 1,3,4-selenadiazines and the kinetic investigations indicate that the selenium derivatives are more stable than the sulfur-containing compounds ([Table 1](#)).

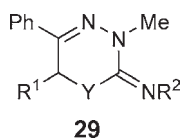


Table 1 Kinetic parameters for dechalcogenation of **29** to pyrazoles in acetic acid

<i>Y</i>	<i>R</i> ¹	<i>R</i> ²	<i>E</i> _A (<i>kJ mol</i> ⁻¹) <i>ln k</i> ₀	$\Delta H^\ddagger$ (<i>kJ mol</i> ⁻¹)	$\Delta S^\ddagger$ (<i>J mol</i> ⁻¹ <i>K</i> ⁻¹)	<i>k</i> _{80°C} (<i>s</i> ⁻¹)	<i>t</i> _{1/2} (<i>min</i>)
S	Ph	Pr ⁱ	104.5 26.8	101.1	-31.7	1.52 × 10 ⁻⁴	76
S	Me	Pr ⁱ	113.9 25.9	112.0	-36.9	2.52 × 10 ⁻⁶	4600 ^a
S	Ph	Ph	88.3 20.1	85.3	-87.1	5.15 × 10 ⁻⁵	225
Se	Ph	Pr ⁱ	106.9 26.7	103.3	-35.2	6.08 × 10 ⁻⁵	190
Se	Me	Pr ⁱ	130.7 30.4	127.2	-3.7	7.42 × 10 ⁻⁷	15 600 ^a
Se	Ph	Ph	93.1 20.9	90.0	-81.1	2.02 × 10 ⁻⁵	570

^aDetermination by extrapolation.

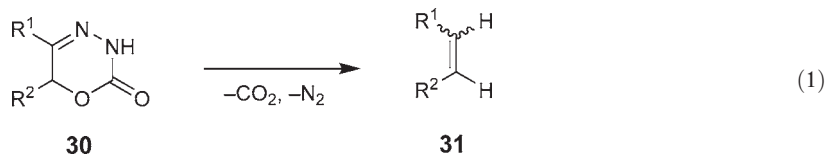
9.08.3.3 Chromatographic Behavior of Chiral 1,3,4-Thiadiazines

6-Substituted 1,3,4-thiadiazines exhibit optical activity. Chiral 1,3,4-thiadiazines can be separated by high-performance liquid chromatography (HPLC) with a chiral stationary phase [<1994PHA401, 2005JCH\(1075\)65>](#), respectively by nonaqueous capillary electrophoresis [<2001JBB155>](#).

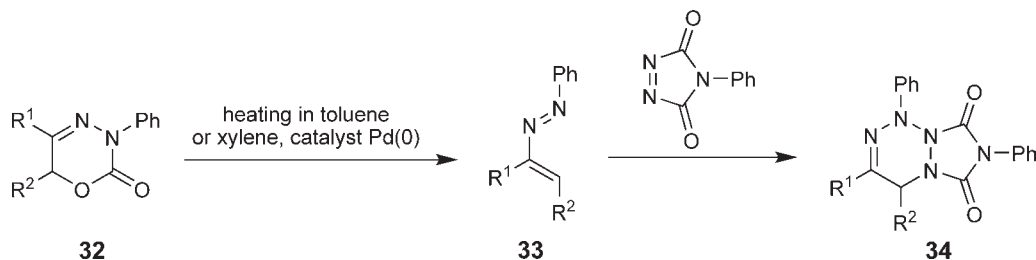
9.08.4 Reactivity of Fully Conjugated Rings

9.08.4.1 Thermal and Photochemical Reactions

3*H*-1,3,4-Oxadiazin-2-ones **30** ($R^1 = R^2 = \text{Ar}$) decompose to alkenes **31** on thermolysis or photolysis (Equation 1) <1998HOU(E9c)427>. The 5,6-diphenyl derivative yields a mixture of *cis*- and *trans*-stilbene in this reaction.

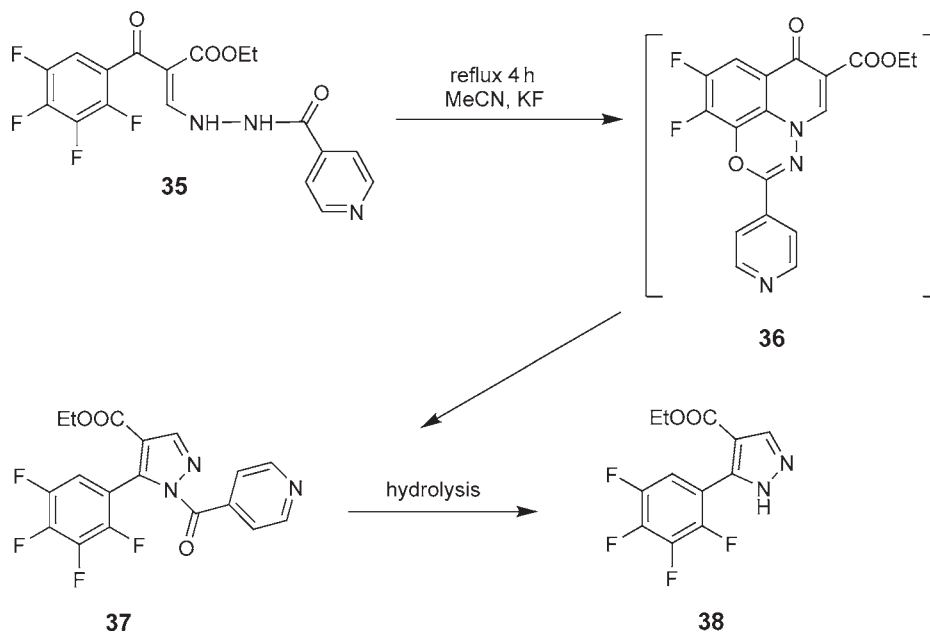


The thermolysis of 1,3,4-oxadiazin-2-ones **32** ($R^1 = R^2 = \text{Alk, Ar, OAr, SAR}$) affords reactive diazadienes **33**, which react with *N*-phenyldiazamaleimide to give Diels–Alder adducts **34** (Scheme 2) <2001OL3647>.



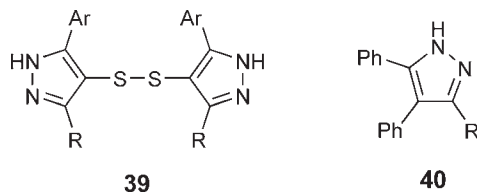
Scheme 2

When 3-(4-pyridylcarbonylhydrazino)-2-(tetra-2,3,4,5-tetrafluorobenzoyl)acrylate **35** was refluxed in acetonitrile in the presence of potassium fluoride for 4 h, cyclization to the intermediate 1,3,4-oxadiazino[6,5-*i,j*]quinoline **36** took place. Ring opening of the 1,3,4-oxadiazine and pyridine ring of **36** and recyclization led to the 4,5-substituted pyrazole **37**, which upon hydrolysis affords compound **38** (Scheme 3) <2001CHE1278>.

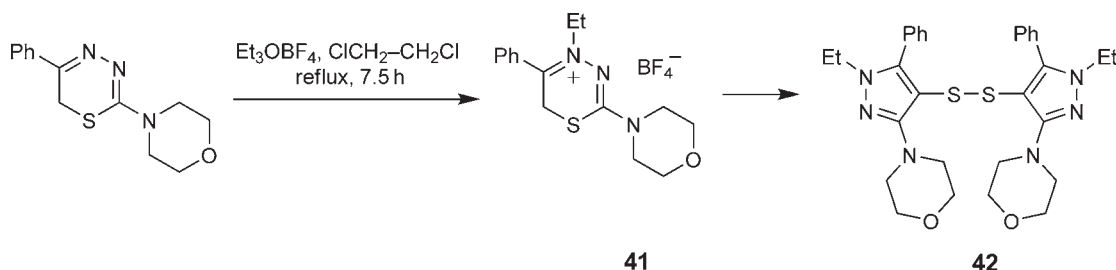


Scheme 3

5-Aryl-1,3,4-thiadiazines unsubstituted in the 6-position can undergo ring contraction on longer heating in toluene with formation of pyrazolyl disulfides **39** ($R = \text{Ar, Bn, NHMe, NHP}^i, \text{NHBu}^n, \text{NHBu}^t, \text{NMe}_2, \text{piperidino, morpholino}$) <1991DEP288824>. The formation of pyrazolyl disulfides **39** ($R = \text{Ar, Bn, NHMe, NHP}^i, \text{NHBu}^n, \text{NHBu}^i, \text{NHBu}^s, \text{NMe}_2, \text{piperidino}$) by heating of 1,3,4-thiadiazines above their melting point has been reported <1992MI173, 1986DEP235640>. The ring contraction of 1,3,4-thiadiazines to pyrazoles **40** also has been carried out using ultrasound in neutral solvents, such as ethanol or toluene, and at lower temperatures <1987ZC296, 1988DEP253030, 1992MI173, 1993KGS565>.

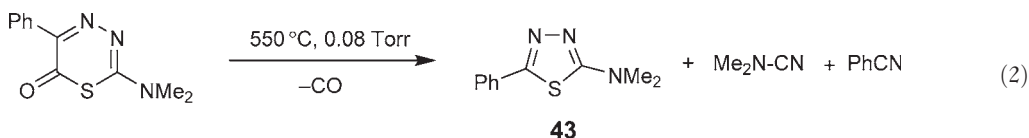


2-Morpholino-5-phenyl-6*H*-1,3,4-thiadiazine reacts on heating with triethyloxonium tetrafluoroborate for 7.5 h to give 35% of the quaternary 1,3,4-thiadiazinium tetrafluoroborate **41** and 55% of the 1,1'-diethyldipyrazolyl disulfide **42** <1998RJO417>. The intermediate tetrafluoroborate **41** undergoes ring contraction with retention of the sulfur atom to form dipyrazolyldisulfide **42** (Scheme 4).

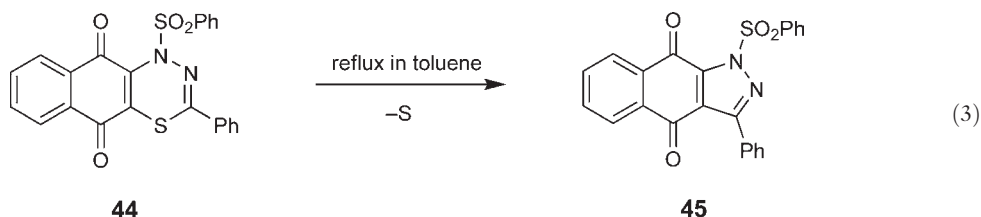


Scheme 4

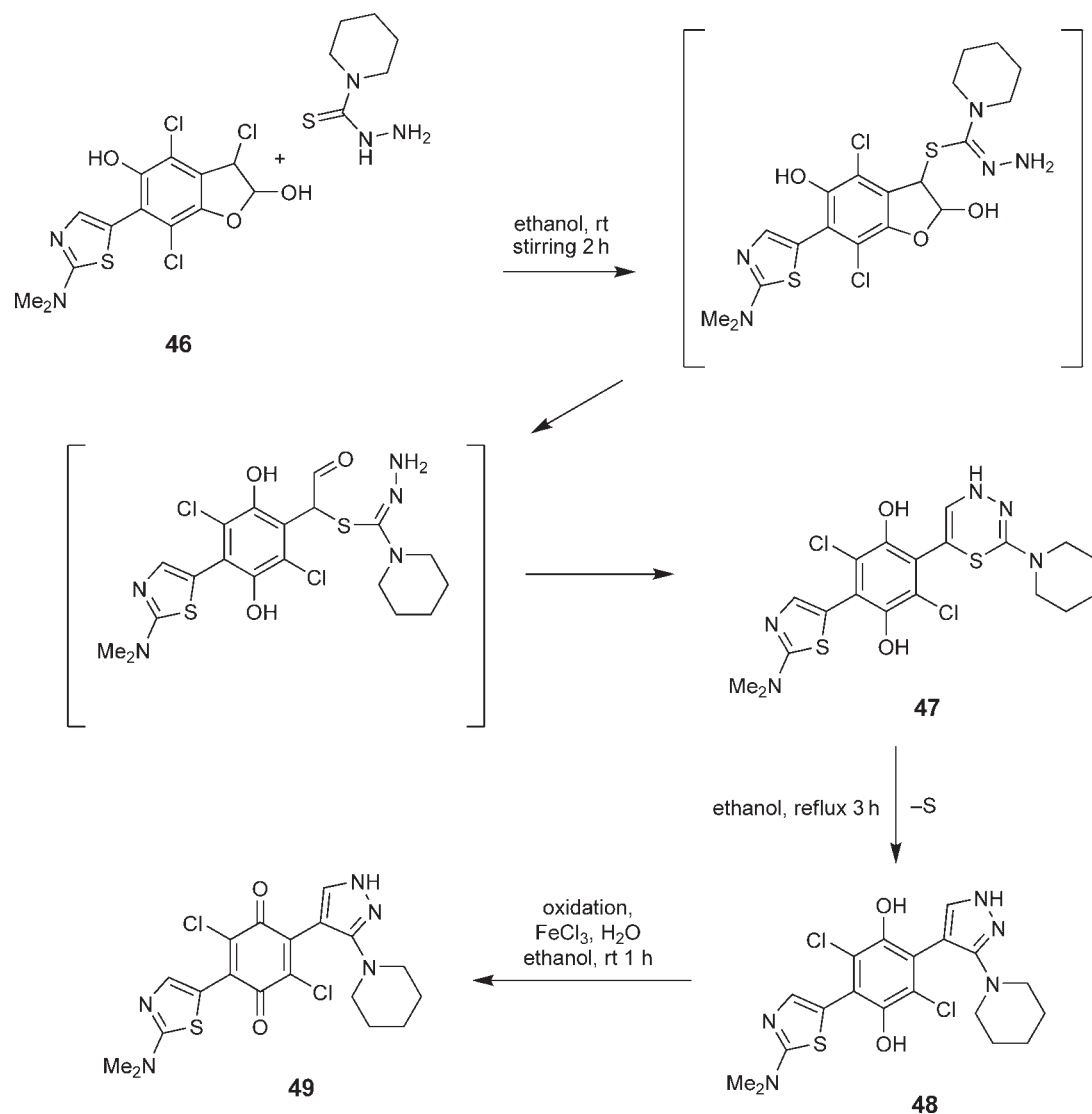
Flash vacuum pyrolysis of 2-dimethylamino-5-phenyl-6*H*-1,3,4-thiadiazin-6-one at 550 °C and 0.08 Torr results in thermal fragmentation and formation of the corresponding *N,N*-dimethyl-5-phenyl-1,3,4-thiadiazol-2-amine **43** together with dimethylcyanamide and benzonitrile (Equation 2) <1981CC1003, 1998HOU(E9c)483>.



1-(Benzenesulfonyl)-3-phenylnaphtho[2,3-*e*]1,3,4-thiadiazine-5,10-dione **44** can be converted to 1-(benzenesulfonyl)-3-phenyl-1*H*-benzo[*f*]indazole-4,9-dione **45** by heating under reflux (Equation 3) <2003PS627>.



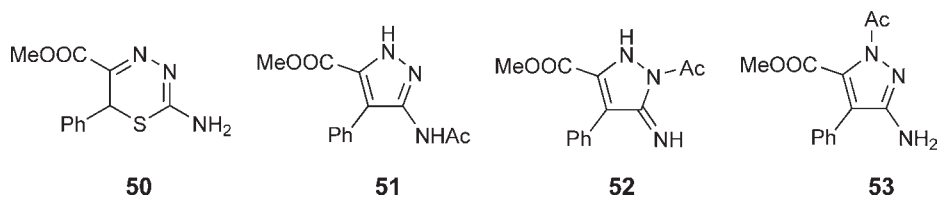
The benzofuran derivative **46** and piperidinothiocarbonylhydrazine react in ethanol at room temperature under stirring to form the 1,3,4-thiadiazine intermediate **47**, which undergoes extrusion of sulfur upon heating to form pyrazole derivative **48**. Subsequent oxidation gives compound **49** (Scheme 5) <2005H(65)1569>.



Scheme 5

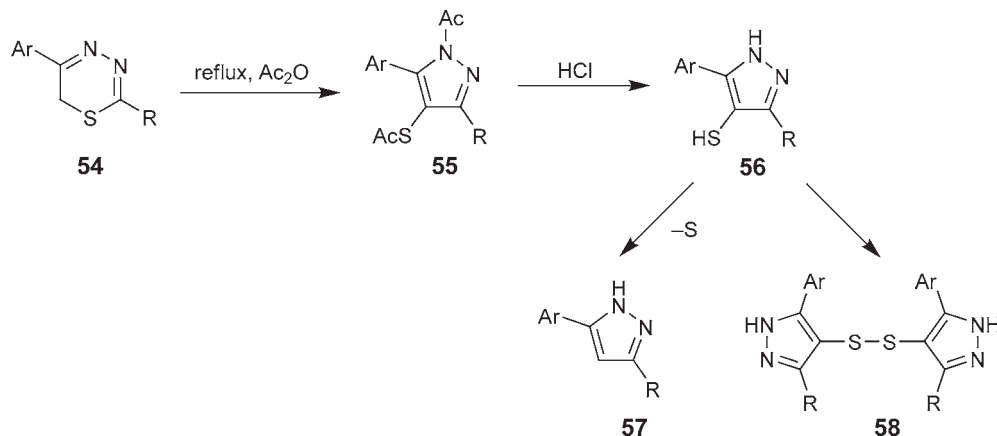
9.08.4.2 Electrophilic Attack at Nitrogen

In boiling acetic anhydride, 1,3,4-thiadiazine **50** undergoes ring contraction with sulfur extrusion to yield acetylpyrazoles **51–53** <1996CHE1089>.



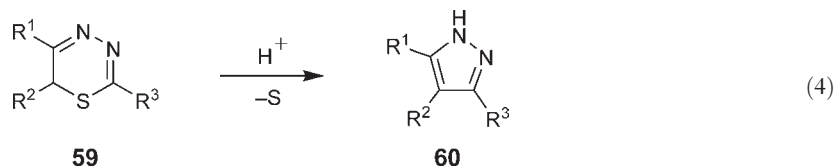
Treatment of 6-unsubstituted 2-dialkylamino-5-aryl-6H-1,3,4-thiadiazines **54** (R = NMe₂, piperidino, morpholino, pyrrolidino, 1-methylpiperazino) with boiling acetic anhydride results in ring contraction to give pyrazoles and simultaneous acetylation, with the sulfur group remaining in the products **55** in the form of a sulfanyl group <1969ZC361, 1970LA45, 1976ZC80, 1991KGS435, 1998HOU(E9c)483, 2006UP2>. The hydrolysis of **55** with

hydrochloric acid gives 4-mercaptopyrazoles **56**, which can be converted into pyrazoles **57** and pyrazolyl disulfides **58** upon aerial oxidation (Scheme 6). Analogously, thiadiazines **54** react in boiling trifluoroacetic anhydride to form 3-substituted 1-trifluoroacetyl-4-trifluoroacetylsulfanyl-5-arylpyrazoles <1991JFC(54)292>.

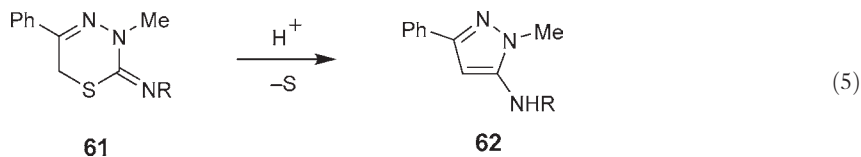


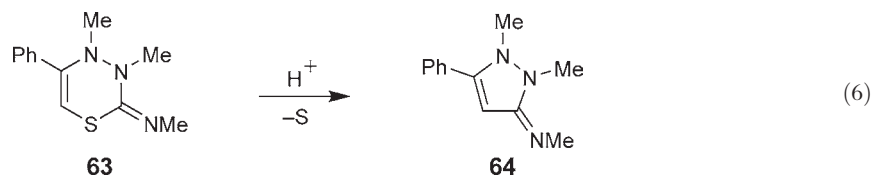
Scheme 6

5,6-Substituted 1,3,4-thiadiazines **59** ($R^1 = \text{H, Me Et, Ar, COOEt, Ac}$; $R^2 = \text{H, Alk, Ar}$; $R^3 = \text{NHAlk, NHA r, NMe}_2$, piperidino, morpholino, pyrrolidino, Ph, Bn) can be converted to pyrazoles **60** by sulfur elimination in ethanolic hydrogen chloride, or dilute or concentrated hydrochloric acid <1969ZC361, 1970LA45, 1976JPR971, 1978MI135, 1978ZC65, 1993PHA732, 1994PHA401, 1998HOU(E9c)483>. The rearrangement of 1,3,4-thiadiazines to pyrazoles also takes place in boiling acetic acid (Equation 4) <1977ZC173, 1977ZC219, 1978CCCC1227, 1978MI135, 1989ZC288, 1992MI173, 1993PHA732, 1994PHA401, 1997PHA831, 1998HOU(E9c)483> or trifluoroacetic acid (TFA) <1991JFC(54)292>. The tendency for pyrazole formation depends very strongly on both the substituents in the 5- and the 6-positions of the 1,3,4-thiadiazines. The best results for a ring contraction are obtained with weak acids if the substituent in the 6-position of the 1,3,4-thiadiazine is phenyl or an electron-withdrawing group, such as ethoxycarbonyl or acetyl. The mechanism of this reaction is shown in Section 9.08.3.1.

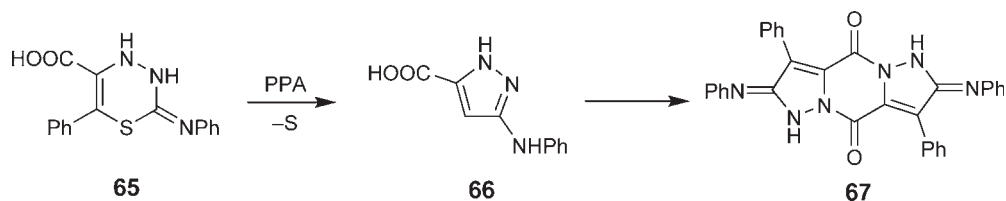


The desulfuration of 6-unsubstituted-3-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **61** ($R = \text{Me, Pr}^i$) in boiling glacial acetic acid affords pyrazoles **62** <2003SL2392>. In contrast to the rapid sulfur extrusion of 6-phenyl- or 6-ethoxycarbonyl-6*H*-1,3,4-thiadiazines **59** ($R^2 = \text{Ph, CO}_2\text{Et}$) to pyrazoles, a much longer reaction time (40 h) was required to achieve a complete desulfuration of **61** (Equation 5). The treatment of 4*H*-1,3,4-thiadiazine **63** with concentrated hydrochloric acid or hydrobromic acid (48%) afforded the 5-imino-1,2-dimethylpyrazoles **64** in 40% and 30% yield, respectively (Equation 6). The yield was increased to 53% by the use of glacial acetic acid. The sulfur extrusion proceeded very rapidly and precipitation of considerable amounts of sulfur was observed even after stirring for only 5 min.



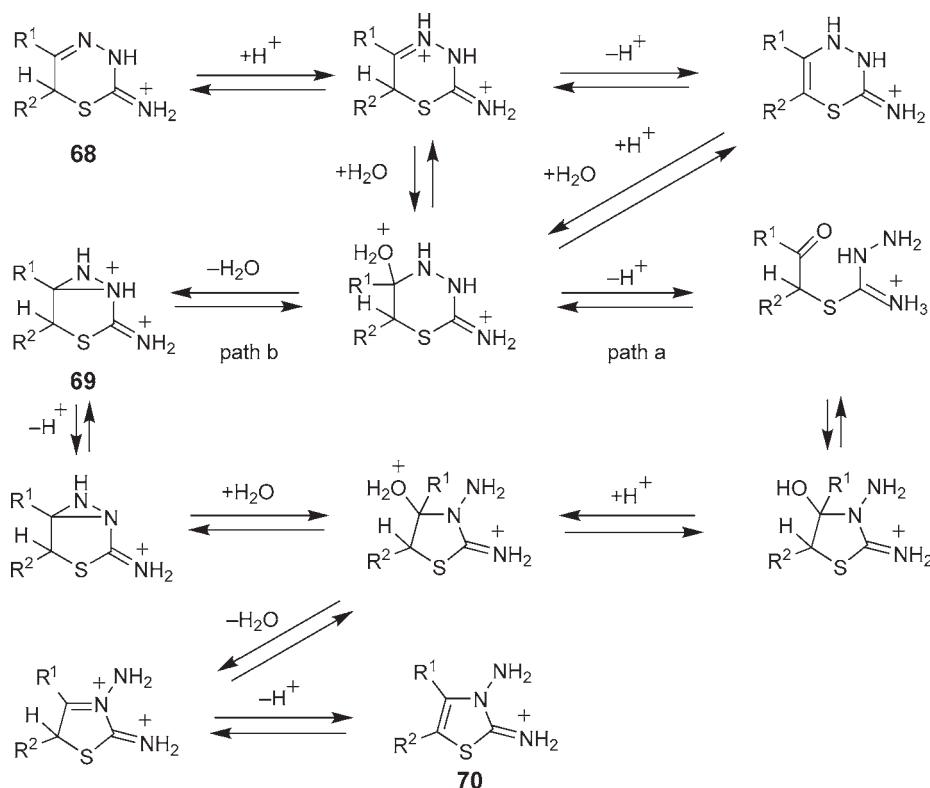


In the presence of polyphosphoric acid (PPA), 5-carboxy-6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine **65** undergoes desulfuration to form the intermediate pyrazole **66**, which affords 3,8-diphenyl-2,7-diphenylimino-1*H*,6*H*-dipyrzolo[1,5-*a*,1',5'-*d*]pyrazine **67** by intermolecular cyclodehydration ([Scheme 7](#) <2005RCB441>).



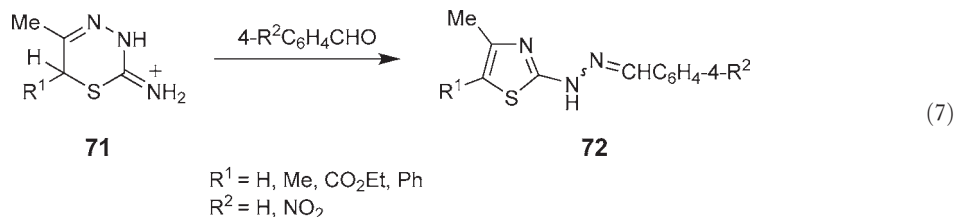
Scheme 7

Depending on the substituents, 1,3,4-thiadiazines can undergo rearrangement to 2,3-dihydrothiazole derivatives upon acid hydrolysis. While 1,3,4-thiadiazines with an aromatic substituent in the 5-position are relatively stable, 2-imino- or 2-alkylimino-5-methyl-6*H*-1,3,4-thiadiazines **68**, for example, undergo ring contraction to give 2-amino- or 2-[alkyl(aryl)amino]-4-methyl-2,3-dihydro-1,3-thiazoles **70** <1978MI135, 1998HOU(E9c)483, 2006UP1>. 5-Alkyl-6*H*-1,3,4-thiadiazines behave like cyclic thiosemicarbazones that are extremely sensitive to protonation; hydrolysis of the N(4)–C(5) double bond is followed by renewed ring closure to give the 2-imino- or 2-[alkyl(aryl)amino]-4-alkyl-2,3-dihydro-1,3-thiazoles **70** ([Scheme 8](#), path a). An alternative mechanism for the 1,3,4-thiadiazine-thiazoline rearrangement involves the formation of the bicyclic diaziridine intermediate **69** ([Scheme 8](#), path b) <1980J(P2)890>.

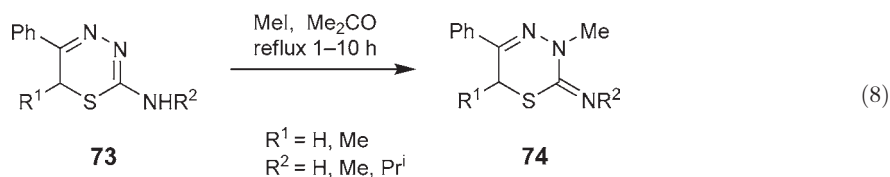


Scheme 8

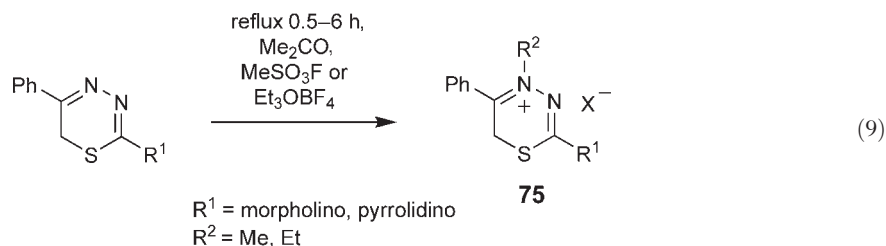
5-Methyl-6*H*-1,3,4-thiadiazinamines **71** ($R^1 = \text{H, Me, COOEt, Ph}$) tend also to undergo ring contraction when heated with benzaldehyde or 4-nitrobenzaldehyde ($R^2 = \text{H, NO}_2$) in the presence of acid, yielding 2-(benzylidenehydrazino) or 2-[(4-nitrobenzylidene)hydrazino]thiazoles **72** (Equation 7) <1978MI135>, <1998HOU(E9c)483>.



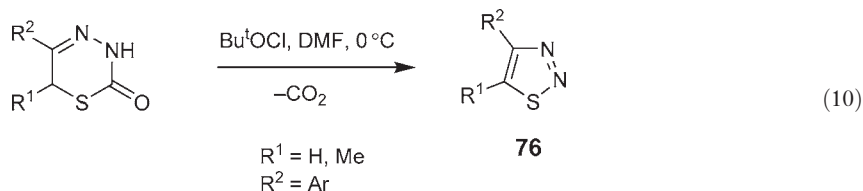
2-Amino- or 2-alkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **73** react with methyl iodide to give 2-alkylimino-3-methyl-4-phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **74** (Equation 8) <2006UP1>. 3-Substituted-2-imino-5-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines are prepared from 2-amino-5-methyl-6*H*-1,3,4-thiadiazine by alkylation with alkyl or arylalkyl halides in the presence of sodium acetate in dimethylformamide (DMF) <1998PHA820>.



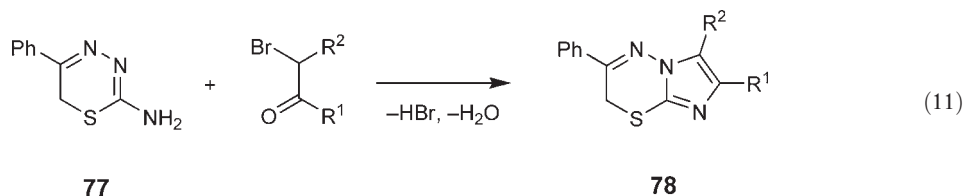
2-Dialkylamino-5-aryl-6*H*-1,3,4-thiadiazines cannot be alkylated with methyl iodide. 1,3,4-Thiadiazine hydroiodides are obtained by the reaction of 2-dialkylamino-6*H*-1,3,4-thiadiazines with methyl iodide in anhydrous ethanol in the presence of dimethyl sulfoxide (DMSO) <1998RJO417>. The reaction of 2-pyrrolidino- or 2-morpholino-5-phenyl-6*H*-1,3,4-thiadiazines with methanesulfonyl fluoride or triethyloxonium tetrafluoroborate affords quaternary 2-dialkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **75** in excellent yields (Equation 9) <1998RJO417>.



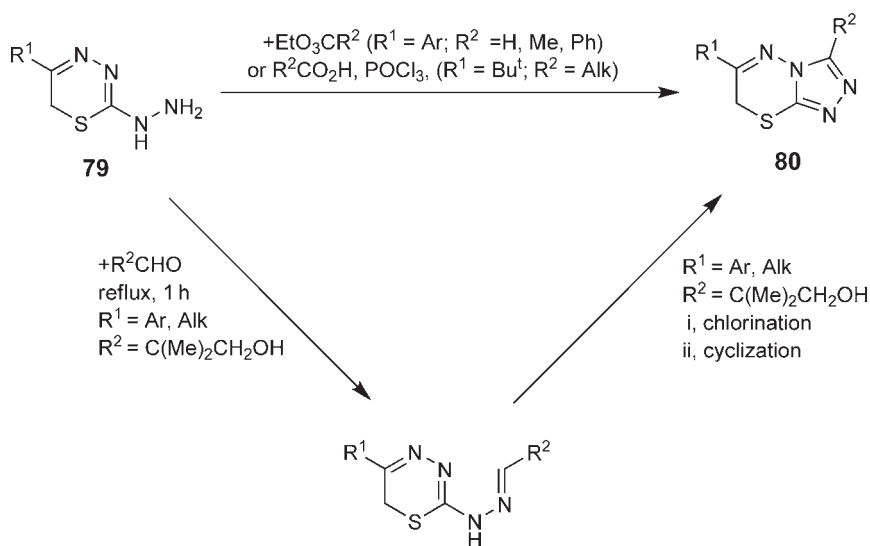
6*H*-1,3,4-Thiadiazin-2(3*H*)-ones eliminate carbon dioxide to yield 1,2,3-thiadiazoles **76** <1998HOU(E9c)483>. The reaction proceeds by an attack of Cl^+ on the N- or S-atom, followed by ring contraction and carbon dioxide elimination (Equation 10).



The reactions of 6*H*-1,3,4-thiadiazin-2-amine **77** with α -halo ketones afford 2*H*-imidazo[2,1-*b*]6*H*-1,3,4-thiadiazines **78** ($R^1 = \text{Ar}$; $R^2 = \text{H, Ph}$; Equation 11). <1975ZC482>.



2-Hydrazino-5-aryl-6*H*-1,3,4-thiadiazines **79** react with orthocarbonate esters to give 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** ($\text{R}^1 = \text{Ar}$; $\text{R}^2 = \text{H, Me, Ph}$; [Scheme 9](#) [<1977ZC15>](#). Compounds **80** are also prepared by reaction of **79** with hydroxypivalaldehyde in acetonitrile under reflux for 1 h, chlorination with 1,3-dichloro-5,5-dimethylhydantoin at 20 °C for 30 min, and cyclization in the presence of triethylamine at 10–45 °C for 80 min ($\text{R}^1 = \text{Ar, Alk}$; $\text{R}^2 = \text{C}(\text{Me})_2\text{CH}_2\text{OH}$) [<2002JPP2002302493>](#). 7*H*-Triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** are also obtained by heating of **79** with carboxylic acids in the presence of PCl_3 or P_4O_{10} or acyl chlorides [<1999JPP11240885, 2000JPP2000143664>](#).

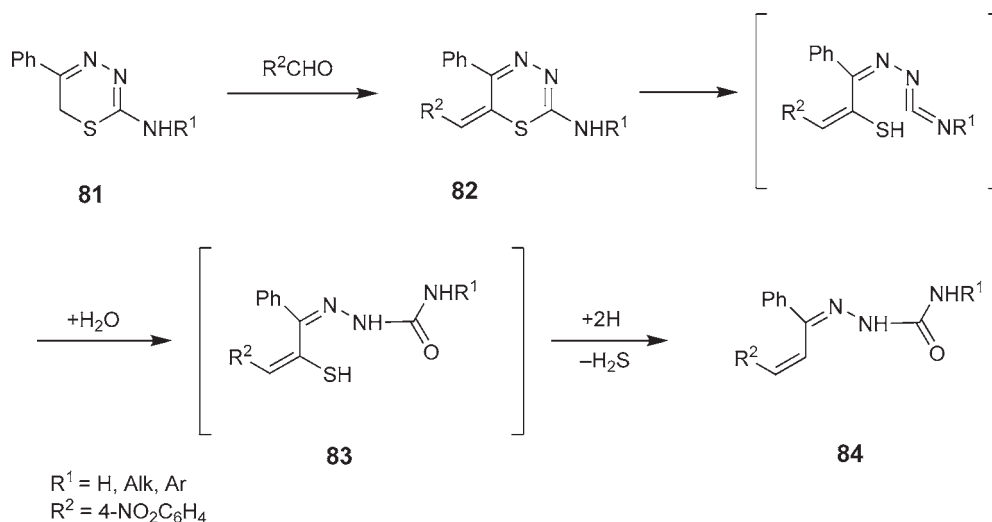


Scheme 9

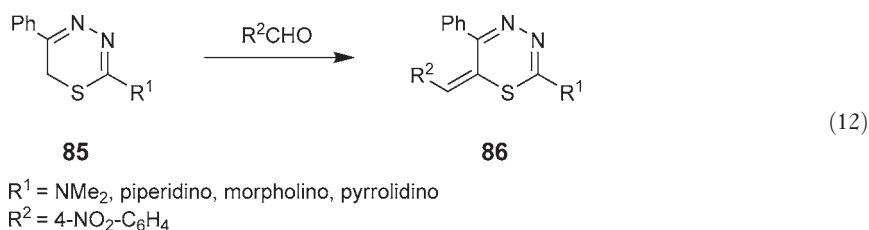
9.08.4.3 Electrophilic Attack at Carbon

A ring cleavage of 2-amino- and 2-alkyl(aryl)amino-5-phenyl-6*H*-1,3,4-thiadiazines **81** is observed on treatment with 4-nitrobenzaldehyde; elimination of hydrogen sulfide is accompanied by formation of semicarbazones **84** ([Scheme 10](#) [<1998HOU\(E9c\)483, 2006UP1>](#). 6-(4-Nitrobenzylidene)-6*H*-1,3,4-thiadiazines **82** are formed in the first step of the reaction. The stability of the thiadiazine ring is reduced markedly by the presence of the electron-attracting 6-(4-nitrobenzylidene) group. Ring cleavage of **82** at the S(1)–C(2) bond and subsequent nucleophilic attack of water on the intermediate carbodiimide unit leads to the semicarbazone **83**, which then takes up two hydrogen atoms and liberates hydrogen sulfide to yield the final product **84**. The reduction may be attributed to ethanol present in the solvent.

In the case of 2-dialkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **85**, the reaction stops at the 6-(4-nitrobenzylidene) compounds **86** since ring opening and formation of a carbodiimide moiety are not possible with the 2-dialkylamino compounds ([Equation 12](#) [<1998HOU\(E9c\)483>](#).

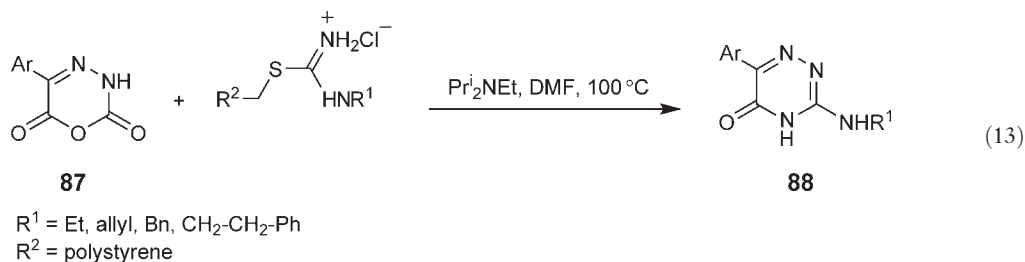


Scheme 10



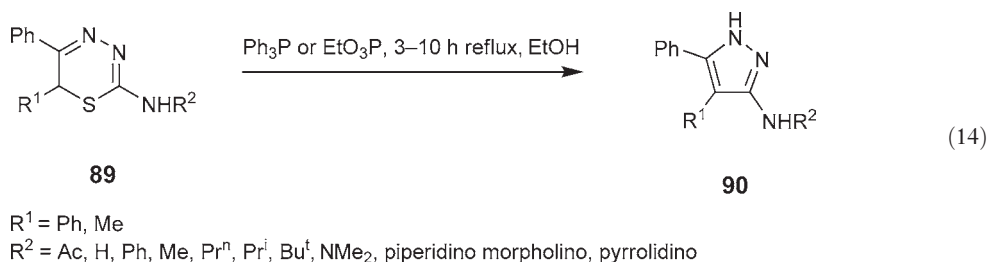
9.08.4.4 Nucleophilic Attack at Carbon

Heating of oxadiazine-2,6-diones **87** with polymer-bound isothioureia in anhydrous DMF in the presence of diisopropylethylamine affords 3-amino-1,2,4-triazin-5(4*H*)-ones **88** (Equation 13) <2001TL4433>.



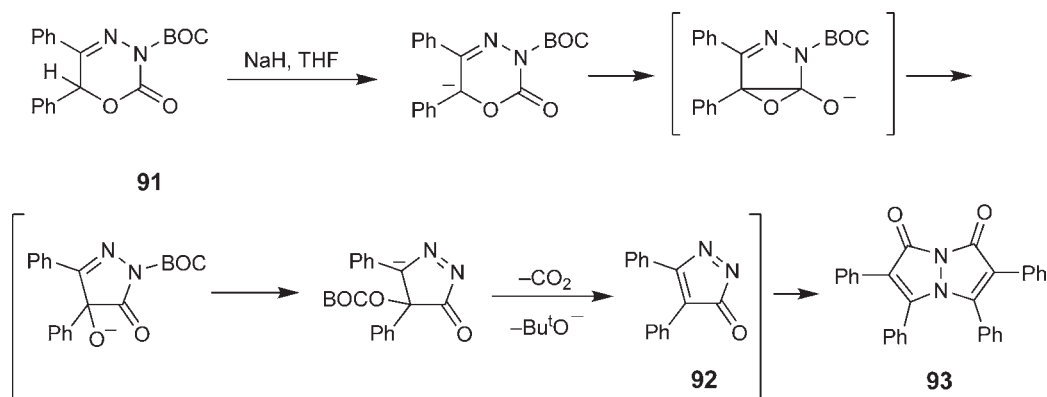
9.08.4.5 Nucleophilic Attack at Sulfur

The ring contraction of 6-unsubstituted 6*H*-1,3,4-thiadiazines **89** with triphenylphosphine or triethylphosphite affords pyrazoles and, by ring opening, mercaptopyrazoles and dipyrazolyl disulfide <1977S485>. This rearrangement also occurs with 6-substituted 1,3,4-thiadiazines (Equation 14) <2006UP1> By the ring contraction of 1,3,4-thiadiazines **89**, only the formation of pyrazoles **90** takes place.



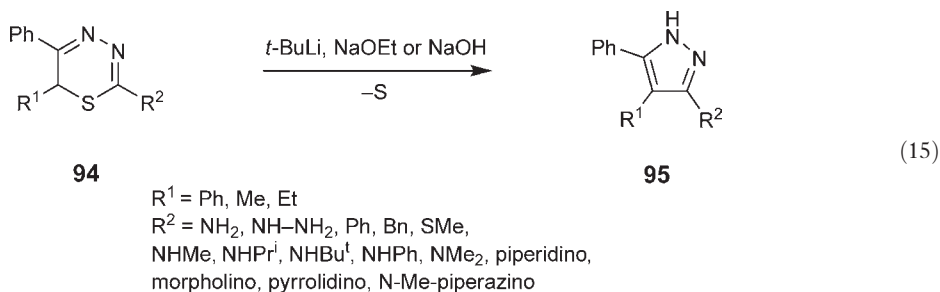
9.08.4.6 Nucleophilic Attack at Hydrogen (Proton Abstraction)

The reaction of 1,3,4-oxadiazin-2-one **91** with sodium hydride in tetrahydrofuran (THF) leads to an unprecedented Favorski-like ring contraction to form the 4,5-diphenylpyrazol-3-one **92**, which then dimerizes with loss of one molecule of nitrogen to give 3,4,6,7-tetraphenyl-1,5-diazabicyclo[3.3.0]octa-3,6-dien-2,8-dione **93** (Scheme 11) <1996TL5039>.



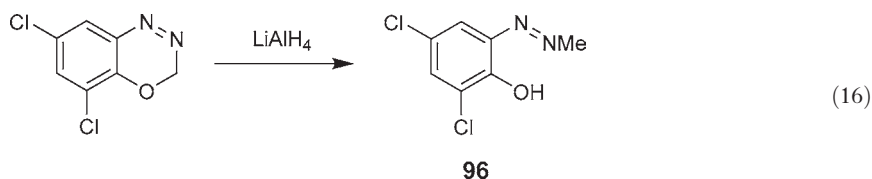
Scheme 11

1,3,4-Thiadiazines **94** can be converted to pyrazoles **95** by sulfur elimination in the presence of *t*-butyllithium or lithium diisopropylamide at -78°C <1975TL33>. Base-induced ring contraction and desulfuration of 1,3,4-thiadiazines to pyrazoles occurs also with sodium ethoxide, aqueous sodium hydroxide, or potassium *t*-butoxide (Equation 15) <1977S196, 1984DEP211343> Kinetic studies of chalcogen extrusion from 1,3,4-thiadiazines **94** and 1,3,4-selenadiazines to yield pyrazoles **95** in the presence of sodium ethoxide or sodium methoxide demonstrate a higher stability for the 1,3,4-selenadiazines <2006UP1>. The base-induced ring contraction of 1,3,4-thiadiazines to pyrazoles takes place via an antiaromatic 1,3,4-thiadiazinyl anion. The mechanism of this reaction is shown in Section 9.08.3.1 (Scheme 1).



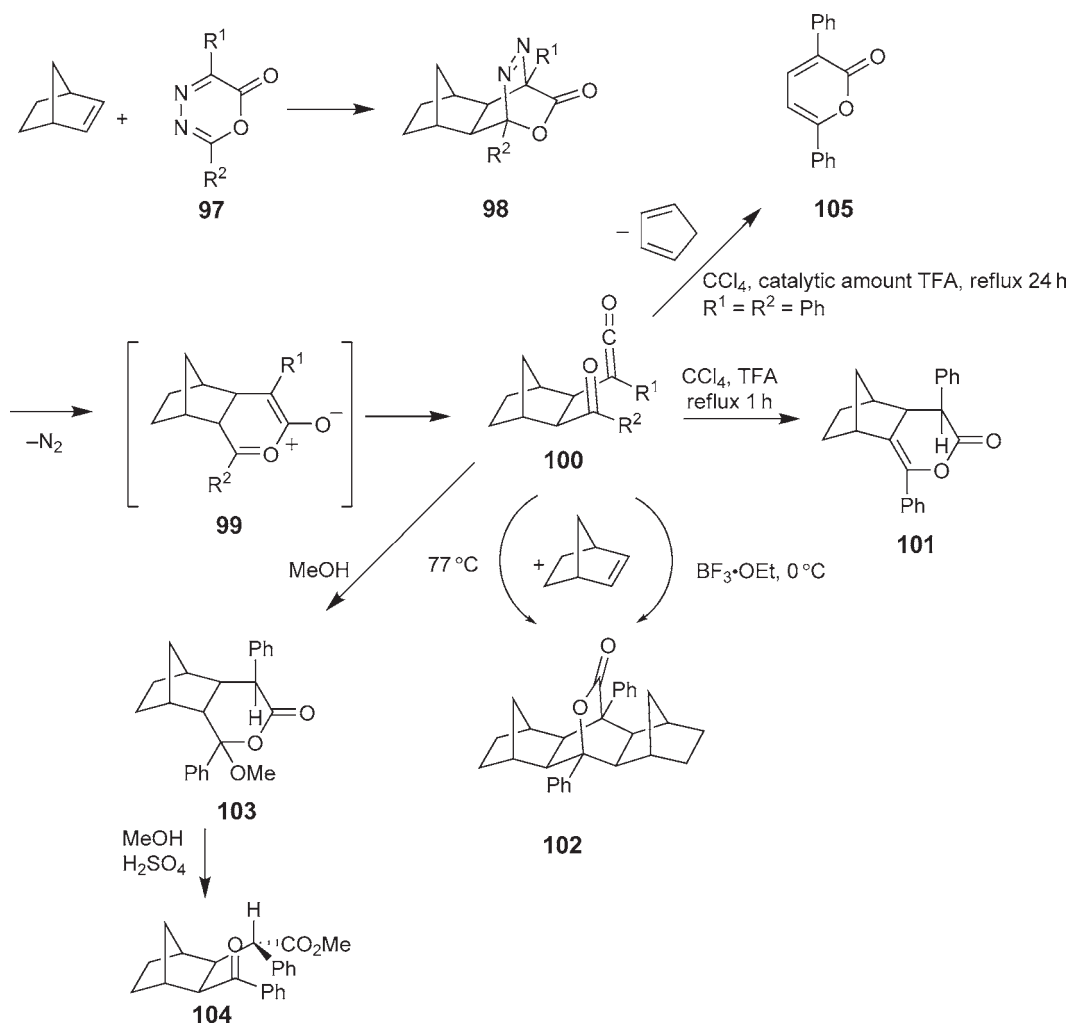
9.08.4.7 Reduction

The heterocyclic ring of 2*H*-benzooxadiazines can be opened by the action of lithium aluminium hydride, as illustrated by the formation of azene **96** <1998HOU(E9c)427> (Equation 16).



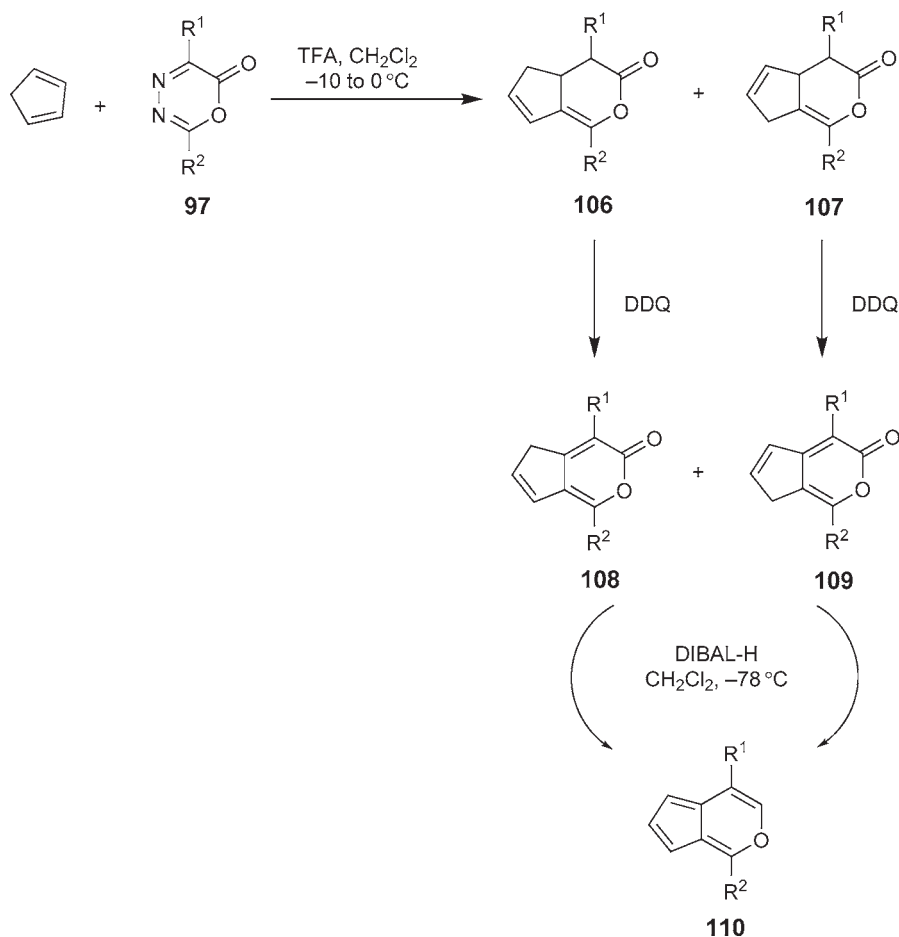
9.08.4.8 Cycloadditions

The cycloaddition of 1,3,4-oxadiazin-6-ones **97** with norbornene proceeds via γ -oxoketenes **100** by loss of N_2 from the initial adducts **98** and subsequent ring opening of intermediates **99** ($R^1 = \text{Ar}, \text{Pr}^i$; $R^2 = \text{Ar}, \text{Me}, \text{CO}_2\text{Me}$) <1995JPR659, 1996LA853>. Isomerization of **100** ($R^1 = R^2 = \text{Ph}$) in hot carbon tetrachloride yields the enol lactone **101**. Heating of **100** ($R^1 = R^2 = \text{Ph}$) in the presence of norbornene leads to the formation of the symmetrical γ -lactone **102**. The treatment of **100** ($R^1 = R^2 = \text{Ph}$) with boron trifluoride etherate proved to be a useful preparative alternative for the formation of **102**. The reaction of **100** ($R^1 = R^2 = \text{CO}_2\text{Me}$) with boron trifluoride etherate affords a γ -pyrone **105**; a product of type **102** is not observed. On treatment with methanol, the pseudo-ester **103** is formed and, in the presence of sulfuric acid, **103** is converted to the methyl ester **104** (Scheme 12).



Scheme 12

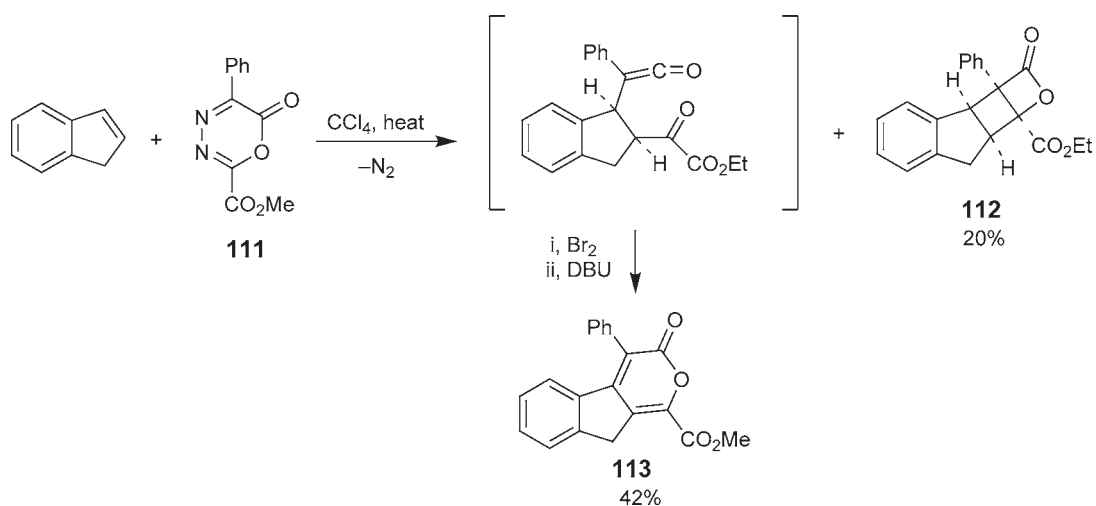
The cycloaddition of 1,3,4-oxadiazin-6-ones **97** ($R^1 = \text{Ph}, \text{Pr}^i$; $R^2 = \text{Ar}, \text{CO}_2\text{Me}$) to cyclopentadiene in the presence of TFA leads to the formation of regioisomeric dihydro- α -pyrones **106** and **107** <1998CC2387>. The dehydrogenation of **106** and **107** with dichlorodicyanoquinone (DDQ) affords the α -pyrones **108** and **109**. The latter are converted to cyclopenta[*c*]pyrans **110** with diisobutylaluminium hydride (DIBAL-H) (Scheme 13).



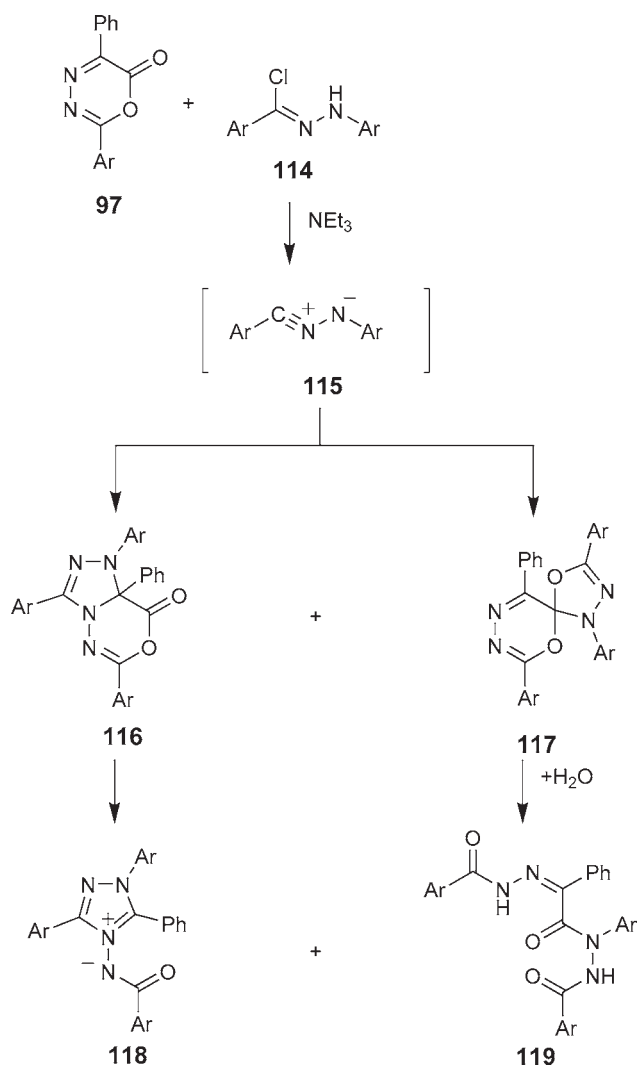
Scheme 13

Similarly, the 2-carboxymethyl-5-phenyloxadiazin-6-one **111** reacts with indene to form primarily a γ -oxoketene. The latter reacts with bromine in the presence of diaza(1,3)bicyclo[5.4.0]undecane (DBU) to give 4-phenylindeno[2,1-*c*]pyran **113**. From this procedure, a β -lactone **112** was isolated as by-product in 20% yield <1998J(P1)2031> (Scheme 14).

Cycloaddition reactions of 1,3,4-oxadiazin-6-ones **97** ($R^1 = \text{Ph}, R^2 = \text{Ar}$), via their 2,3-diaza-1,3-diene functionality, are observed by treatment with dipolarophiles. Thus, 2,5-diaryl-1,3,4-oxadiazines **97** react with diaryl nitrilimines **115**, which are liberated *in situ* from the corresponding hydrazonoyl chlorides **114** and triethylamine, to give 1*H*-1,2,4-triazole *N*-imines **118** and open-chain products **119** <1996JHC591>. It is reasonable to conclude that intermediates **116** are formed initially from cycloaddition across the adjacent carbonyl-carbon nitrogen double bond and that subsequent CO abstraction gives 1*H*-1,2,4-triazole *N*-imine derivatives **118**. The open-chain adducts **119** are formed from intermediates **117**, which result from the reaction of **115** at the carbonyl double bond of the oxadiazinones **97** (Scheme 15).



Scheme 14

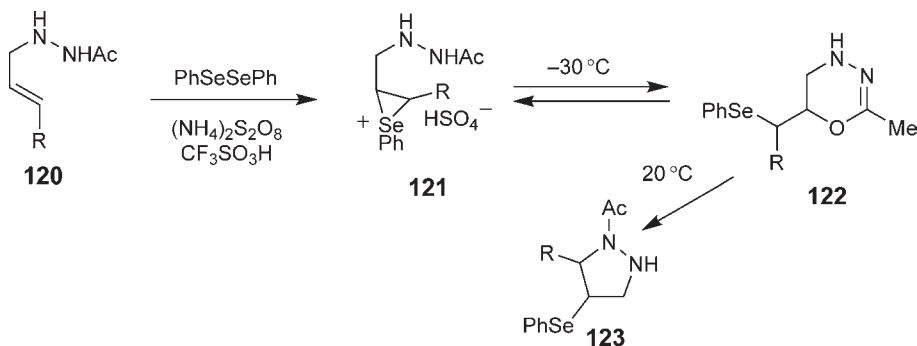


Scheme 15

9.08.5 Reactivity of Nonconjugated Rings

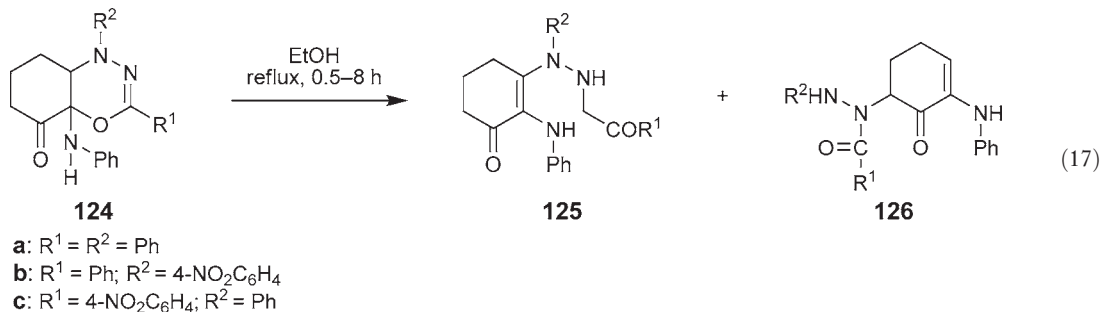
9.08.5.1 Thermal Reactions

The treatment of *N*-allylacetylhydrazides **120** with diphenyl diselenide at -30°C affords 5,6-dihydro-4*H*-1,3,4-oxadiazines **122** via intermediates **121** <1996T11841>. At room temperature, the initially formed 1,3,4-oxadiazines **122** are converted completely to *N*-acetyl pyrazolidines **123** (Scheme 16).

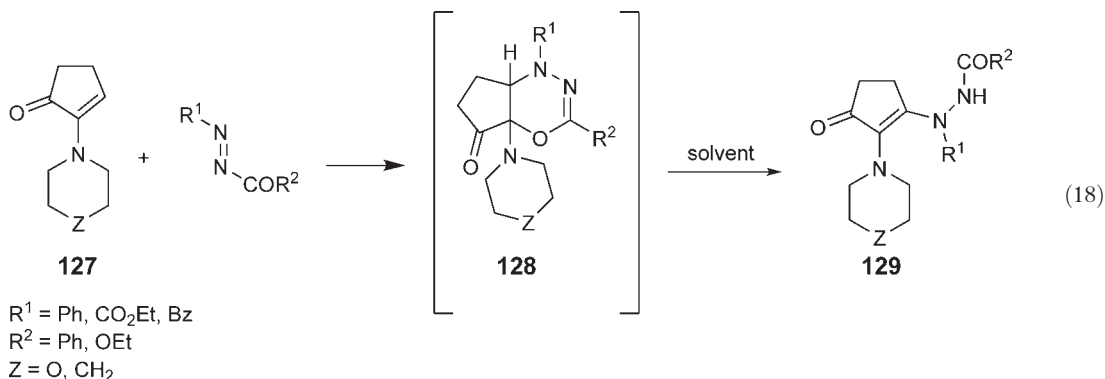


Scheme 16

The oxadiazine derivatives **124** undergo ring opening by heating in ethanol to give keto enamines **125** and **126** <1996G297>. The tendency to ring opening is very strongly dependent on the substituents R^1 and R^2 . The ring stability is elevated by the presence of a nitro group in the aromatic ring. The conversion of the nitro compounds **124b** and **124c** to the open-chain adducts **125b,c** and **126b,c** occurs only by treatment in ethanol under reflux for 5–8 h. In contrast, an ethanolic solution of **124a** undergoes ring opening to **125a** and **126a** at room temperature after standing for 72 h or after only 30 min heating (Equation 17).

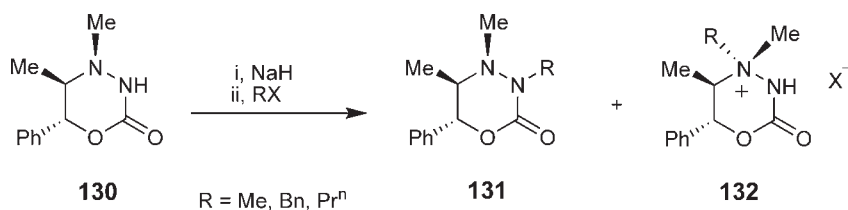


Treatment of the ketoenamine **127** ($\text{Z} = \text{O}$) with a diazene ($\text{R}^1 = \text{R}^2 = \text{Ph}$) affords a mixture of 1,3,4-oxadiazine cycloadducts **128** and the open-chain isomeric compounds **129**. In all other cases of this reaction, **128** cannot be isolated since these heterocyclic compounds are unstable at room temperature. The intermediates undergo rearrangement to form the monoadducts **129** (Equation 18) <1997G387>.



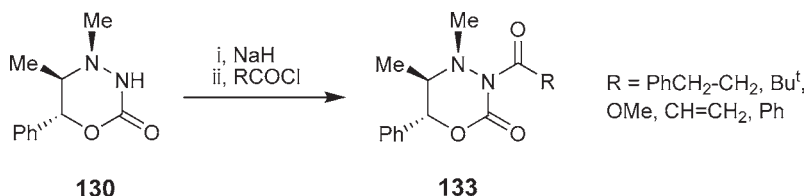
9.08.5.2 Electrophilic Attack at Nitrogen

The perhydro-1,3,4-oxadiazin-2-one **130** yields the 3-alkyl-substituted perhydro-1,3,4-oxadiazin-2-ones **131** and the perhydrooxadiazinium salts **132** upon treatment with sodium hydride and subsequent alkylation with iodomethane, 1-iodopropane, or benzyl bromide (Scheme 17) <2002JOC8871>.

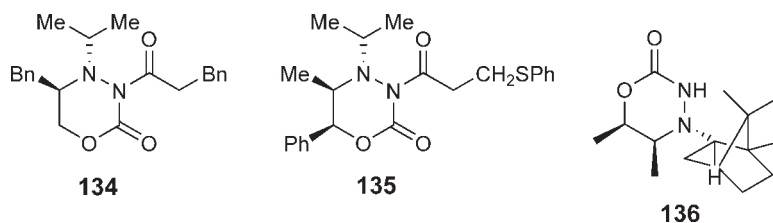


Scheme 17

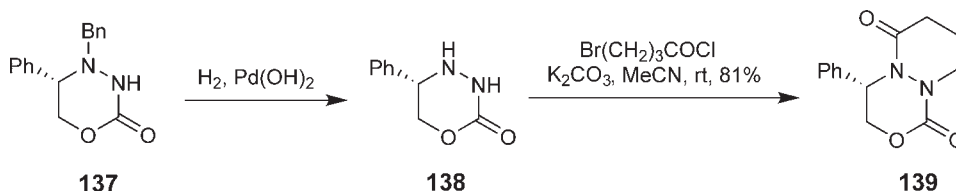
Similarly, **130** reacts with sodium hydride and acyl halides to give 3-acyl-perhydro-1,3,4-oxadiazin-2-ones **133** (Scheme 18) <2002JOC8871, 2001T9789>. Compounds **134–136** have also been prepared by this method <2004JOC714, 2005TA1047, 2006TA2386>.



Scheme 18



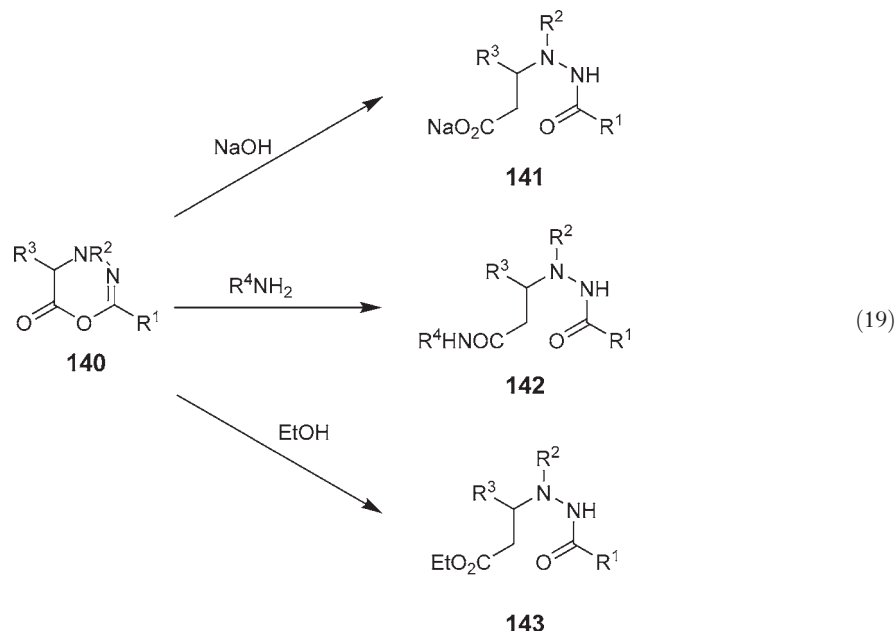
Compound **138** is obtained from 4-benzyl-5-phenylperhydro-1,3,4-oxadiazin-2-one **137** by N-debenzylation with hydrogen under pressure in the presence of Pd(OH)₂ as catalyst. Subsequent treatment with 4-bromobutanoyl chloride yields a bicyclic hydrazinolactam derivative **139** (Scheme 19) <1998TL8081>.



Scheme 19

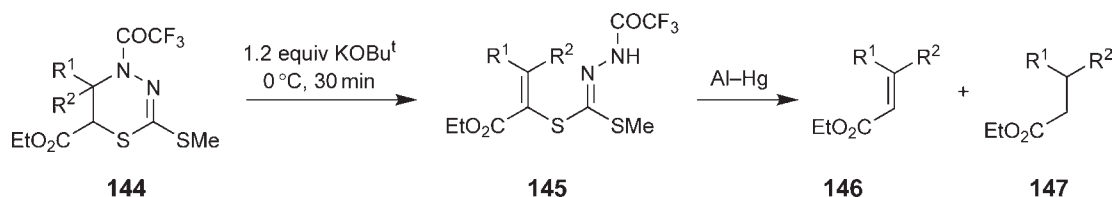
9.08.5.3 Nucleophilic Attack at Carbon

4,5-Dihydro-4*H*-1,3,4-oxadiazines **140** ($R^1 = R^2 = R^3 = \text{Ar, Alk, H}$; $R^4 = \text{Ar, Alk}$) behave like lactones, being hydrolyzed by sodium hydroxide to sodium salts of acyl hydrazinocarboxylic acids **141**. Compounds **140** also react with amines or alcohols to give amide or esters of acylhydrazinocarboxylic acids **142** and **143** (Equation 19) <1998HOU(E9c)427>.



9.08.5.4 Nucleophilic Attack at Hydrogen (Proton Abstraction)

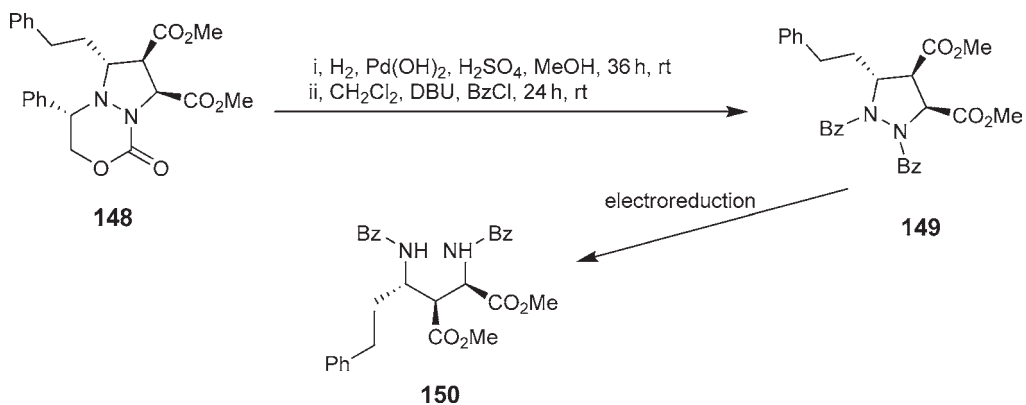
The reaction of 2-methylsulfanyl-5,6-dihydro-1,3,4-thiadiazines with trifluoroacetic anhydride yields the *N*-trifluoroacetyl compounds **144**. Treatment of **144** in THF or benzene with 1.2 molar equiv of KO^tBu at 0°C gives *S*-alkenyl hydrazinocarbodithiolates possessing an ester group **145** (Scheme 20). These compounds are converted to **146** and **147** by reductive desulfuration using Al-Hg . Treatment of **144** with an excess amount of base at room temperature affords 2-methylsulfanyl-6-alkylidene-4*H*-1,3,4-thiadiazin-5-ones <1998CL329> (see Section 9.08.9.2).



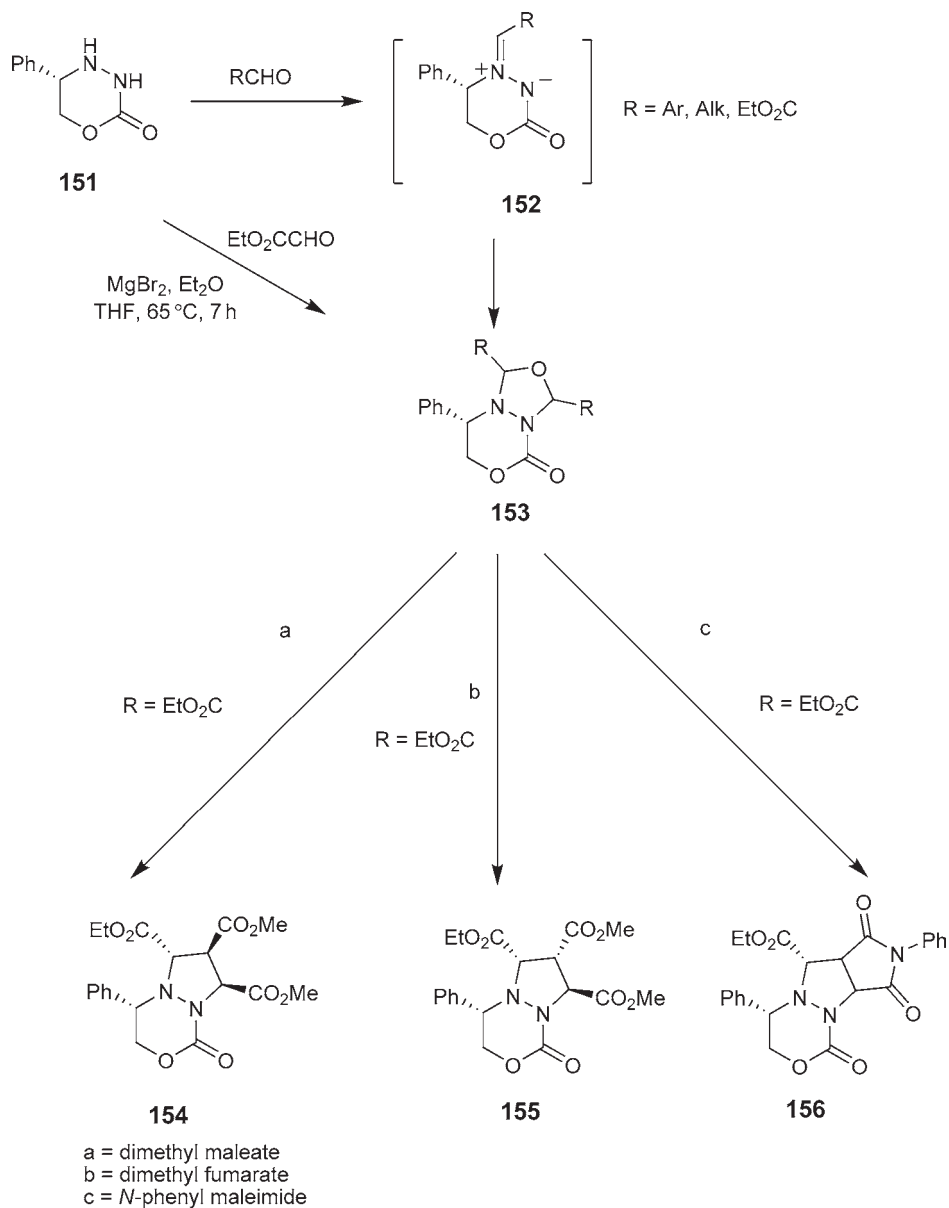
Scheme 20

9.08.5.5 Reduction

Tetrahydropyrazolo[1,2-*c*][1,3,4]oxadiazine **148** undergoes a ring cleavage by treatment with hydrogen in the presence of $\text{Pd}(\text{OH})_2$ and sulfuric acid in methanol to give pyrazolidine **149** (Scheme 21) <2002S1885, 2004TL3127>. Unprotected pyrazolidines are unstable and are readily oxidized into the corresponding Δ^2 -pyrazolines. Accordingly, this intermediate type was protected by treatment of the crude hydrogenolysis reaction products with benzoyl chloride under basic conditions. Full protection of both nitrogen atoms could be realized by performing the benzoylation with DBU. For example, pyrazoline **149** is obtained from **148** in a yield of 79%. The electroreduction of pyrazolidine **149** affords diamines **150** by cleavage of the N–N bond (Scheme 21).



Scheme 21

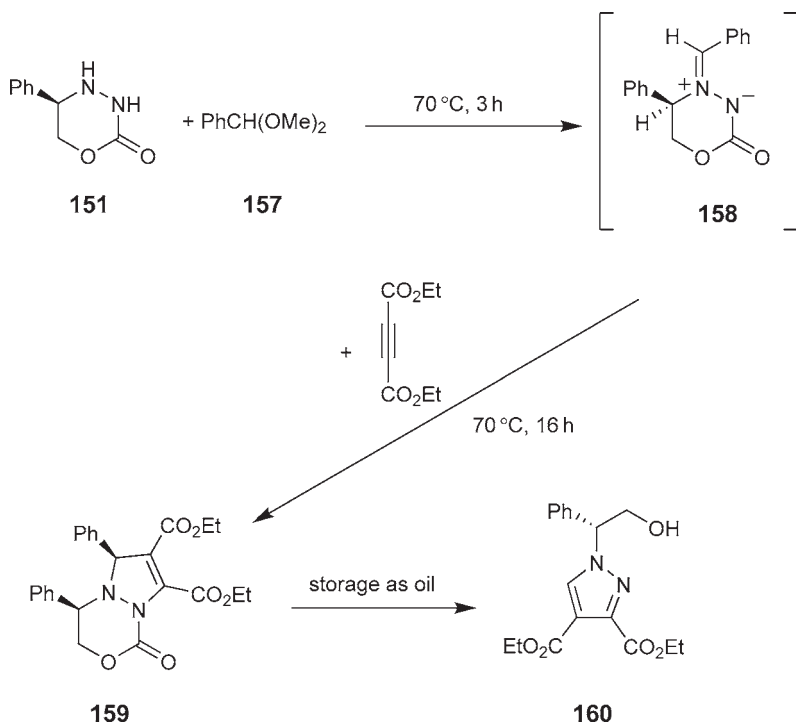


Scheme 22

9.08.5.6 Cycloadditions

5-Phenylperhydro-1,3,4-oxadiazin-2-ones **151** react with aliphatic or aromatic aldehydes or ethyl 2-oxoacetate to give the intermediates **152**. The azomethine imine ylides **152** yield primary oxazolidines **153** <2000S1170, 2002S1885, 2004TL3127>. These compounds can be synthesized also by treatment of **151** with ethyl oxoacetate or aldehydes in the presence of magnesium bromide etherate. The tandem cycloreversion–cycloaddition of **153** with various electron-poor dipolarophiles then leads to pyrazolidines **154–156** (Scheme 22).

The reaction of **151** with benzaldehyde dimethylacetal **157** proceeds in a similar fashion <1999TL3727, 2000S1170>. The resulting azomethine imine intermediate **158** reacts with the dipolarophilic diethyl acetylenedicarboxylate to give **159**. When kept as an oil, the latter is oxidized rapidly in the presence of air to give pyrazole **160** (Scheme 23).

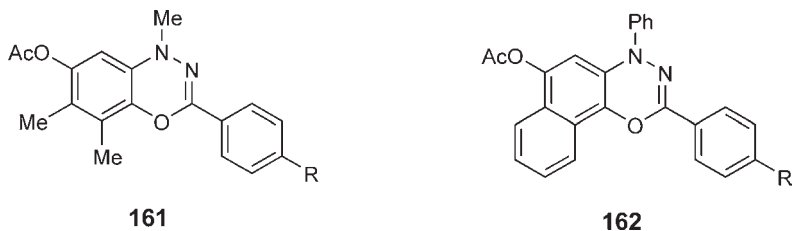


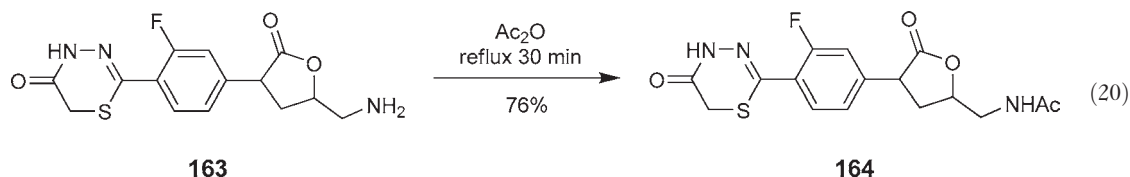
Scheme 23

9.08.6 Reactivity of Substituents Attached to Ring Carbon Atoms

9.08.6.1 Substituted Arenes and Heterocycles

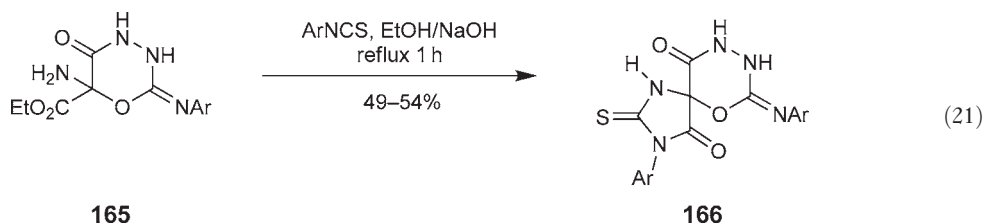
7-Hydroxy-1,5,6-trimethyl-3-aryl-1*H*-benzo[1,3,4]oxadiazines and 9-hydroxy-1-phenyl-3-aryl-1*H*-naphtho[3,4-*e*]-1,3,4-oxadiazines afford 7-hydroxy-1,5,6-trimethyl-3-aryl-1*H*-benzo[1,3,4]oxadiazin-7-yl acetates **161** (R = H, MeO) and 3-aryl-1-phenyl-1*H*-naphtho[1,2-*e*]oxadiazin-9-yl acetates **162** (R = Me, MeO) in excellent yields by heating in acetic anhydride <2000T5137, 2003CPA342>. Acylation of the 5-aminomethyloxazolidine derivative **163** yields the corresponding *N*-acyl compound **164** (Equation 20) <2003WO2003066631>. This thiadiazinone derivative is useful for treatment of bacterial infections.



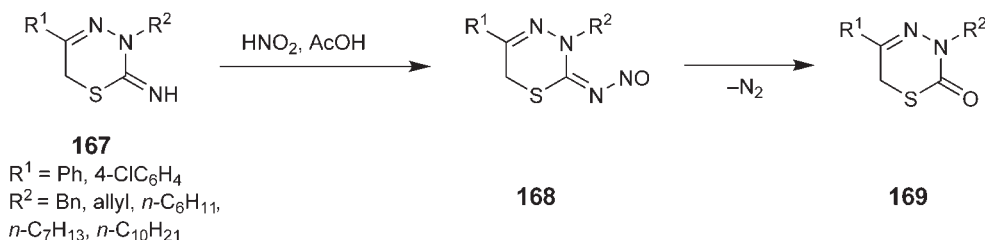


9.08.6.2 Amino Groups

2-Alkyl(aryl)imino-6-amino-6-carboethoxy-5-oxo-3*H*,4*H*-1,3,4-thiadiazines **165** afford the spiro[5.4]decane derivatives **166** upon reflux with aryl isothiocyanates in ethanolic sodium hydroxide solution (Equation 21) <1999IJB932>.

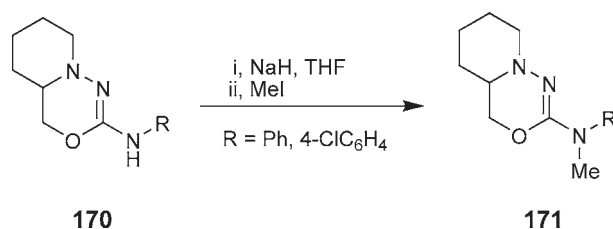


3-Alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thiadiazines **167** react with nitrous acid in glacial acid at 0 °C to give 2-(nitrosoimino)-3-alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thiadiazines **168** <1998PHA820>. Upon standing, these intermediates **168** undergo decomposition with elimination of molecular nitrogen to yield 2-oxo-3-alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thiadiazines **169** (Scheme 24).



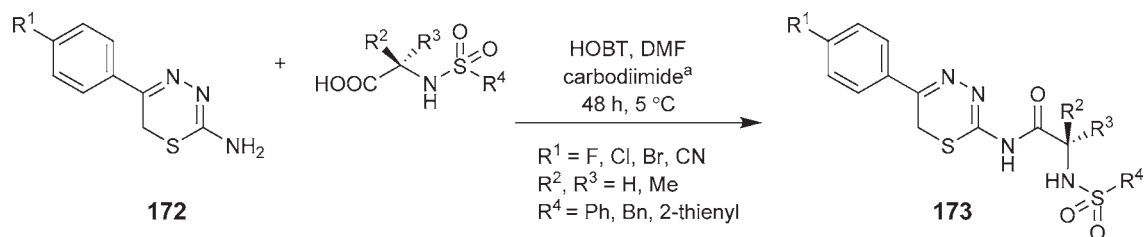
Scheme 24

When the perhydropyrido[1,2-*d*][1,3,4]oxadiazines **170** are treated with sodium hydride, followed by methyl iodide, the 2-(*N*-aryl-*N*-methylamino) derivatives **171** are formed (Scheme 25) <1997H(45)927>. The NMR spectra and X-ray crystallographic analysis indicated that the 1,3,4-oxadiazines adopt rigid *cis*- or *trans*-fused ring conformations. It was found that for the 1,3,4-oxadiazines **170** involving a potential tautomeric equilibrium, the amino form is most likely to be predominant.



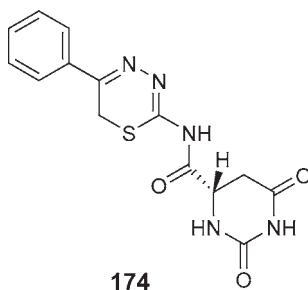
Scheme 25

Acylation of 5-substituted 6*H*-1,3,4-thiadiazines **172** with the carboxylic group of carboxysulfonamides was mediated by a mixture of *N*-ethyl-*N'*-(3-dimethylamino propyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole (HOBT), and 4-methylmorpholine in DMF at 5 °C to yield 1,3,4-thiadiazin-2-yl-2-[(phenylsulfonyl)amino]propanamides **173** (Equation 22) <2001JME3231>. Analogous dihydroorotic acid derivatives **174** were also prepared. Such 1,3,4-thiadiazine derivatives are important matrix metalloproteinase inhibitors.

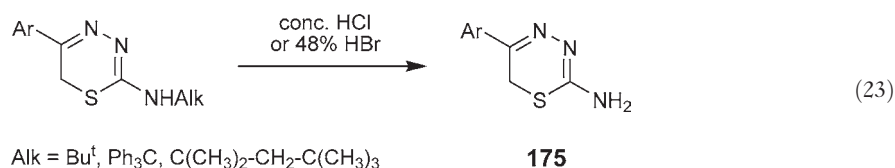


^a*N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide hydrochloride

(22)



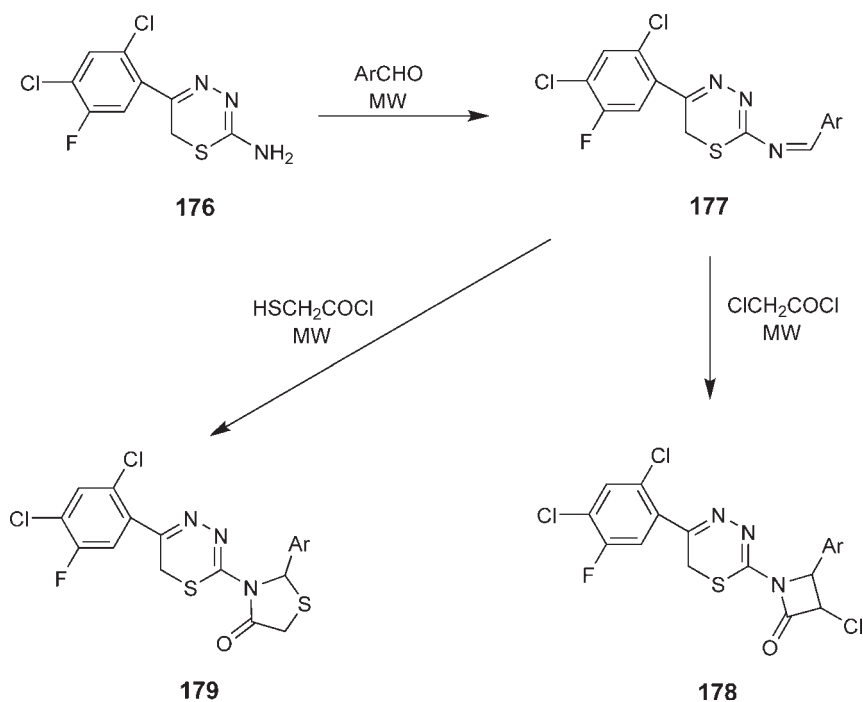
2-Alkylamino-5-aryl-6*H*-1,3,4-thiadiazines undergo N-dealkylation to give the corresponding 2-amino-5-aryl-6*H*-1,3,4-thiadiazines **175** by heating in concentrated hydrochloric acid or 48% hydrobromic acid <1978ZC65, 2006UP1> (Equation 23).



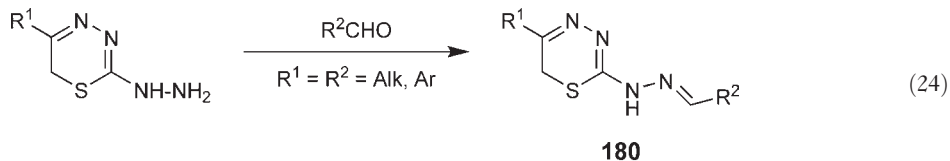
The condensation of 2-amino-5-(2,4-dichloro-5-fluorophenyl)-6*H*-1,3,4-thiadiazine **176** with various aromatic aldehydes under microwave irradiation furnished 2-arylideneamino-6*H*-1,3,4-thiadiazines **177**. The cyclocondensation of **177** with chloroacetyl chloride under microwave irradiation afforded 2-oxoazetidine derivatives **178** in excellent yields. The reaction of **177** with 2-sulfanylacetic acid yielded 4-thiazolidinones **179** (Scheme 26) <2005IJB2158>.

9.08.6.3 Hydrazino Groups

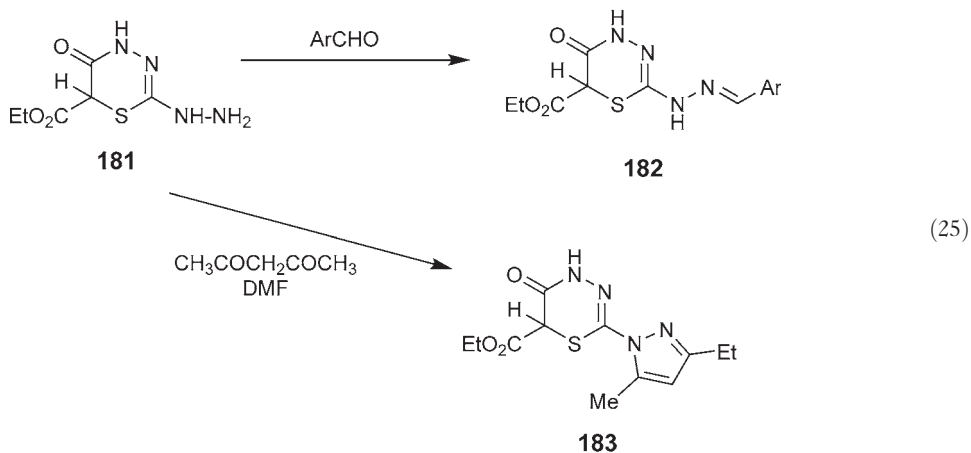
2-Hydrazino-1,3,4-thiadiazines react with aldehydes to give 2-alkyl(aryl)idenehydrazino-6*H*-1,3,4-thiadiazines **180** <2001JPP2001072682, 2002JPP2002302493> (Equation 24). These compounds are starting materials for the synthesis of 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines <2002JPP2002302493> (Section 9.08.4.2). 2-Hydrazino-6*H*-1,3,4-thiadiazines cyclize with acyl chlorides or carboxylic acids in the presence of PCl₃ or P₄O₁₀ to yield 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** (Section 9.08.4.2) <1999JPP11240885, 2000JPP2000143664>.



Scheme 26

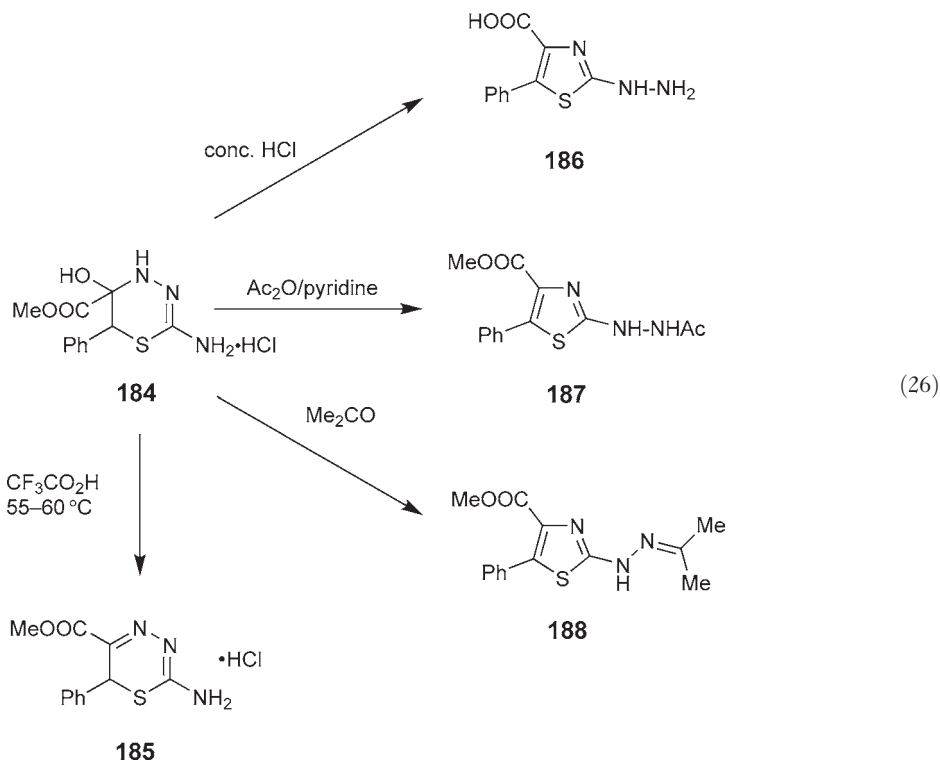


The reaction of 6-carbethoxy-2-hydrazino-4*H*,6*H*-1,3,4-thiadiazine **181** with aromatic aldehydes provides the corresponding Schiff's bases **182**. 2-Pyrazol-1-yl-1,3,4-thiadiazine **183** is produced by reaction of **181** with acetylacetone (Equation 25) <2000IJB603>.



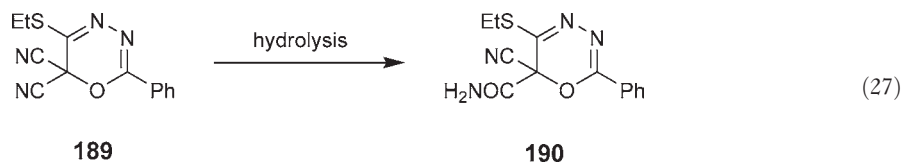
9.08.6.4 Hydroxy Groups

Dehydration of 2-amino-5-carboxymethyl-5-hydroxy-6-phenyl-2,3,4,5-6*H*-1,3,4-thiadiazine hydrochloride **184** to the 1,3,4-thiadiazine hydrochloride **185** takes place with TFA in acetonitrile at 55–60 °C <1996CHE1089>. Dehydration and subsequent ring transformation to 2-hydrazino-4-carboxy-5-phenyl-1,3-thiazole **186** occurs by heating **184** in concentrated hydrochloric acid <1996CHE1089>. Compound **184** also exhibits a tendency to undergo ring contraction to 2-hydrazino-1,3-thiazole derivatives **187** and **188** when heated with acetic anhydride in pyridine or acetone (Equation 26).



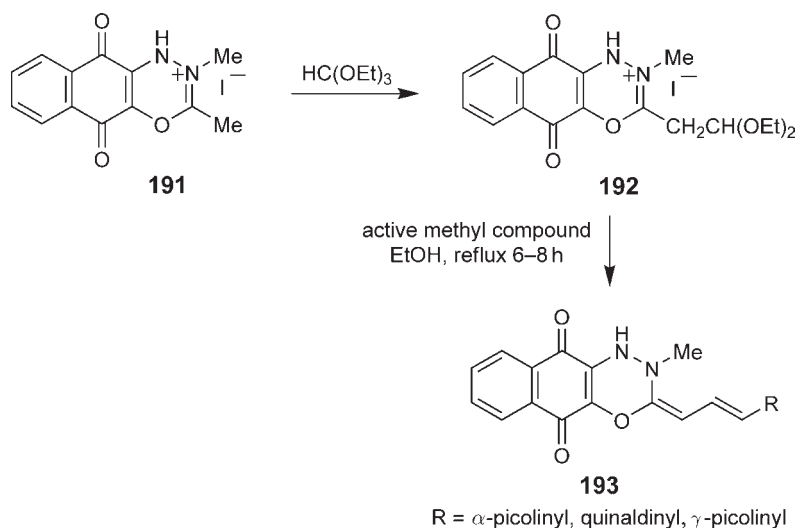
9.08.6.5 Cyano Groups

The hydrolysis of 2-ethylsulfanyl-2-phenyl-6*H*-1,3,4-oxadiazine-6,6-dicarbonitrile **189** affords the corresponding amide derivative **190** (Equation 27) <1997JCM144>.



9.08.6.6 Alkyl Groups

Naphthoquinone[2,3-*e*]oxadiazine derivative **191** reacts with triethyl orthoformate in the presence of acetic anhydride to give compound **192**. Further reaction with active methyl compounds (α -picoline, γ -picoline, quinaldine) affords the corresponding cyanine dyes **193** (Scheme 27) <1996IJH305>.

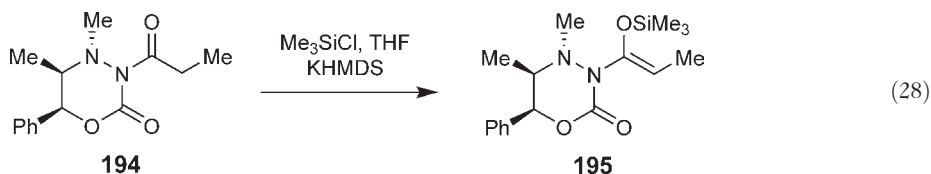


Scheme 27

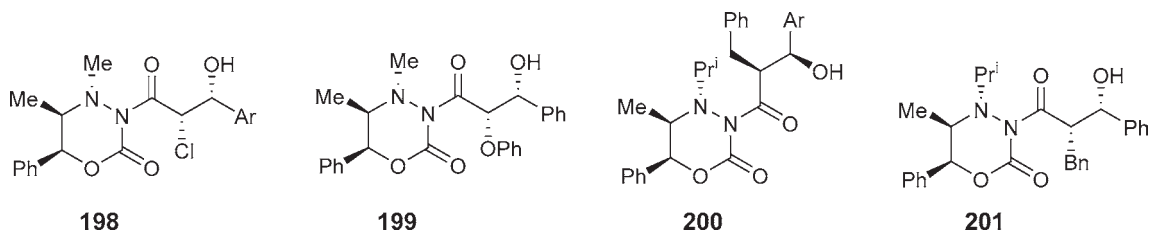
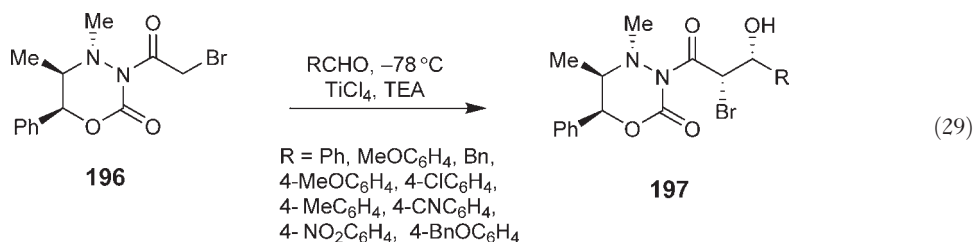
9.08.7 Reactivity of Substituents Attached to Ring Heteroatoms

9.08.7.1 Carbonyl and Acyl Groups

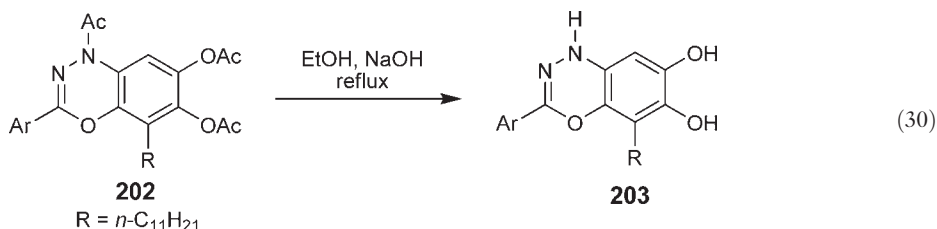
The treatment of 3-propionyl-1,3,4-oxadiazin-2-one **194** with chlorotrimethylsilane in the presence of the non-nucleophilic base, potassium hexamethyldisilazane (KHMDs), in THF yields enol silane **195** (Equation 28) <2002OL3739>. Compound **195** is used as a starting material for subsequent aldol reactions.



The asymmetric aldol reaction of 3-acyl-1,3,4-oxadiazin-2-ones **196** with aldehydes in the presence of titanium tetrachloride and triethylamine (TEA) at -78°C furnishes ephedrine-based 1,3,4-oxadiazin-2-ones **197** (Equation 29) <2006TA1831>. Further ephedrine-based compounds **198–201** have been prepared by this method <2002JHC1113, 2003TA517, 2003TA3233, 2004JOC714, 2004JOC727, 2004TA3449, 2005T10965>.



Deacylation of 3-acetyl-2-aryl-6,7-diacetoxy-8-undecyl-4*H*-1,3,4-benzoxadiazines **202** to give **203** occurs upon heating in ethanolic sodium hydroxide (Equation 30) <1997IJB68>.

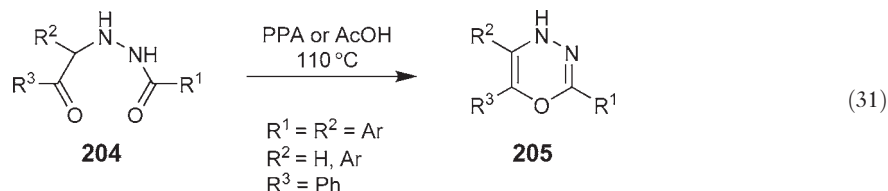


9.08.8 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

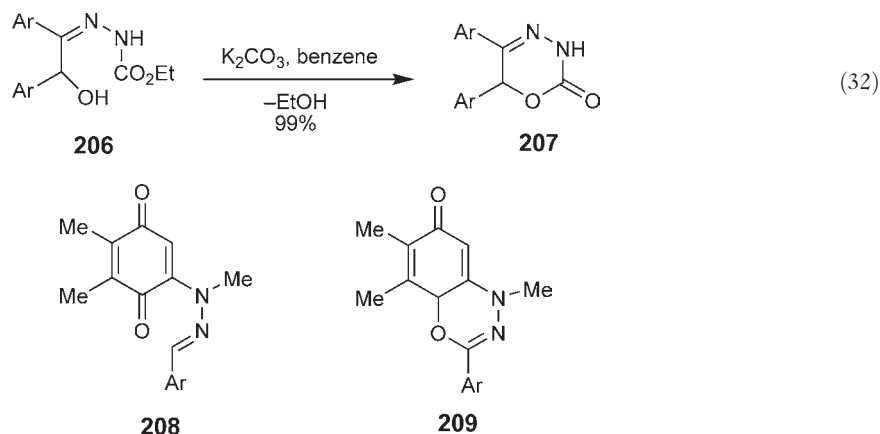
9.08.8.1 By Formation of One Bond

9.08.8.1.1 Between carbon and oxygen (fragment)

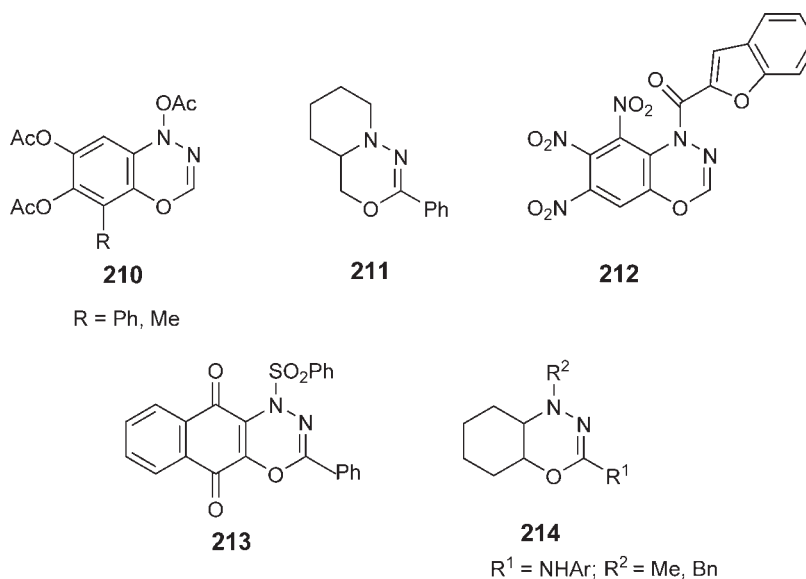
2,6-Diaryl-4*H*-1,3,4-oxadiazines **205** can be prepared by dehydration of 1-aryloxy-2-phenacylhydrazine derivatives **204** with polyphosphoric acid or acetic acid at 110 °C (Equation 31) <1998HOU(E9c)427>.



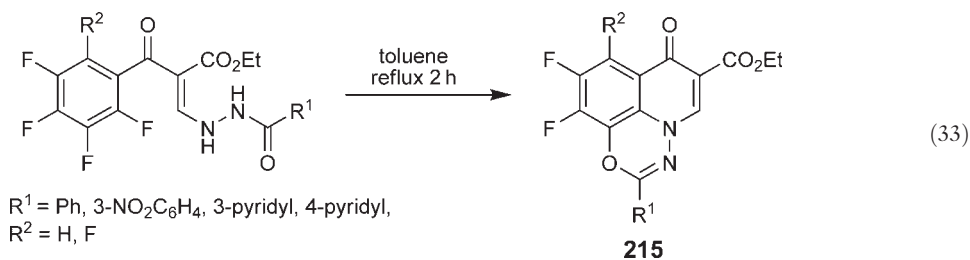
Treatment of ethoxycarbonylhydrazones of α -hydroxyketones **206** with base readily affords 3*H*-1,3,4-oxadiazin-2(6*H*)-ones **207** <1998HOU(E9c)427> (Equation 32). Bicyclic 1,3,4-oxadiazinones **209** are obtained by brief heating of 5-(*N'*-arylidene-*N*-methylhydrazino)-2,3-dimethyl-1,4-benzoquinones **208** in methanol <2000T5137>.



4*H*-1,3,4-Benzoxadiazine **210** is obtained from 2-acyl-hydrazino-1,4-quinones by heating in acetic anhydride <1997IJB68>. 2-Phenylperhydropyrido[1,2-*d*][1,3,4]oxadiazine **211** is obtained from 1-benzoylamino-2-chloromethylpiperidine <1997H(45)95>. *N*-Picryl-*N,N'*-di-(2-furoyl)hydrazine cyclizes in the presence of triethylamine to yield the 1,3,4-oxadiazine derivative **212** <1999RJO933>. Cyclization of 2-chloro-3-(*N*-benzoylhydrazino)-1,4-naphthoquinone with benzenesulfonyl chloride in DMF/triethylamine affords the 1-benzenesulfonyl-3-phenylnaphtho[2,3-*e*][1,3,4]-oxadiazine-5,10-dione **213** <2003PS627>. 1-(2-Hydroxycyclohexyl)-4-arylthiosemicarbazides cyclize by treatment with methyl iodide and methanolic potassium hydroxide to the corresponding hexahydro-4*H*-1,3,4-benzoxadiazines **214** <1999ACS103>. Similarly, perhydropyrrolo[1,2-*d*][1,3,4]oxadiazines **169** and perhydropyrido[1,2-*d*][1,3,4]oxadiazines **171** are obtained from pyrrolidino or piperidinothiourea derivatives <1997H(45)927> (see Section 9.08.6.2).

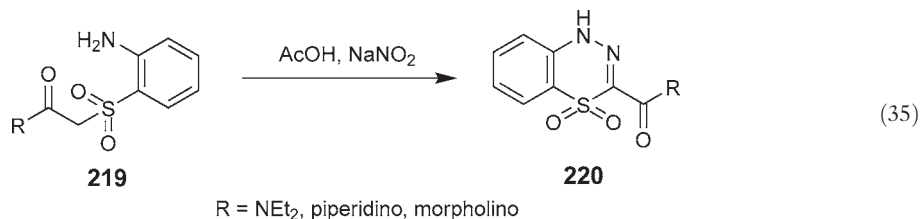
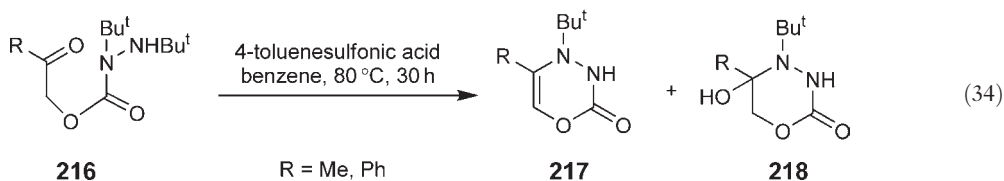


3-(Acylhydrazino)-2-tetra(penta)fluorobenzoylacrylates are converted readily to 1,3,4-oxadiazino[6,5,4-*i,f*]quinolines **215** by heating in toluene (Equation 33) <2001CHE1278, 1998MC131>.



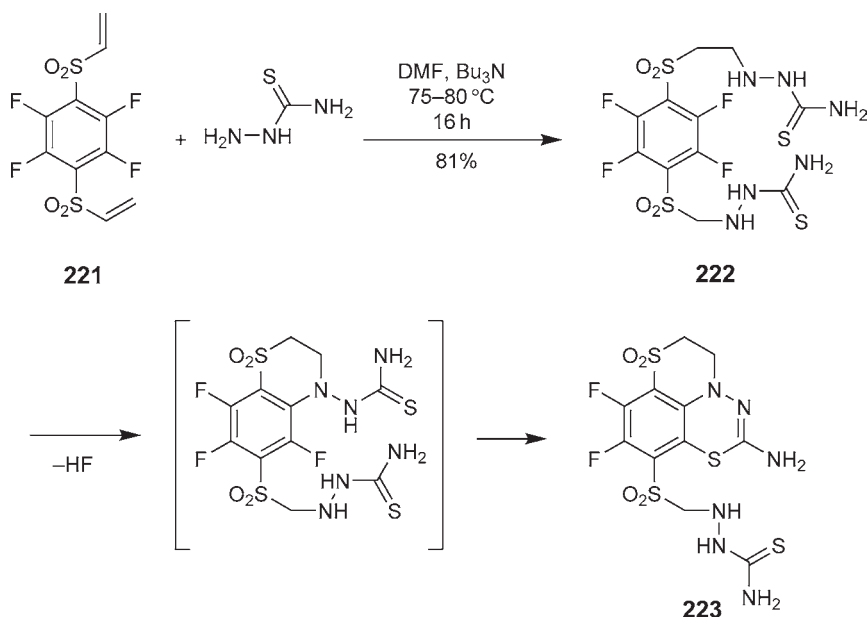
9.08.8.1.2 Between carbon and nitrogen (fragment)

When acylmethyl carbazates **216** are treated with a catalytic amount of 4-toluenesulfonic acid in benzene at 80 °C, 1,3,4-oxadiazin-2-one derivatives **217** and **218** are obtained (Equation 34) <2000H(52)541>. The reaction of 2-[(2-aminophenyl)sulfonyl]-*N,N*-dialkylacetamides **219** with acetic acid and sodium nitrite affords 4,2,1-benzothiadiazin-3-carboxylate 4,4-dioxides **220** via diazonium salt intermediates (Equation 35) <1996JHC347>.



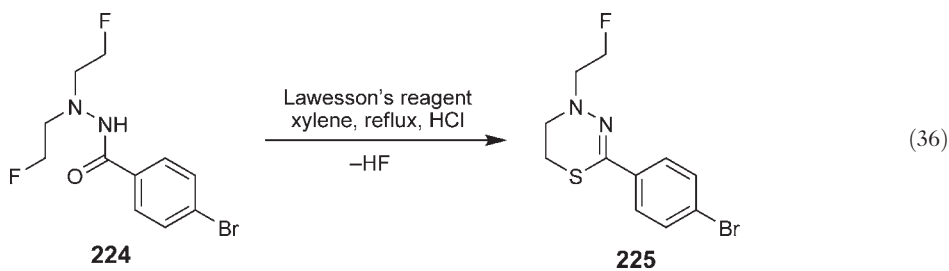
9.08.8.1.3 Between carbon and sulfur (fragment)

Heating vinylsulfonylfluorobenzene **221** with thiosemicarbazide in DMF at 75–80 °C in the presence of tributylamine affords 5,6-dihydro[*h,i*]-1,4-thiazino[4,3-*d*]1,3,4thiadiazine-7,7-dioxide **223** (Scheme 28) <2004MI269>. The formation of compound **223** takes place by initial addition of the 1-NH₂ group of the thiosemicarbazide to both activated double bonds of vinylsulfonylfluorobenzene **221** to give the adduct **222**. Subsequent intramolecular substitution of fluorine atoms occurs in the *o*-position by the NH group, and in the *m*-position by the second nucleophilic center in the thiosemicarbazide, the sulfur atom. Increasing the reaction temperature to 75–80 °C under conditions of medium basicity facilitates the nucleophilic substitution of fluorine atoms in the benzene ring, affording **223**.



Scheme 28

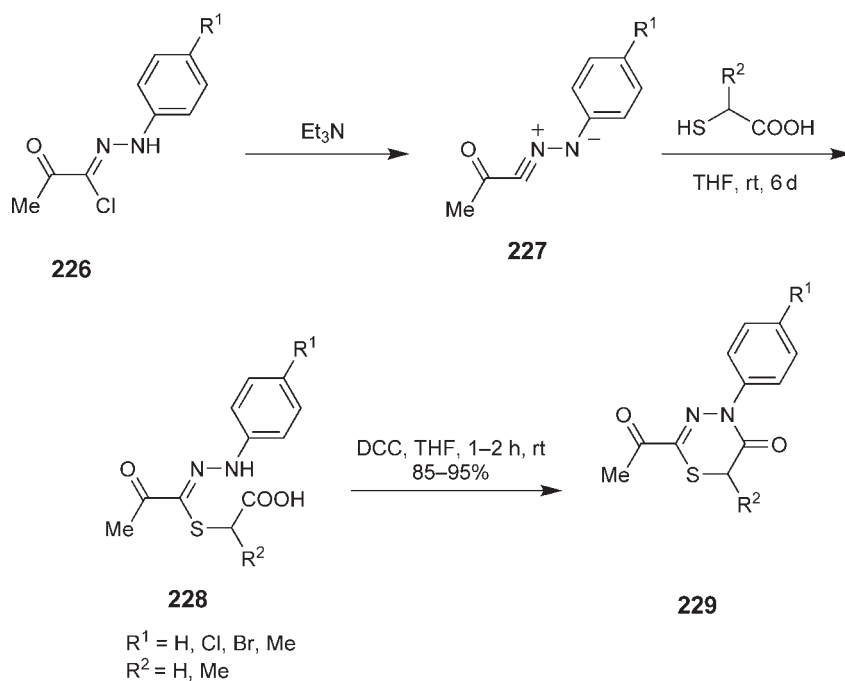
2,2-Bis(2-fluoroethyl)-4-bromobenzhydrazide **224** reacts with Lawesson's reagent in *para*-xylene and, following treatment of the filtrate with gaseous hydrogen chloride, gives 2-aryl-4-fluoroethyl-5,6-dihydro-4*H*-1,3,4-thiadiazine **225** (Equation 36) <1998WO9838181>.



9.08.8.2 By Formation of Two Bonds

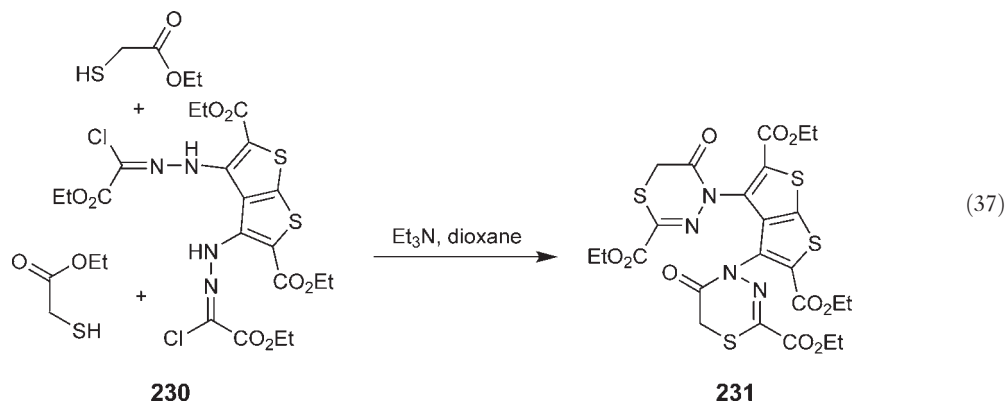
9.08.8.2.1 [3+3] Fragments

The *N*-aryl-substituted hydrazonoyl chlorides **226** react with 2-sulfanylacetic acid or 2-sulfanylpropanoic acid. In the presence of triethylamine, nitrilimines **227** are generated first and these intermediates react with the 2-sulfanylalkanoic acids to form the corresponding adducts **228** with yields of 70–80%. The latter cyclize in THF by reaction with dicyclohexylcarbodiimide (DCC) at room temperature to furnish 1,3,4-thiadiazine-5-ones **229** (Scheme 29) <2002M1011>.



Scheme 29

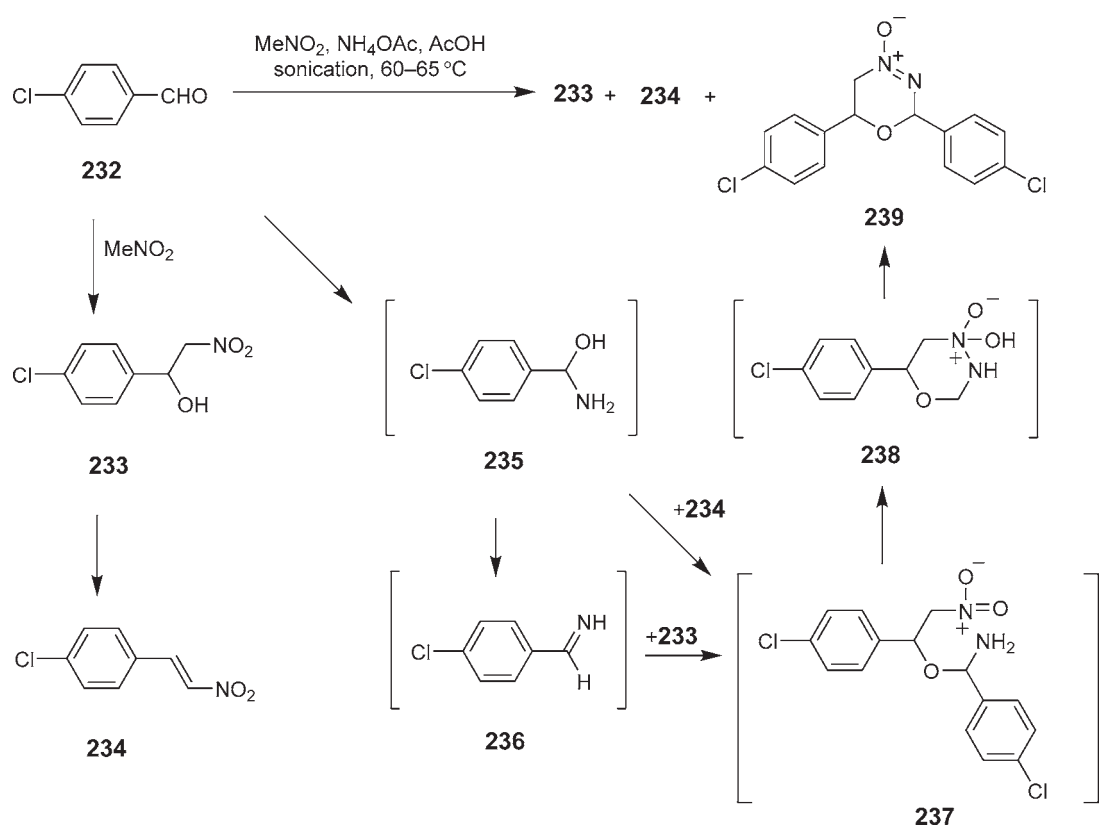
Similarly, the hydrazonoyl chloride **230** reacts with ethyl sulfanylacetate via a reactive nitrileimine to form the 1,3,4-thiadiazine derivative **231** (Equation 37) <2003PS1689>.



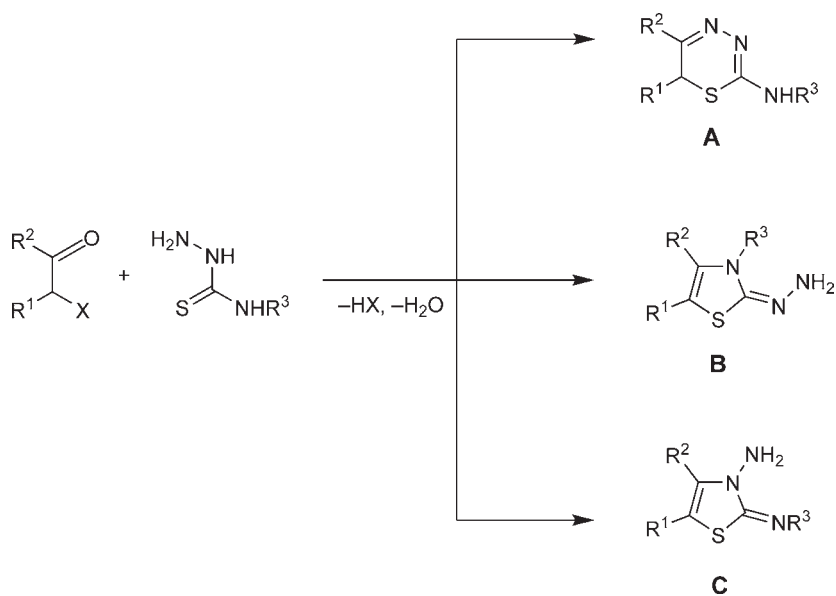
4-Chlorobenzaldehyde **232** reacts with ammonium acetate and acetic acid in nitromethane under ultrasonic irradiation to give the 1,3,4-oxadiazine derivative **239** <2000JOC4750>. From chromatographic investigations the formation of the intermediates **233** and **234** was indicated. A reaction mechanism is proposed in Scheme 30.

9.08.8.2.2 [4+2] Fragments

1,3,4-Thiadiazines are prepared best by condensation of thiohydrazides with α -halocarbonyl compounds. As thiohydrazide components, most substituted thiosemicarbazides, aryl and alkyl thiocarbonylhydrazides, or *O*-alkyl dithiocarbazates can be used. The cyclocondensation with thiosemicarbazides and α -halocarbonyl compounds can provide three isomeric compounds, 2-amino-1,3,4-thiadiazines **A**, 2-hydrazino-1,3-thiazoles or 2-hydrazono-2,3-dihydro-1,3-thiazoles **B**, and 2-alkyl(aryl)imino-3-amino-2,3-dihydro-1,3-thiazoles **C** (Scheme 31). The course of the cyclization of thiosemicarbazides with α -halocarbonyl compounds depends on the acidity of the reaction medium and the substituents R^1 , R^2 , and R^3 . The reaction of aromatic α -halo ketones with thiosemicarbazides leads under neutral

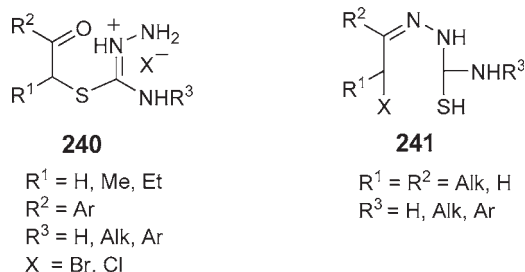


Scheme 30

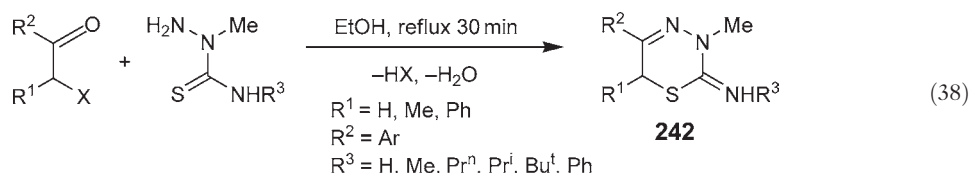


Scheme 31

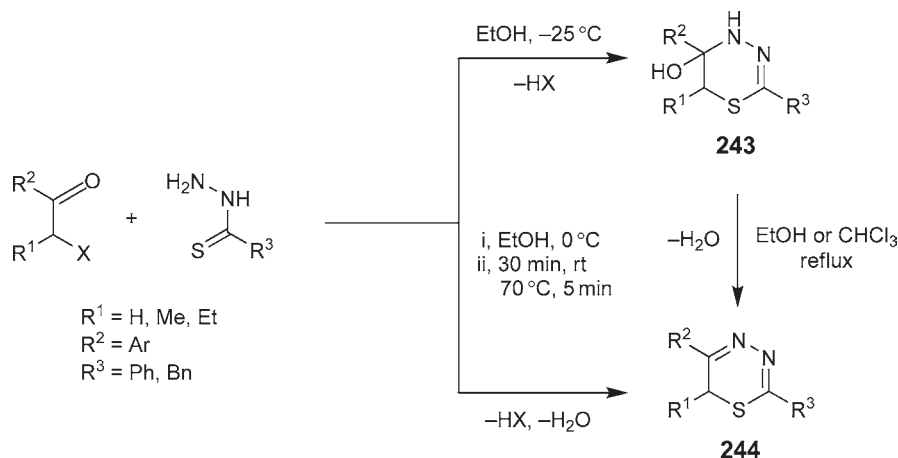
conditions (ethanol) at 0°C to isolable *S*-ketonyl-isothiosemicarbazide hydrohalogenides **240**. In a weakly acidic environment, α -halo keto-thiosemicarbazones **241** are formed. The compounds **240** and **241** can be converted to 1,3,4-thiadiazines by heating in ethanol <1998HOU(E9c)483>.



2-Alkyl(aryl)imino-3-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **242** are obtained exclusively from α -halo ketones and 2-methyl-4-alkyl(aryl)thiosemicarbazides (Equation 38) <1997PHA831>.

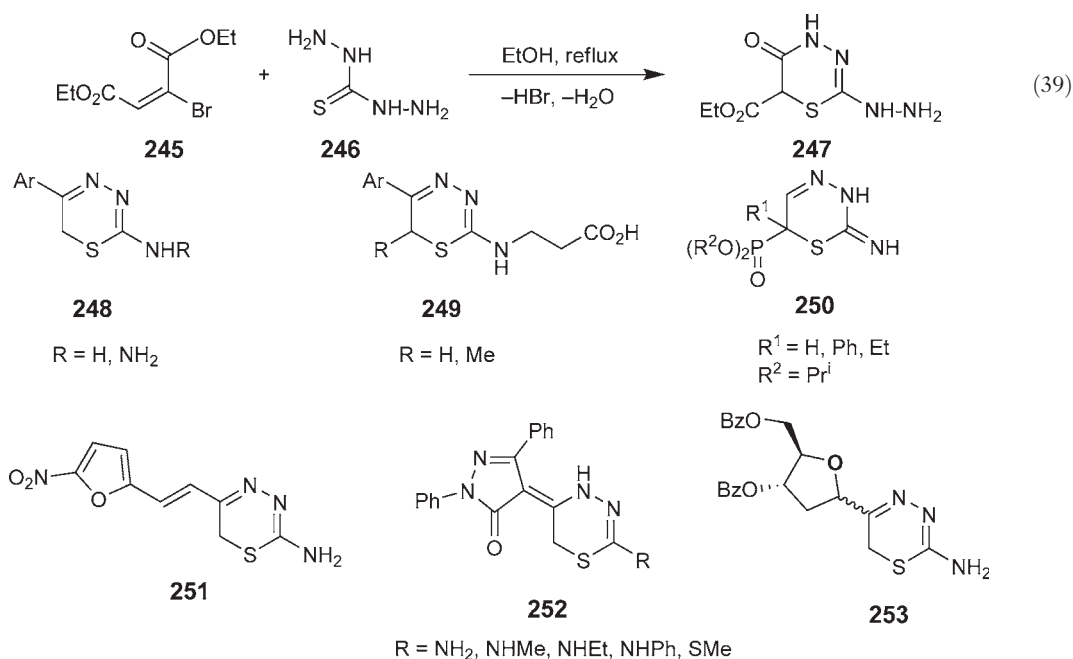


2-Phenyl- and 5-aryl-benzyl-6*H*-1,3,4-thiadiazines are synthesized by cyclocondensation of α -halocarbonyl compounds with thiobenzhydrazide or phenylthioacetic acid hydrazide <1998HOU(E9c)483>. Under appropriate conditions, it is possible to isolate the initially formed 4,5-dihydro-6*H*-1,3,4-thiadiazin-5-ol intermediates **243**. For this purpose, the thiohydrazide is added to an equimolar amount of sodium ethoxide solution, followed by, at -25°C , an ethanolic solution of the respective α -halocarbonyl compound. The corresponding intermediate **243** separates as a colorless precipitate. The compounds **243** undergo dehydration by heating in ethanol or chloroform. When the thiohydrazides are allowed to react with the α -halocarbonyl compounds in sodium ethoxide solution under initial cooling in ice/salt, followed by warming, the 1,3,4-thiadiazines **244** are formed directly (Scheme 32).

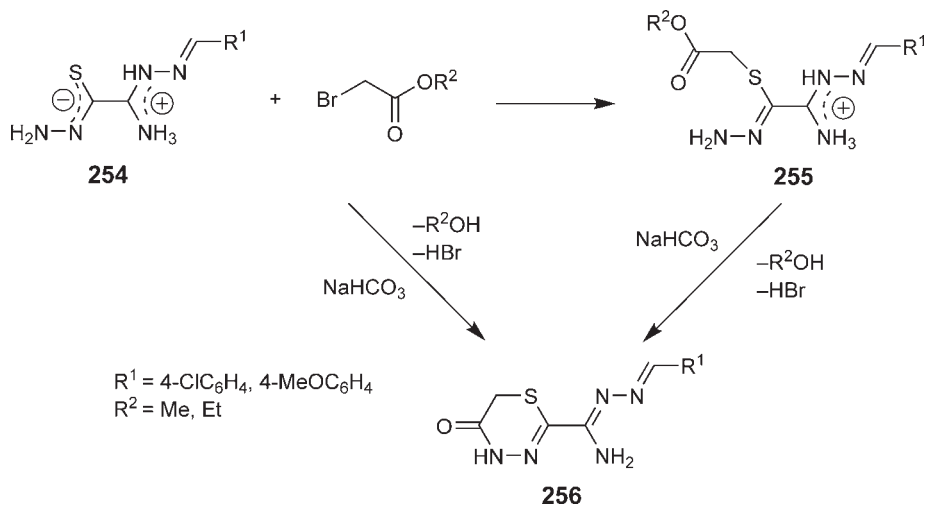


Scheme 32

As an α -halocarbonyl compound, diethyl bromomaleate **245** can also be used. The cyclization of this compound with thiocarbonylhydrazide **246** affords a 5-oxo-1,3,4-thiadiazine derivative **247** <2000IJC(B)603> (Equation 39). Thiosemicarbazide or thiocarbonylhydrazide and α -halo ketones cyclize readily by microwave irradiation under basic conditions to give 2-amino- or 2-hydrazino-6*H*-1,3,4-thiadiazines **248** <2002JHC1045>. 3-[5-(Aryl-6*H*-1,3,4-thiadiazin-2-yl)amino]propanoic acid **249** are obtained by cyclization of the corresponding 4-substituted thiosemicarbazides with α -halo ketones <2002TL3309>. The cyclocondensation of phosphoryl- α -chloroacetaldehydes with thiosemicarbazide yields 6-diisopropoxyphosphoryl-2-imino-2,3-dihydro-6*H*-1,3,4-thiadiazines **250** <2003CHE671>. Heterocyclic substituted thiosemicarbazides or methyl dithiocarbazate afford the 1,3,4-thiadiazines **251–253** by reaction with α -halo ketones <1998H557, 2004H2079, 2004T841>.

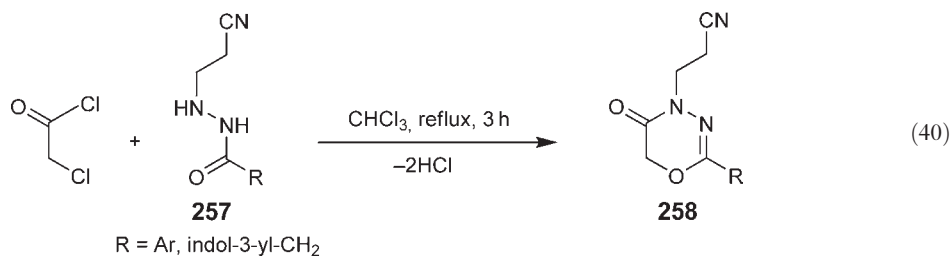


Zwitterionic monobenzyldene thiooxamic acid derivatives **254** react with alkyl bromoacetates in the absence of a base to give the intermediates **255**. The cyclization under basic conditions furnishes 5-oxo-4,6*H*-1,3,4-thiadiazines **256**. These compounds are also obtained by heating of **254** with alkyl bromoacetates in the presence of NaHCO_3 (Scheme 33) <1998SUL163>.

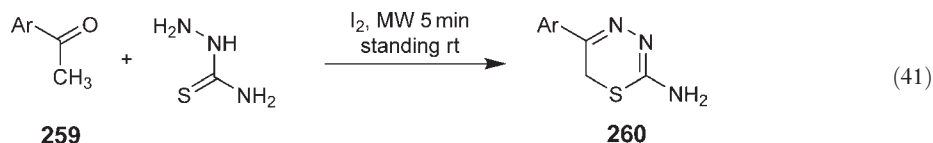


Scheme 33

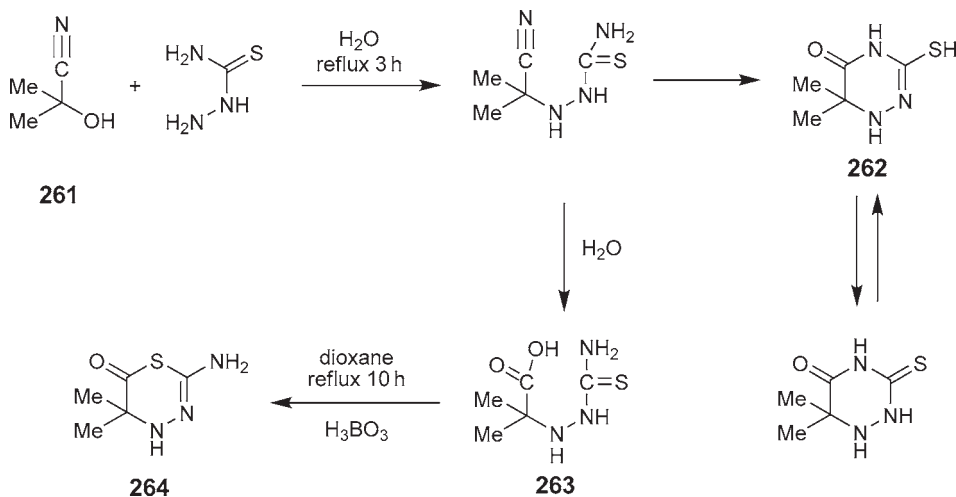
2-Substituted 5,6-dihydro-5-oxo-4*H*-1,3,4-oxadiazines **258** are obtained by cyclocondensation of 2-chloroacetyl chloride with 2-(2-cyanoethyl)hydrazides **257** under basic conditions (Equation 40) <2002HCA559>.



An interesting synthetic method is the one-pot reaction of arylketones **259** with iodine and thiosemicarbazides under microwave irradiation. Initially, the α -halo ketones are formed by this reaction, followed by cyclization with the thiosemicarbazide to afford the 1,3,4-thiadiazine derivatives **260** (Equation 41) <2004IJH283, 2005IJB2158>.

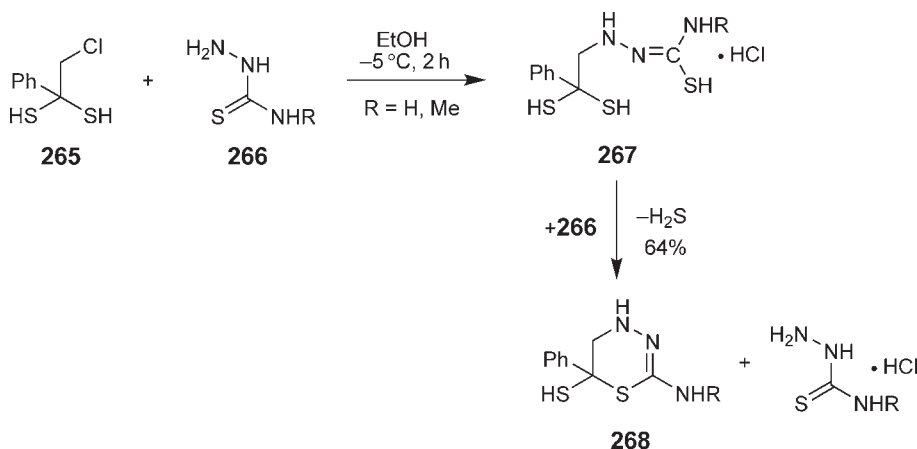


When acetone cyanohydrin **261** is heated with thiosemicarbazide in water, 3-sulfanyl-6,6-dimethyl-1,2,3-triazin-5-one **262** and 2-methyl-2-thiosemicarbazidopropanoic acid **263** are formed <2002CHE992>. Cyclization of **263** in dioxane in the presence of H_3BO_3 yields 2-amino-5,5-dimethyl-1,3,4-thiadiazin-6-one **264** (Scheme 34).



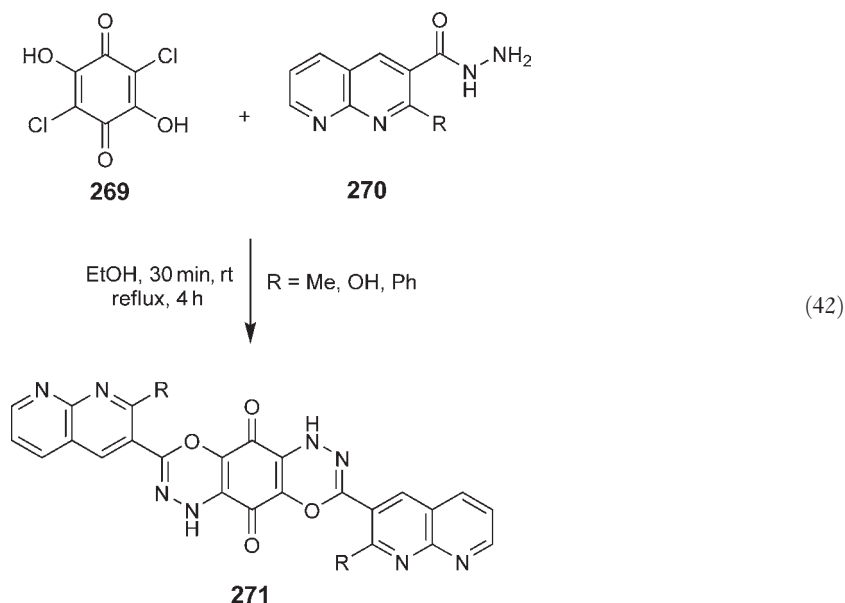
Scheme 34

Reaction of 2-chloro-1-phenylethane-1,1-dithiol **265** with thiosemicarbazides **266** in methanol at -5°C affords 2-amino- or 2-methylamino-6-sulfanyl-6-phenyl-5,6-dihydro-1,3,4-thiadiazines **268** via an isolated intermediate **267** (Scheme 35) <2005CHE946>.

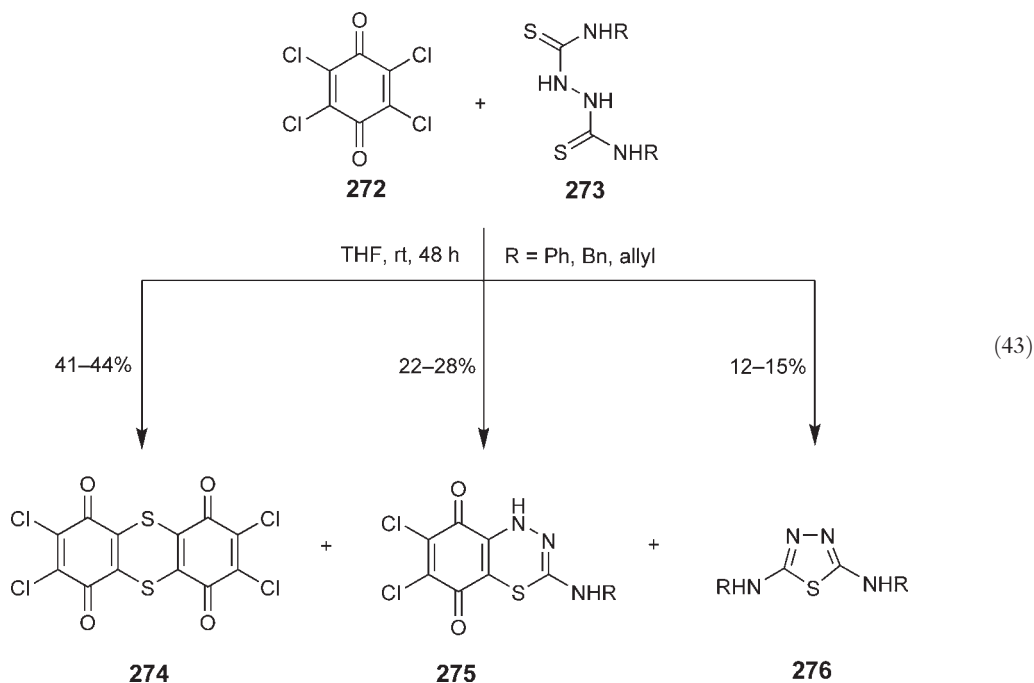


Scheme 35

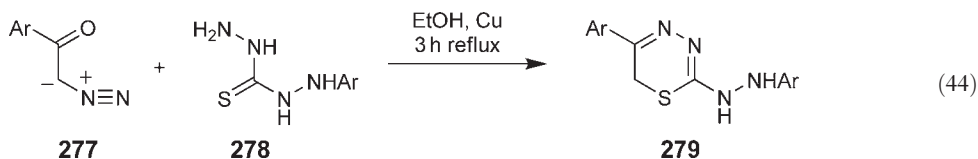
The treatment of 2,5-dichloro-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione **269** with 2-substituted-1,8-naphthyridine-3-carboxylic acid hydrazides **270** in ethanol under reflux resulted in the formation of 3,8-di(2-substituted-1,8-naphthyridin-3-yl)benzo(1,2-*e*:4,5-*e'*)bis[1,3,4]oxadiazine-5,10[1*H*,6*H*]diones **271** <2000IJH311> (Equation 42).



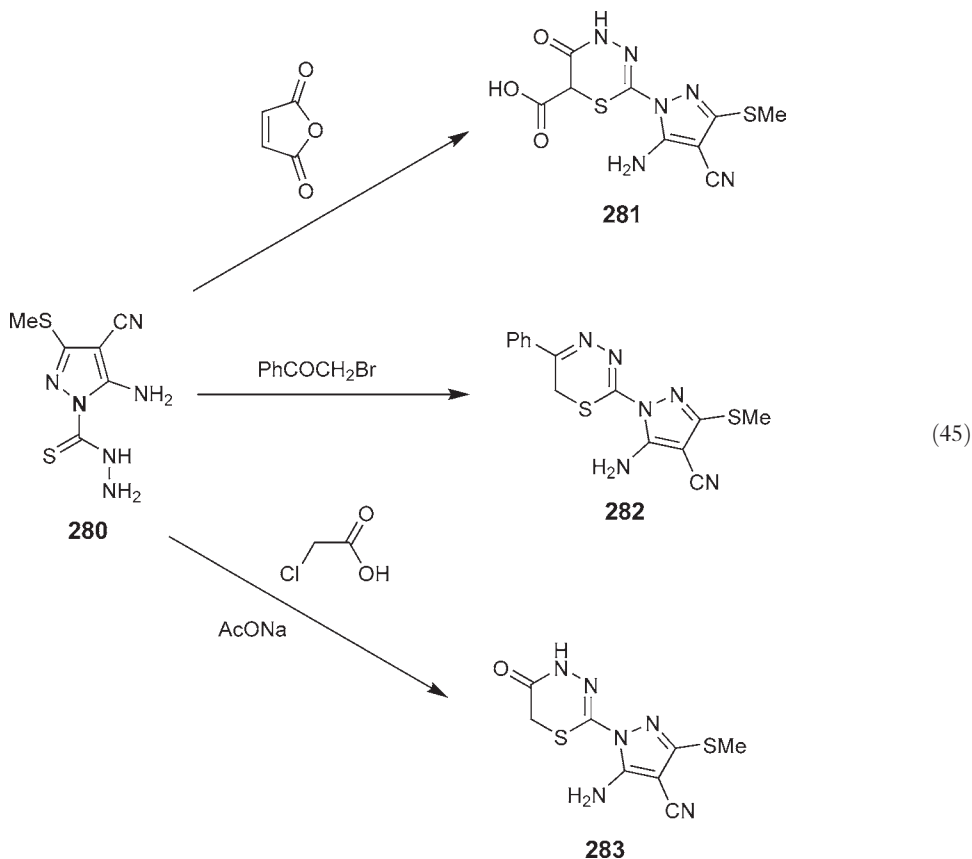
Similarly, the cyclization of 2,3,5,6-tetrachloro-1,4-quinone **272** with thiourea derivatives **273** in THF at room temperature leads to 2,3,7,8-tetrachlorothianthrene-1,4,6,9-tetrone **274** as the major products (41–44%) and 2,5-disubstituted 3-amino-6,7-dichloro-2,3-dihydro-1*H*-4,1,2-benzothiadiazine-5,8-diones **275** (22–28%), together with 2,5-diamino-1,3,4-thiadiazoles **276** (12–15%) (Equation 43) <2006JHC471>.



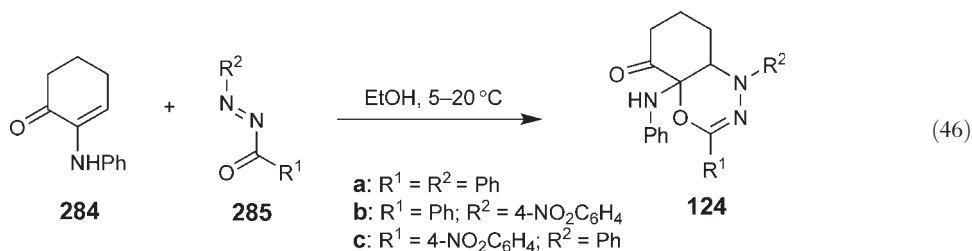
2-Arylhydrazino-5-aryl-6*H*-1,3,4-thiadiazines **279** are obtained by the cyclocondensation of aryl diazoketones **277** with 1-arylthiocarbohydrazides **278** in boiling ethanol in the presence of copper <1998HOU(E9c)483> (Equation 44).



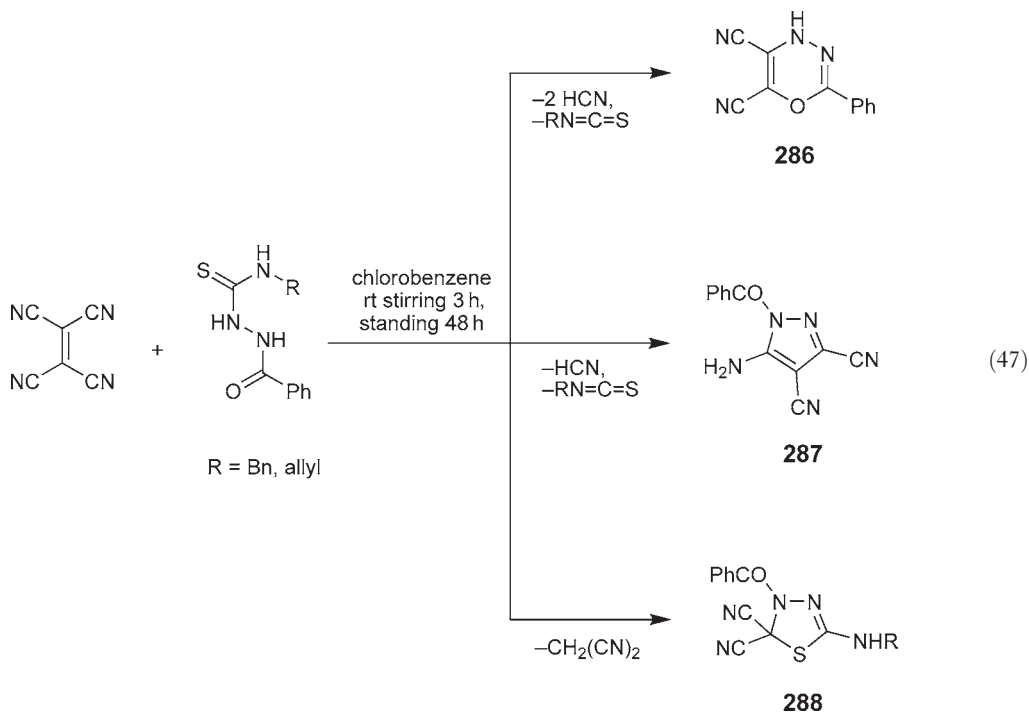
Treatment of the pyrazolyl-1-thiocarbonylhydrazide derivative **280** with maleic anhydride furnishes **281** <2000JCM544>, whereas the reaction of **280** with phenacyl bromide yields the 1,3,4-thiadiazine **282**. Cyclization of **280** with chloroacetic acid affords the 4,5-dihydro-1,3,4-thiadiazin-5-one **283** (Equation 45). However, when chloroacetyl chloride is used instead of chloroacetic acid, with the aim of obtaining the same product **283**, a thiadiazolylpyrazole derivative was formed <2000JCM544>. The starting material **280** is produced by the reaction of a ketene dithioacetal with thiocarbohydrazide or hydrazinolysis of pyrazolyldithiocarbonate <2000JCM544>.



The cyclization of aromatic α -ketoenamines **284** with electrophilic diazenes **285** at 5–20 °C in ethanol furnishes 1,3,4-oxadiazine derivatives **124** (Equation 46) <1996G297, 1997G387>. Compounds **124b** and **124c** exhibit greater stability than **124a**, which undergoes ring opening after 30 min heating in ethanol to give keto enamines **125a** and **126a** (see Section 9.08.5.1). In contrast, ring opening of **124b,c** to form **125b,c** and **126b,c** takes place by refluxing for 5–6 h in ethanol.

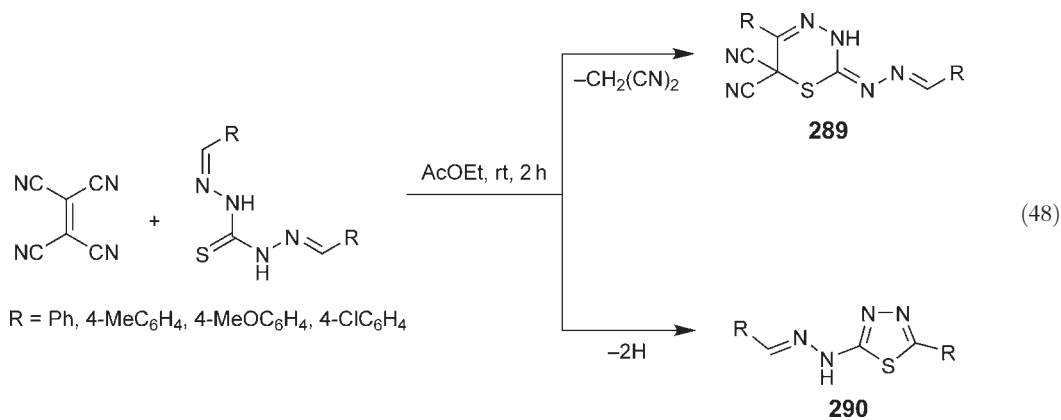


Ethenetetra carbonitrile reacts with 1,4-disubstituted thiosemicarbazides in chlorobenzene to give 2-phenyl-1,3,4-oxadiazine **286**, pyrazole **287**, and 1,3,4-thiadiazoles **288** (Equation 47) <2005HAC12>.

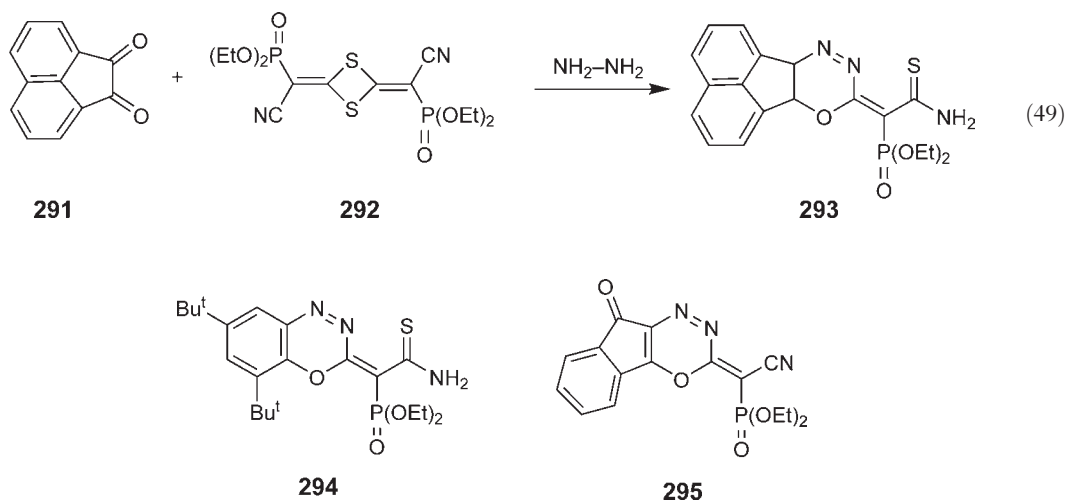


9.08.8.2.3 [5+1] Fragments

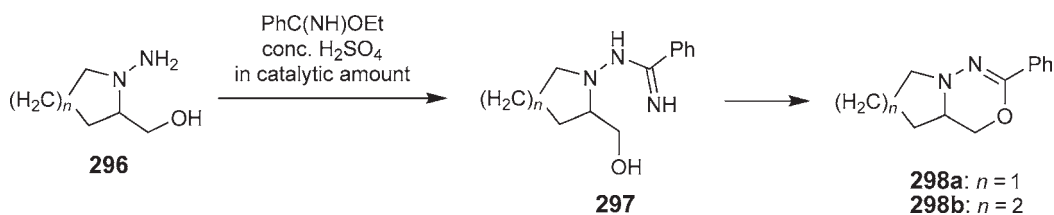
The cyclization of ethenetetracarbonitrile with diarylidenethiocarbonylhydrazides affords 1,3,4-thiadiazine derivatives **289**. 1,3,4-Thiadiazoles **290** are obtained as by-products through oxidative cyclization of the diarylidenethiocarbonylhydrazides (Equation 48) <1997M61>.



The condensation of acenaphthenequinone **291** with hydrazine in ethanol furnishes a monohydrazone derivative which, by heating with a half equivalent of 1,3-dithietane **292**, provides the fused 1,3,4-oxadiazine **293** (Equation 49) <2002PS1885>. The treatment of 3,5-di-*tert*-butylbenzoquinonehydrazone or 1,3-indandione-2-hydrazone with 1,3-dithietane **292** affords the 1,3,4-oxadiazine derivatives **294** and **295**.

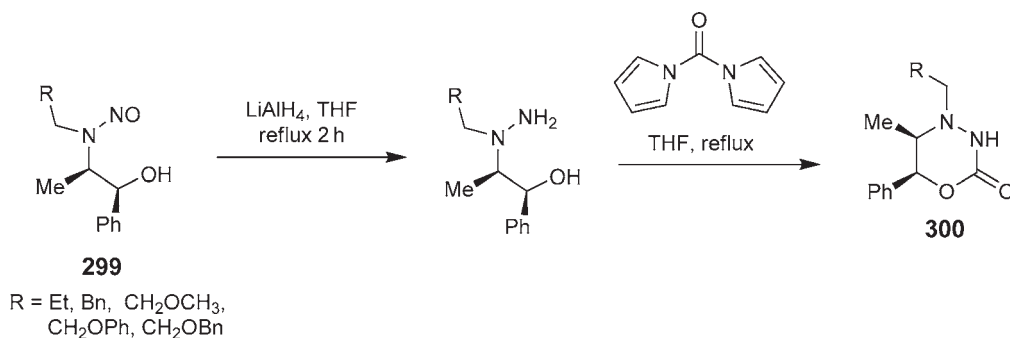


Hydrazino alcohols **296** react with ethyl benzimidate to form pyrrolo[1,2-*d*][1,3,4]oxadiazine **298a** or pyrido[1,2-*d*]-[1,3,4]oxadiazine **298b** via the intermediates **297** (Scheme 36) <1997H(45)95>.

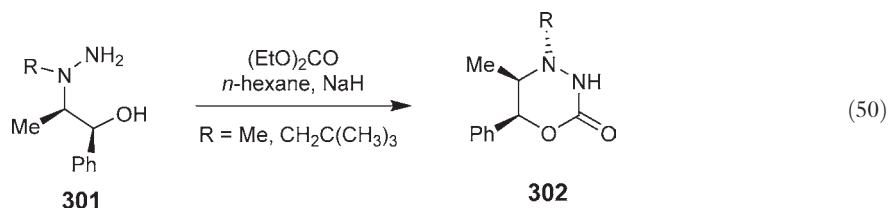


Scheme 36

Oxadiazinan-2-ones **300** are obtained from norephedrine in good yield via N-alkylation, nitrosation, reduction, and cyclization <2002JHC823, 1996JME3938>. The nitroso compounds **299** are reduced with lithium aluminium hydride and the intermediate hydrazine alcohols cyclized with carbonyldiimidazole to afford compounds **300** (Scheme 37). Similarly, 1,3,4-oxadiazinan-2-one derivatives **302** are obtained by reaction of hydrazino alcohols **301** with diethylcarbonate and sodium hydride (Equation 50) <2004SC835>.



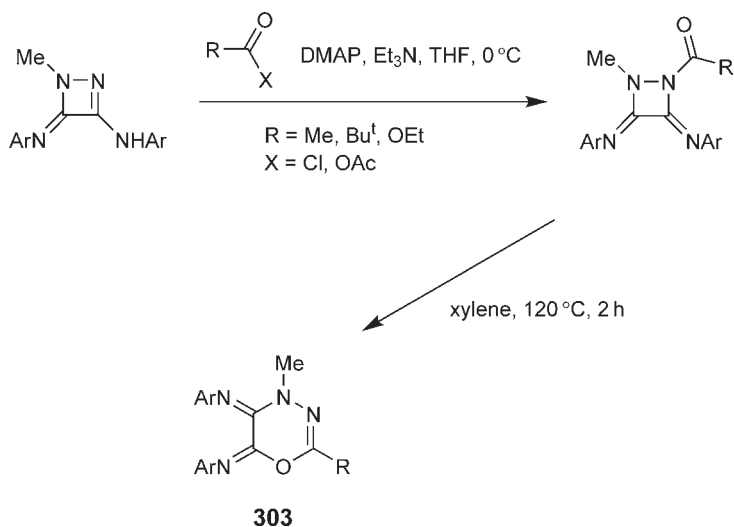
Scheme 37



9.08.9 Ring Syntheses by Transformations of Another Ring

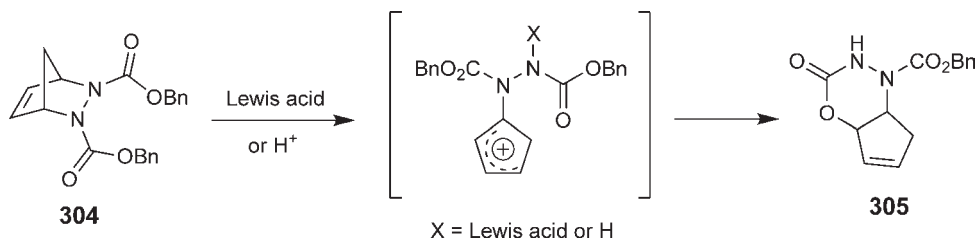
9.08.9.1 1,3,4-Oxadiazines

Treatment of Δ^2 -1,2-diazetines with acid chlorides or anhydrides in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) affords acylated 1,2-diazetidines which undergo a thermally induced ring transformation to 1,4,3-oxadiazines **303** (Scheme 38) <2006S514>.



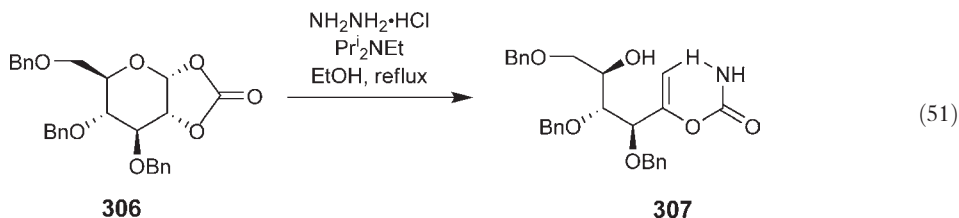
Scheme 38

The acid-catalyzed ring opening of 2,3-dibenzoyloxycarbonyl-2,3-diazabicyclo[2.2.1]heptene **304** gives the bicyclic 1,3,4-oxadiazine derivative **305** via an intermediate cation (Scheme 39) <2003OL4771, 2005JOC3316>.

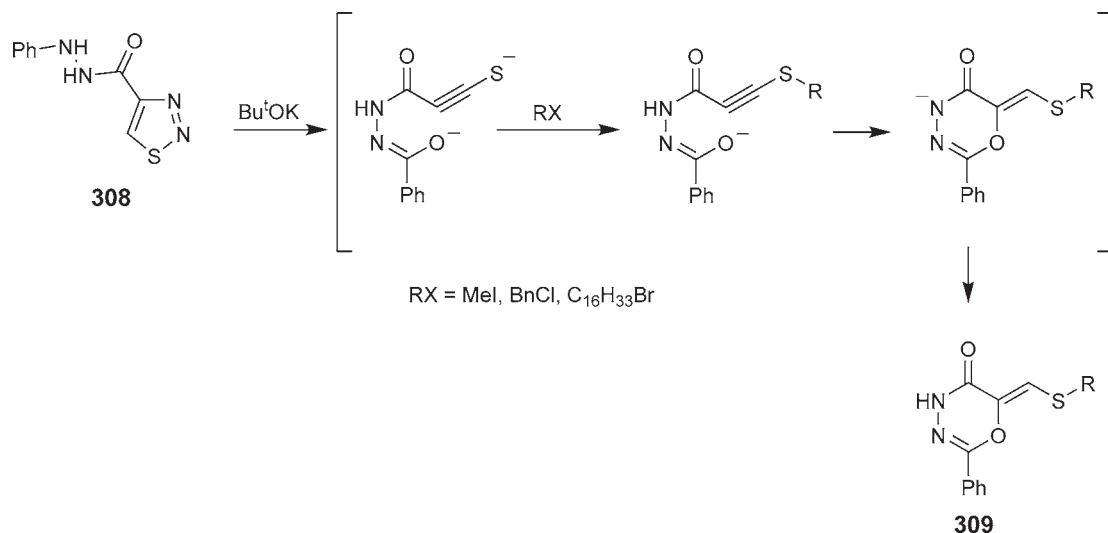


Scheme 39

The reaction of the cyclic carbonate **306** with hydrazine hydrochloride and Pr_2NEt in ethanol at reflux produced the cyclic hydrazone **307** via partial, regioselective hydrazinolysis of **306** followed by intramolecular condensation of the resultant hydrazide with the unmasked hemiacetal group (Equation 51) <2005SL2607>.

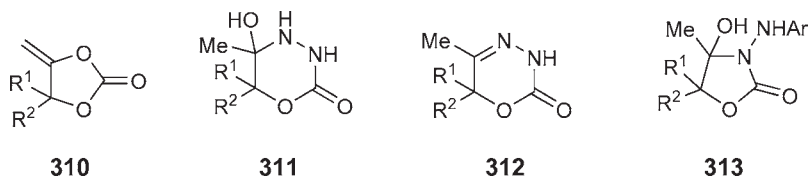


The ring cleavage of hydrazide **308** in the presence of 2 equiv of Bu^tOK, followed by alkylation, results in 1,3,4-oxadiazin-5-one derivatives **309** (Scheme 40) <2002TL1015>.



Scheme 40

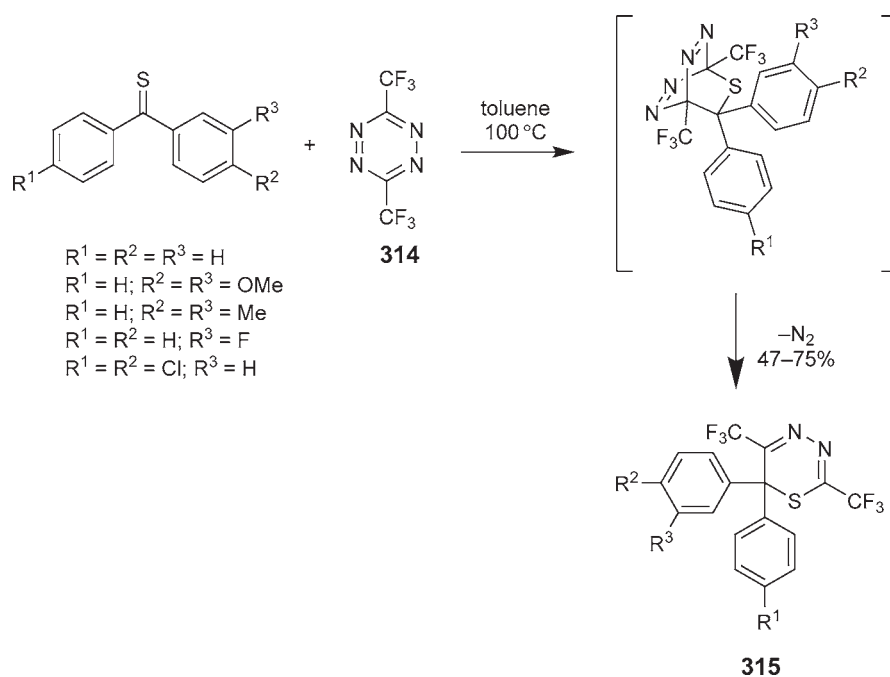
The treatment of 2-methylene-1,3-dioxolan-2-ones **310** ($R^1 = R^2 = \text{Me}$; $R^1 + R^2 = (\text{CH}_2)_5$; $R^1 = \text{Me}$, $R^2 = \text{Me}_2\text{C}=\text{CH}-\text{CH}_2-\text{CH}_2$) with hydrazine hydrate leads to carbamate intermediates, which undergo cyclization to give 5-hydroxy-5,6-dihydro-4*H*-1,3,4-oxadiazin-2(3*H*)-ones **311**. The thermal dehydration of **311** gives 1,3,4-oxadiazin-2(3*H*)-ones **312** <2003CHE1057>. In contrast to the case with hydrazine hydrate, the reaction of aromatic hydrazines with 1,3-dioxolan-2-ones **310** provides 3-arylamino-4-hydroxyoxazolidin-2(3*H*)-ones **313**.



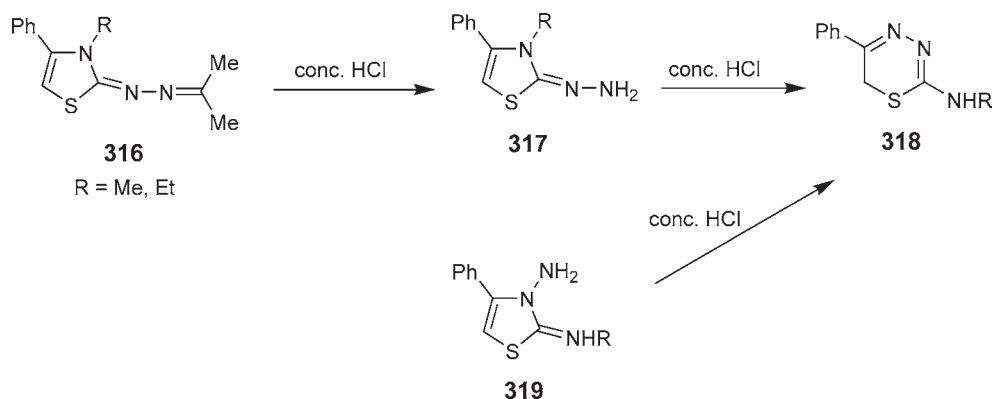
9.08.9.2 1,3,4-Thiadiazines

3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine **314** reacts with substituted thiobenzophenones by [4+2] cycloaddition via a Diels–Alder adduct which is not isolable. Cycloreversion, with elimination of nitrogen, then gives 6*H*-1,3,4-thiadiazines **315** in yields of 47–75% (Scheme 41) <1998EJO2861>. Similarly, the treatment of **314** with alkylthioformates yields 2,5,6-substituted-6*H*-1,3,4-thiadiazines <1984AGE890>.

Hydrolysis of 3-alkyl-2-(isopropylidenehydrazono)-4-phenyl-2,3-dihydro-1,3-thiazoles **316** with concentrated hydrochloric acid proceeds via the intermediate 3-alkyl-2-hydrazono-4-phenyl-2,3-dihydro-1,3-thiazoles **317** with ring expansion to the *N*-alkyl-5-phenyl-6*H*-1,3,4-thiadiazine-2-amines **318** (Scheme 42) <1998HOU(E9c)483, 2006UP1>.

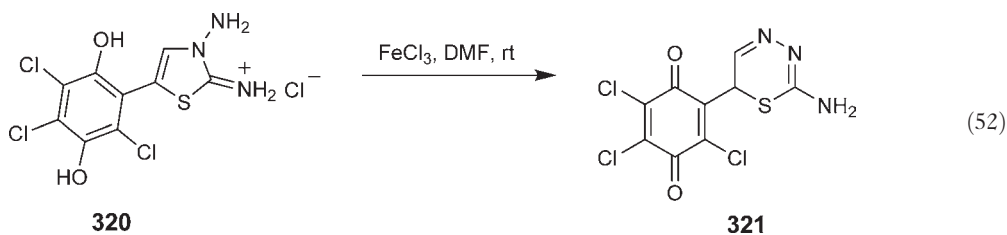


Scheme 41

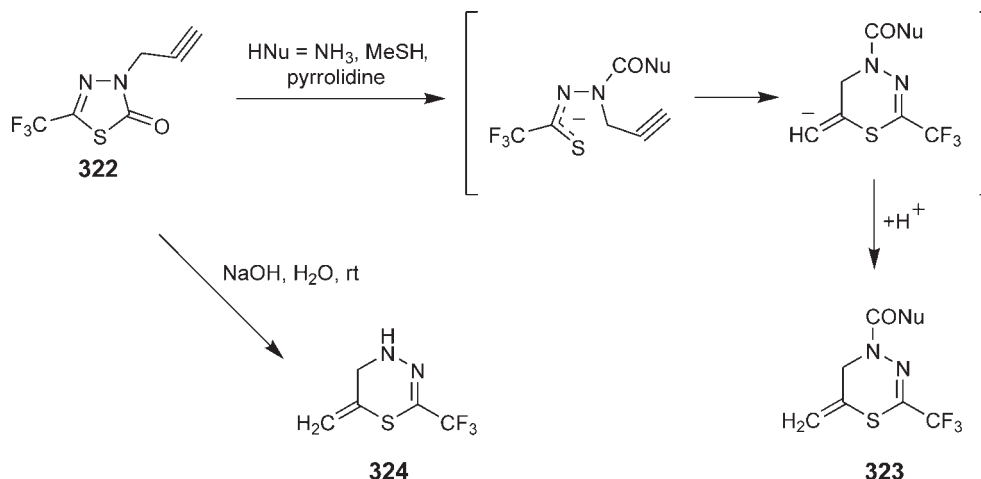


Scheme 42

The 2-(alkylimino)-3-amino-4-phenyl-2,3-dihydro-1,3-thiazol-3-amines **319** behave similarly and undergo ring expansion on heating with concentrated hydrochloric acid to give the 1,3,4-thiadiazines **318**. The 1,3-thiazole derivative **320** also undergoes a ring expansion to the 1,3,4-thiadiazine **321** by treatment with $FeCl_3$ in DMF (Equation 52) <1996KGS1424>.

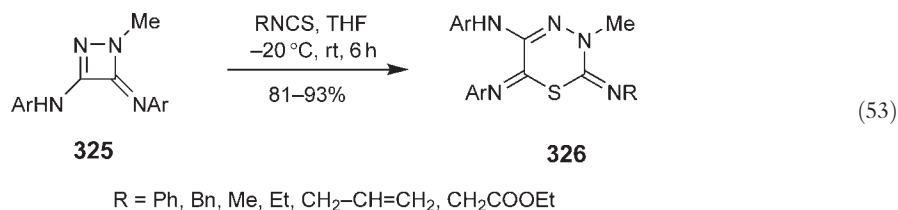


3-(Prop-2-ynyl)-5-(trifluoromethyl)-1,3,4-thiadiazol-2(3*H*)-one **322** reacts with nucleophiles (ammonia, pyrrolidine, or potassium methylthiolate) to form 6-methylene-2-(trifluoromethyl)-5,6-dihydro-4*H*-1,3,4-thiadiazine-4-carboxamides or *S*-methyl 6-methylene-2-(trifluoromethyl)-5,6-dihydro-4*H*-1,3,4-thiadiazine-4-thiocarboxylates **323**. The reaction of aqueous sodium hydroxide with **322** gives the 4*H*-1,3,4-thiadiazine **324**, which also bears an exocyclic methylene group (Scheme 43) <1998HOU(E9c)483>.

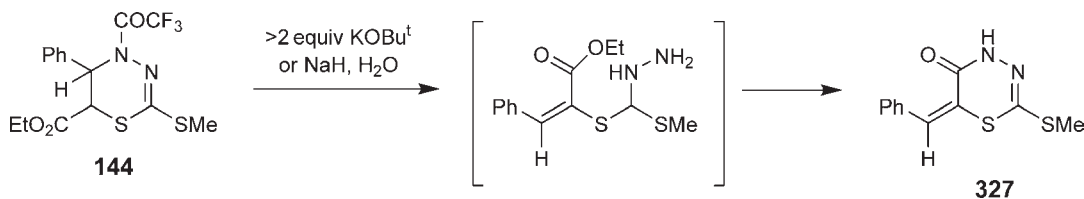


Scheme 43

On treatment with isothiocyanates, 1,2-diazetines **325** undergo ring transformation under mild conditions to afford 1,3,4-thiadiazines **326** (Equation 53) <2005H(65)1311>. The mechanism proceeds via an electrocyclic ring-opening–cycloaddition pathway or, at lower temperatures, via a nucleophilic attack of the *N*-methyl nitrogen atom of **325** on the isothiocyanate followed by ring expansion to **326**.

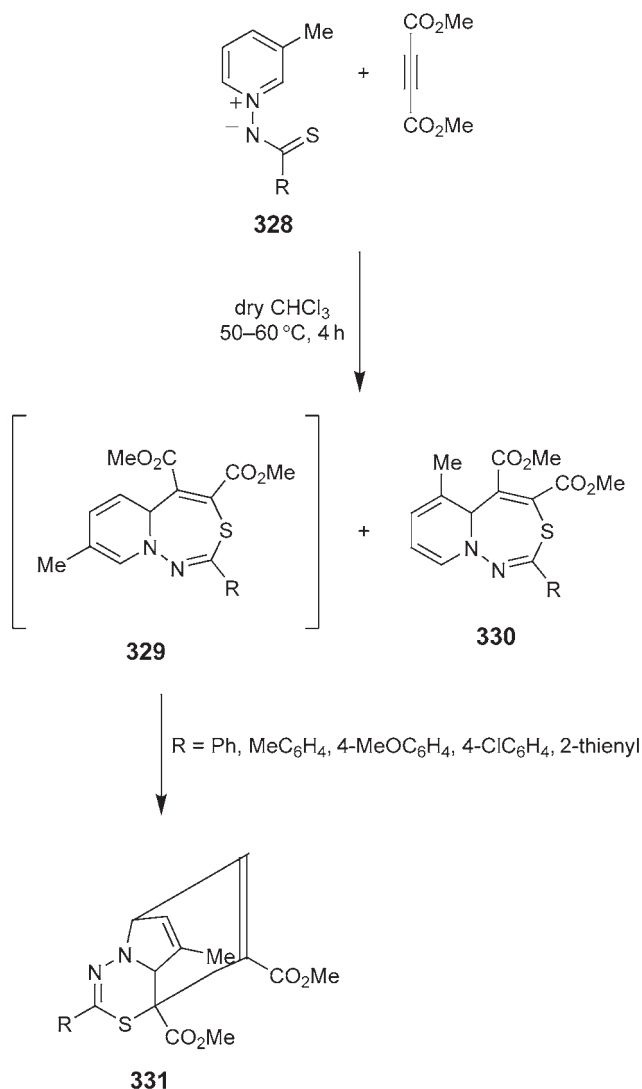


Rearrangement of 2-methylsulfanyl-4-trifluoroacetyl-5-phenyl-6-ethoxycarbonyl-4,5-dihydro-6*H*-1,3,4-thiadiazine **144** (see Section 9.08.5.4) by treatment with an excess of potassium *t*-butoxide or sodium hydride affords 6-alkylidene-4*H*-1,3,4-thiadiazin-5-one **327** (Scheme 44) <1998CL329>.



Scheme 44

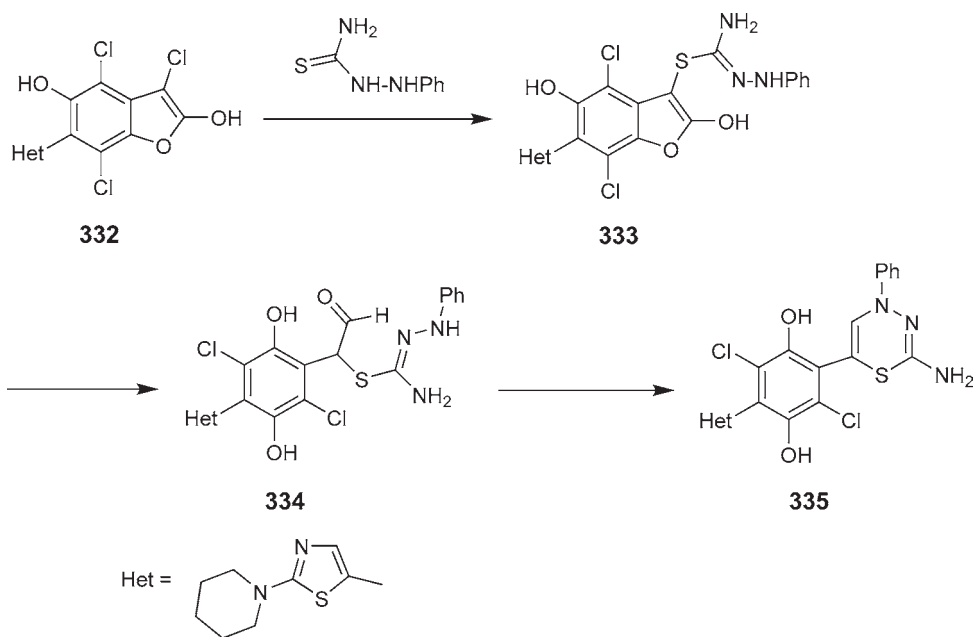
1-Pyridino- or 1-(3-methylpyridino)arenethiocarbonyl amidates **328** cyclized with dimethyl acetylenedicarboxylate (DMAD) by heating in chloroform to give primarily the bicyclic adducts **329** and **330**. Compounds **330** can be isolated, whereas the intermediates **329** undergo a rearrangement to the tricycles **331** (Scheme 45) <1997JOC7788>.



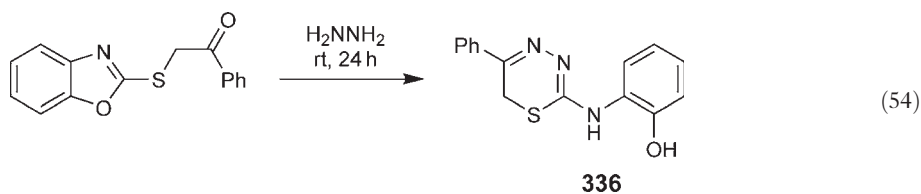
Scheme 45

Benzofuran **332** reacts with 1-phenylthiosemicarbazide to give the benzofuran derivative **333**, which undergoes ring cleavage to the intermediate **334** and subsequent cyclization to the 1,3,4-thiadiazine **335** <2005H(65)1569>. The reactions of benzofuran **332** with 4,4-dialkylthiosemicarbazides proceed with extrusion of a sulfur atom from the 1,3,4-thiadiazine intermediate and the formation of pyrazole derivatives (Scheme 46) <2005H(65)1569>.

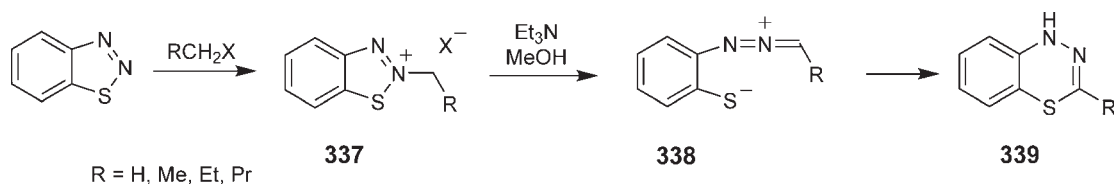
The α -(benzoxazol-2-ylsulfanyl) ketone reacts with hydrazine hydrate in acetic acid to yield *N*-(2-hydroxyphenyl)-5-phenyl-6*H*-1,3,4-thiadiazine-2-amine **336** (Equation 54) <1998HOU(E9c)518>.



Scheme 46



1*H*-4,1,2-Benzothiadiazines **339** can be prepared by ring expansion of intermediate 3-alkyl-1,2,3-benzothiadiazolium salts **337**, possibly via nitrogen ylides **338** (Scheme 47) <1998HOU(E9c)518>.



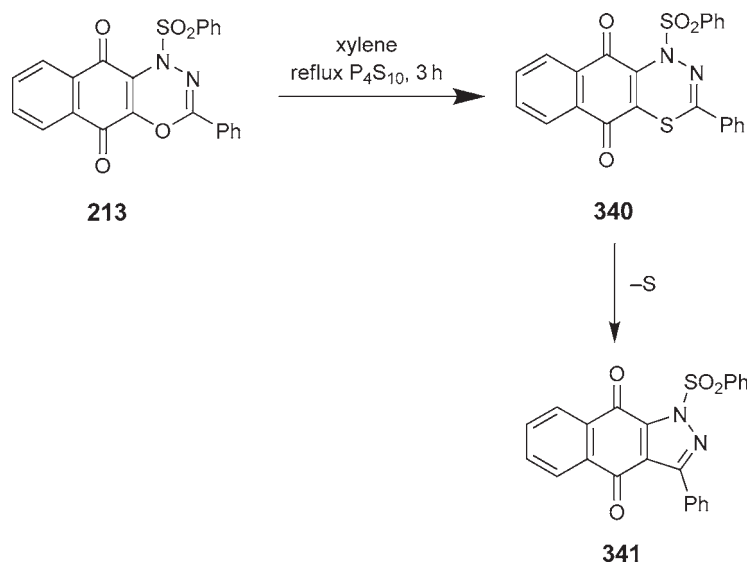
Scheme 47

Heating the 1,3,4-oxadiazine **213** (see Section 9.08.8.1.1) with phosphorus pentasulfide in xylene effects ring transformation to give the corresponding 1,3,4-thiadiazine **340** and the pyrazole derivative **341** (Scheme 48) <2003PS627>.

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

9.08.10.1 1,3,4-Oxadiazines

Diaryl-4*H*-1,3,4-oxadiazines can be prepared by hydration of 1-aryl-2-phenacyl hydrazine derivatives (Section 9.08.8.1.1). 3*H*-1,3,4-Oxadiazin-2-ones are obtained by cyclization of ethoxycarbonylhydrazones of α -hydroxy ketones (Section 9.08.8.1.1). 4*H*-1,3,4-Oxadiazin-5-ones are synthesized by ring closure of 1-acetyl-2-chloroacetylhydrazines.



Scheme 48

Cyclization of 2-chloro-3-(*N*-benzoylhydrazino)-1,4-naphthoquinones with benzenesulfonyl chloride affords the 4-naphtho[2,3-*e*][1,3,4]oxadiazines (Section 9.08.8.1.1). The diazotization of 2-[(2-aminophenyl)sulfonyl]-*N,N*-dialkylacetamides affords 4,1,2-benzothiadiazin-3-carboxylate 4,4-dioxides (Section 9.08.8.2). 1,3,4-Oxadiazines are the products of a remarkable ring transformation of 2,3-dibenzoyloxycarbonyl-2,3-diazabicyclo[2.2.1]heptenes (Section 9.08.9.1). In addition, 1,3,4-oxadiazines are obtained by the interesting ring cleavage and recyclization of 1,2,3-thiadiazol-4-yl-carboxyarylhydrazides (Section 9.08.9.1).

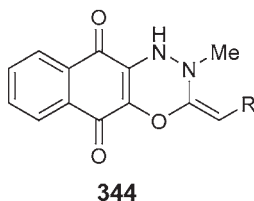
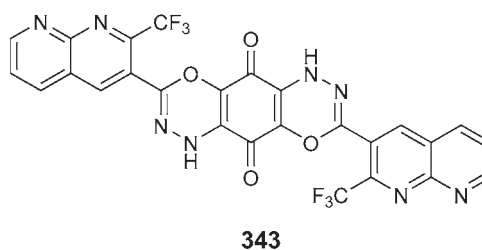
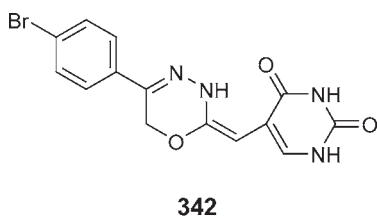
9.08.10.2 1,3,4-Thiadiazines

1,3,4-Thiadiazines are prepared best by cyclocondensation of thiohydrazides with α -halo ketones (Section 9.08.8.2.2). Pharmacologically interesting 2,3-dihydro-1,3,4-thiadiazin-2-ones are obtained by cyclocondensation of *O*-alkyl thiocarbazates (Section 9.08.8.2.2). By the reactions of α -halo carboxylic acids or α -halo carbonic esters, 1,3,4-thiadiazin-5-ones are formed (Section 9.08.8.2.2). Hydrazonyl chlorides react with ethyl sulfanylacetate to afford 1,3,4-thiadiazin-5-ones (Section 9.08.8.2.1). A rare example of the synthesis of 1,3,4-thiadiazines is the cyclization of 1-phenyl-2-thiocyanatoethan-1-one and hydrazine <1956CB107>. Transformation of 1,3,4-oxadiazines to 1,3,4-thiadiazines with phosphorus pentasulfide has been reported (Section 9.08.9.2). The ring transformation of tetrazines with thioformate is a remarkable method for the synthesis of 1,3,4-thiadiazines (Section 9.08.9.2). The ring expansion of 3-alkyl-2-hydrazono-4-aryl-2,3-dihydro-1,3-thiazoles by heating in concentrated hydrochloric acid is also a useful reaction (Section 9.08.9.2).

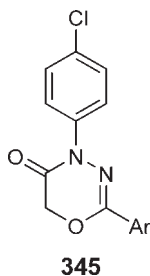
9.08.11 Important Compounds and Applications

9.08.11.1 1,3,4-Oxadiazines

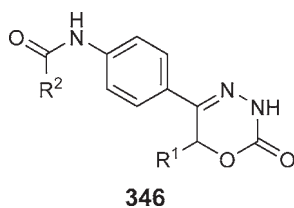
1,3,4-Oxadiazines show a broad spectrum of biological activity. 2-(4-Uracilmethylene)-(4-bromophenyl-6-hydroxy-2,3-dihydro-6*H*-1,3,4-thiadiazine **342** (trade name Oxadin) exhibits antiviral (herpes simplex virus, HSV) and antibacterial activities <1997PHA409, 1998MI57, 1999MI31, 1999MI63, 1999MI67, 2000PHA548, 2000MI53, 2001MI79, 2002PHA337, 2002MI73>. Antibacterial activity is exhibited by 3,8-bis-(2-substituted 1,8-naphthyridin-3-yl)benzo [1,2-*e*:4,5-*e'*]bis[1,3,4]oxadiazine-5,10(1*H*,6*H*)dione **343** <2000IJH311> and 1*H*-naphtho[2,3-*e*][1,3,4]oxadiazine-5,10-dione **344** (R = *N*-methylpyridinium iodide, *N*-methylquionolinium iodide, *N*-methylisoquinolinium iodide residues) <1995CPA192>.



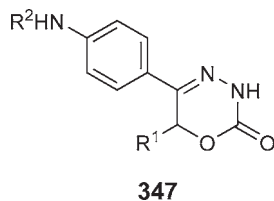
2-Aryl-4-(chlorophenyl)-6*H*-1,3,4-oxadiazin-5-ones **345** are α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists [<2000WO2000047567>](#).



N-[4-(2-Oxo(3*H*,6*H*-1,3,4-oxadiazin-5-yl))hetaryl]amides **346** ($R^1 = H$, Alk; $R^2 = \text{HetAr}$) can be used for treatment of anemia [<2001WO2001000601>](#).

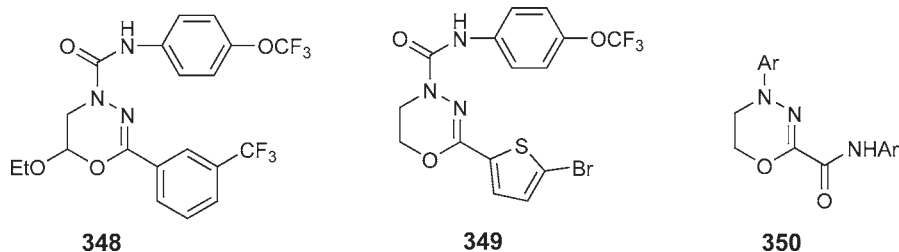


Cardiotonic activity is shown by 3,6-dihydro-5-aminophenyl-2*H*-1,3,4-oxadiazin-2-one derivatives **347** ($R^1 = H$, Alk; $R^2 = \text{HetAr}$) [<1995JPP07291971>](#).

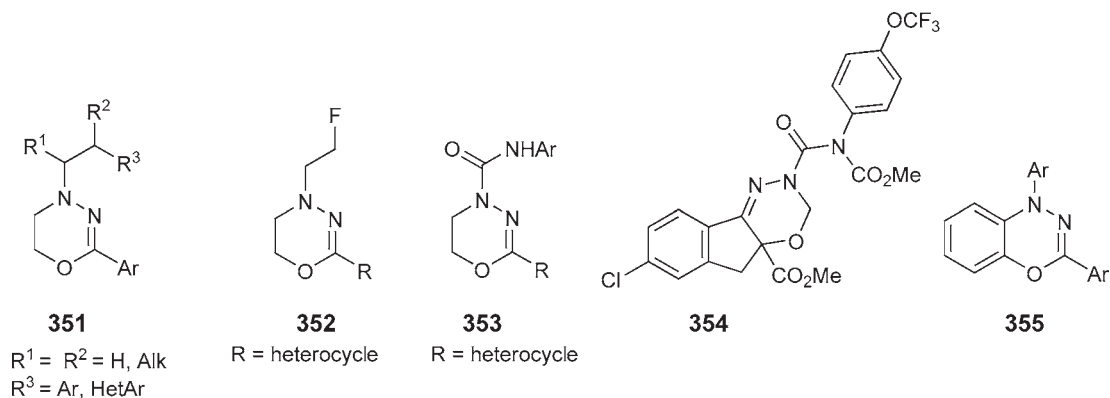


1,3,4-Oxadiazine derivatives are widely used in agrochemistry as insecticides, herbicides, fungicides, and pesticides. For example, 2-aryl-4-alkyl-5,6-dihydro-1,3,4-oxadiazines are useful insecticidal and acaricidal compounds

<1999JPP11049755>. [6-Ethoxy-2-(3-trifluoromethylphenyl)-5,6-dihydro-1,3,4-oxadiazin-4-yl]-*N*-[4-(trifluoromethoxyphenyl)]carboxamide **348** <2001USP6197766>, [2-(5-bromo-2-thienyl)-5,6-dihydro-1,3,4-oxadiazin-4-yl]-*N*-[4-(trifluoromethoxyphenyl)]carboxamide **349** <1998USP5804579, 1999WO9941245>, and 4-aryl-5,6-dihydro-1,3,4-oxadiazin-2-yl-*N*-arylcarboxamides **350** are also insecticides <1998USP5728693>.

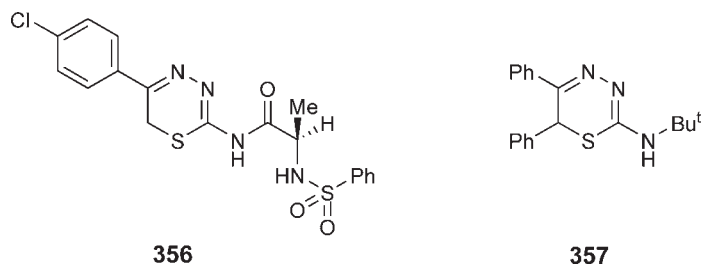


Some 4-substituted-2-aryl-5,6-dihydro-1,3,4-oxadiazines **351** <1996DEP4444865>, 2-heterocyclic-substituted 4-fluoroethyl-5,6-dihydro-1,3,4-oxadiazines **352** <2000USP6083942>, 2-aryl-5,6-dihydro-1,3,4-oxadiazin-4-yl-carboxamides **353** <1998WO9833794>, and 7-chloro-3*H*-indano[1,2-*e*]1,3,4-oxadiazine derivatives **354** <1999USP5869657, 1995WO9529171> exhibit pesticidal activity. Benzo[4,2,1]oxadiazines are used as herbicides **355** <1998USP5739326>.



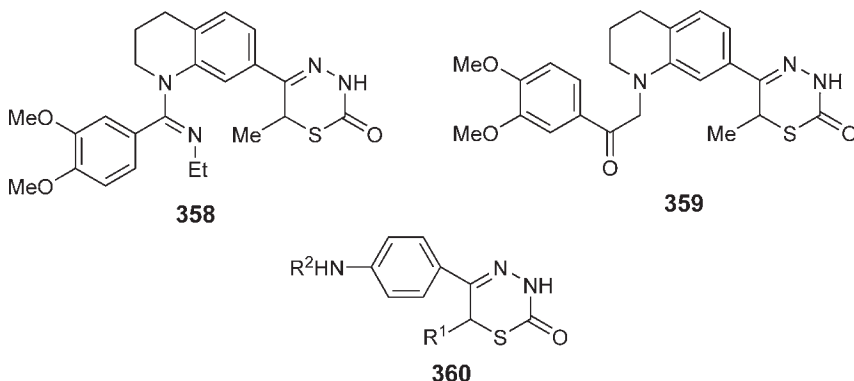
9.08.11.2 1,3,4-Thiadiazines

1,3,4-Thiadiazines are biologically very active compounds. Many 1,3,4-thiadiazine-2-yl-amine derivatives **356** are important matrix metalloproteinase inhibitors <2002EPP1191024, 2001JME3231>. 2-*tert*-Butylamino-5,6-diphenyl-6*H*-1,3,4-thiadiazine **357** <2006UP3> shows antituberculostatic activity against *Mycobacterium tuberculosis* with an inhibition of 96% at a concentration of 12.5 μg ml⁻¹.

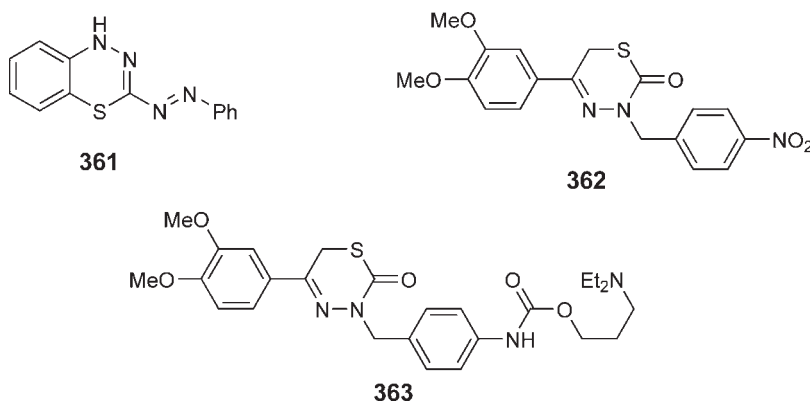


1,3,4-Thiadiazines display excellent cardiotonic and hypertensive activities. For example, (+)-5-[1-(α -ethylimino-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroquinoline-6-yl]-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one **358** <1997MI733, 1999JPP55, 1999MI301> (EMD60263) is a cardiotonic with calcium-sensitizing activity. The (–)-enantiomer of this compound (EMD60264) exhibits phosphodiesterase inhibition. 5-[1-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydroquinoline-6-yl]-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one **359** shows similar properties <1996EPP721950, 1996EPP723962,

1996MI334, 1997JPR315, 2005BJ905>. 5-(4-Hetarylamino-phenyl)-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one (**360**) ($R^1 = \text{H}$, Alkyl, $R^2 = \text{HetAr}$) <1995EPP679651> also exhibits cardiotonic activity.

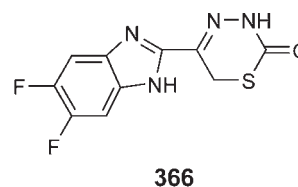
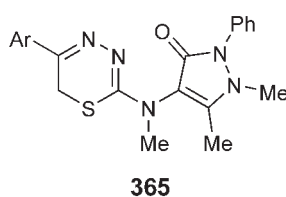
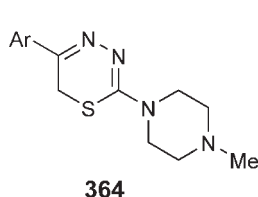


2-Alkylimino- and 2-alkylamino-1,3,4-thiadiazines are used as cardiotonic and spasmolytic agents <1983DEP204092, 1984DEP209196, 1985DEP220311, 1990DEP280760, 1991DEP293351, 1991DEP289272>. 5-Aryl-1,3,4-thiadiazin-2-ones are phosphodiesterase III/IV inhibitors <1999WO9947505>. 1,3,4-Thiadiazin-2-ones <1998WO9810765> are nonsteroidal contraception agents for females <1998WO9810765>. Some 1,3,4-thiadiazin-2-ones can be used for the treatment of erectile dysfunction <2000USP6156753>. 5-(1,2,3,4-Tetrahydroquinolin-6-yl)-6-methyl-1,3,4-thiadiazin-2-one can be used for preventing and/or treating anemia <2001WO2001000188>. 3-Phenylazo-1*H*-4,2,1-thiadiazine **361** is an agent for treating deficient bone growth <1997WO9715308>. 3-Nitrobenzyl-5-aryl-1,3,4-thiadiazin-2-ones **362** <1996EPP723962> and 1,3,4-thiadiazin-2-ones <2003DEP10150517, 2004WO2004067006> are phosphodiesterase IV inhibitors and can be used for treatment of tumors and acquired immune deficiency syndrome (AIDS) <2003DEP10150517, 2004WO2004067006>. 3-(*N,N*-diethylamino)propyl *N*-[4-(5-(3,4-dimethoxyphenyl)-2-oxo-2,3-dihydro-6*H*-1,3,4-thiadiazin-3-ylmethyl)phenyl]carbamic acid ester **363** is used for treatment of asthma and allergies <1997DEP19604388>.



N-Morpholinyl-, *N*-thiomorpholinyl-, or *N*-piperidinyl-1,3,4-thiadiazines exhibit antithrombotic <2005RUP2259371> and bactericidal activities <1996RUP2058307>.

2-Nitrosimino-3,6-dihydro-2*H*-1,3,4-thiadiazines exhibit antiplatelet and antithrombotic properties <1998PHA820>. 2-(*N*-methylpiperazino)-5-aryl-6*H*-1,3,4-thiadiazine dihydrobromides **364** display antiarrhythmic activity <1996RUP2058314>. Thiadiazinone derivatives are useful in the treatment of bacterial infections <2003WO2003066631>. Substituted 6*H*-1,3,4-thiadiazine-2-amines <1997WO9724353> and *N*-(1-phenyl-2,3-dimethylpyrazol-5-on-4-yl)-6*H*-1,3,4-thiadiazine-2-amines **365** <1997WO9724354> are anesthetics and cardiovascular and hypometabolic agents. (+)-[[4-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propane dinitrile is an anti-inflammatory drug <2002WO2002040025>. 5,6-Difluoro-2-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)benzimidazole hydrochloride **366** is used for treatment of heart failure <1995JPP07101954>.



1,3,4-Thiadiazines may be used in agriculture as herbicides <1971JPP7041593, 1974USP377936, 1975USP3854924, 1975USP3862183, 1981USP4254259, 1984USP4436549>, fungicides <1967MI539, 1967JPP8033, 1969MI689>, pesticides <1973HCA2186>, insecticides <1979USP4144335, 1998WO9838181>, and plant-growth regulators <1981USP4254259>. 1,2,4-Triazolo[1,3,4-*b*][1,3,4]thiadiazines can be used as photographic magenta couplers <2000JPP2000143664, 2001JPP2001072682, 2002JPP2002302493>. 1,3,4-Thiadiazin-2-yl amines are used as agents for radiator protection <1980MI31, 1999MI223>.

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Biographical Sketch



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9.09

1,3,5-Oxadiazines and 1,3,5-Thiadiazines

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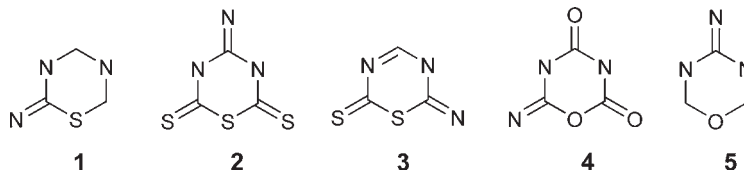
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9.09.1 Introduction

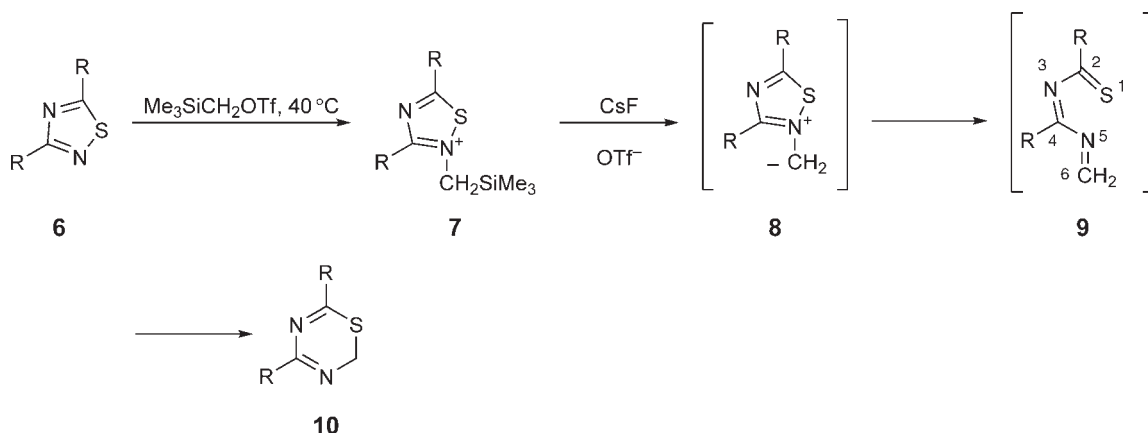
Since the review by R. K. Smalley in the CHEC-II(1996) <1996CHEC-II(2)783>, approximately a thousand new publications have appeared in the literature, wherein a mention of 1,3,5-oxadiazines or 1,3,5-thiadiazines has been made. This chapter serves as an update to this earlier review. Apart from the ring systems mentioned in CHEC-II(1996), the other common systems encountered in publications over the last decade are shown (1–5).



The presence of an imine functionality attached to the ring is a characteristic of reports in recent years. A number of fused ring systems have also been reported. The discovery of the potent nicotinoid insecticide, thiamethoxam, has prompted intensive research in the area of 1,3,5-oxadiazines (see Section 9.09.12.1). Tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives have been used as prodrugs, due to their high lipid solubility and enzymatic rate of hydrolysis (see Section 9.09.12.2). A number of reports appear on the use of 1,3,5-oxadiazines as the fundamental building blocks for the synthesis of curcubituril, its derivatives, and congeners (see Section 9.09.12.1). On the synthesis front, new syntheses involving ring expansions of the imidazole and thiazole rings have been reported (see Section 9.09.10). Synthesis on solid supports, gas phase, and electrochemical syntheses have also appeared (see Sections 9.09.9.1.3 and 9.09.9.4). The first report of a naturally occurring 1,3,5-oxadiazine system has been made <1997T2055>. Sensitive analytical methods to detect very small concentrations of pesticides such as thiomethoxam have been reported <2005ANA21, 2005JSC735>. A number of these compounds have been subjected to crystallographic analysis (see Section 9.09.3.2).

9.09.2 Theoretical Methods

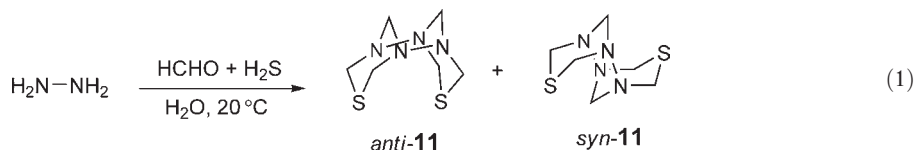
Ab initio molecular orbital (MO) calculations with the GAUSSIAN94 series of programs, using the HF/6-31G* theoretical level, have been studied for the quaternization of 3,5-diaryl-1,2,4-thiadiazoles **6** (R = Ph) with trimethylsilyl triflate at 40 °C. Quaternization occurs at the N-2 position. Desilylation of the salts results in ring expansion to substituted 2*H*-1,3,5-thiadiazines **10** <1999J(P1)1709>. It is envisaged that the ring expansion progresses through the unstable intermediates **8** and **9**, which in turn yield **10**, by 1,6-heteroelectrocyclization (Scheme 1). Theoretical



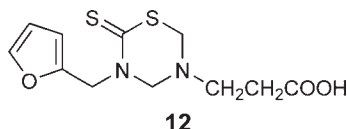
Scheme 1

calculations for this conversion of the unsubstituted derivative **7** (R=H) showed that the dipole **8** opens to the intermediate **9** where the C=S bond is nearly perpendicular to the rest of the molecule. This is followed by rotation around the C(4)–N(5) single bond. The methylene group then rotates up to meet the S-atom out of the CNCN plane to form the CS bond. Although a second avenue exists for the rotation around the CN bond, the substantial energy barrier between transition states for that route renders it unfavorable (Scheme 1) <1999J(P1)1709>.

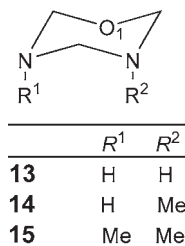
Semi-empirical AM1 and PM3 quantum-chemical calculations (standard Hyperchem 6.0 2000 program package) have been used to determine the structure of **11**, formed by the thiomethylation of hydrazine at 20 °C (Equation 1) <2004RCB1717>.



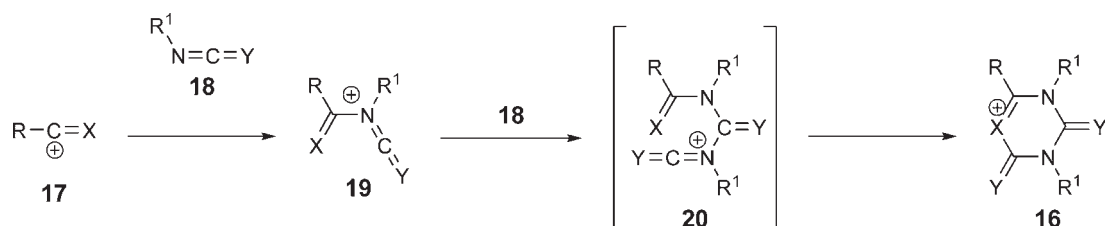
Compound **11** could exist either in the *anti*- or the *syn*-form. Calculations show that the *anti*-form is more favorable when compared to the *syn*-, as the formation of *syn*-form is prevented by steric hindrance between the bridging methylene groups <2004RCB1717>. Semi-empirical AM1 and *ab initio* HF/3-21G* and HF/6-31G* calculations have been performed on 5-carboxy-ethyl-3-(2'-furfurylmethyl)tetrahydro-2*H*-1,3,5-thiadiazine-2-thione **12**, a representative example of 3,5-disubstituted-tetrahydro-2*H*-1,3,5-thiadiazines, to determine the most favorable conformation <2001T7361> (see Section 9.09.4.2).



Although the AM1-predicted values compare quite well with experimental data (X-ray crystallographic analysis), some remarkable deviations in bond distances, especially involving sulfur atoms, are seen. More reliable results are obtained with the use of both HF/3-21G* and HF/6-31G* methods. Nuclear Overhauser effect (NOE) experiments confirm the presence of this conformation in solution <2001T7361>. *Ab initio* studies of axial and equatorial structures for 1-oxa-3,5-diazine **13**, and *N*-methyl and *N,N*-dimethyl derivatives **14** and **15**, are reported in the gas phase and aqueous solutions. The compounds are completely optimized, without restrictions, at the HF/6-31G** level, and single-point calculations on the optimized geometries are performed using the 6-31++G** basis set to establish the effect of the diffuse functions relevant to the lone pairs of electrons. Single-point calculations MP2/6-31G** and MP2/6-31++G** have also been performed to investigate the electron correlation effects. The data have proven that the most stable conformation of the *N*-methyl derivative has the *N*-methyl group in the axial position, while the preferred conformer for the *N,N*-dimethyl derivative contains one axial and one equatorial methyl group <1997JOC6144>.

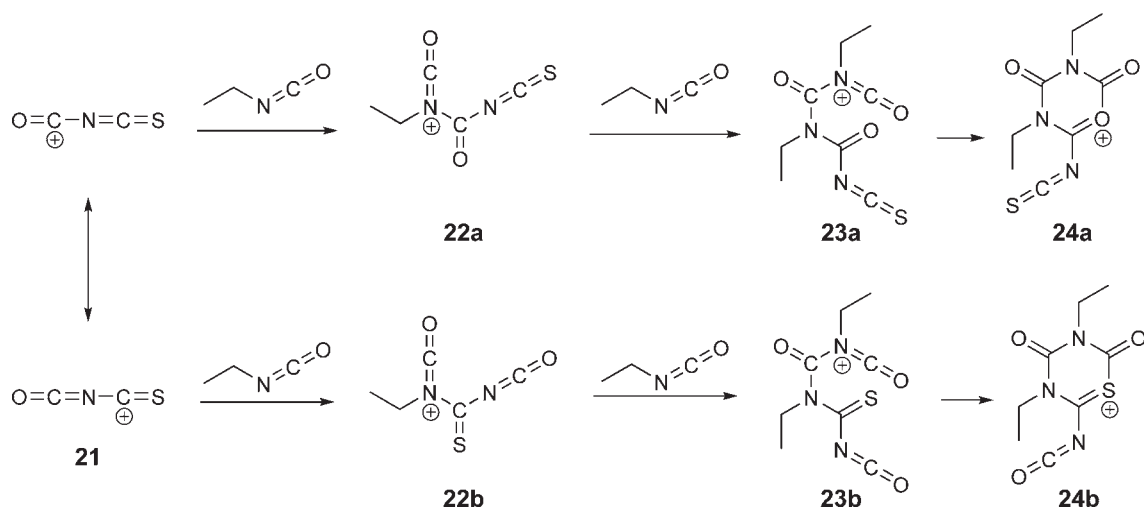


Gas-phase synthesis of 3,4-dihydro-2,4-dioxo-2*H*-1,3,5-oxadiazinium ions (**16**: X=Y=O) via cyclization of acylium (**17**: X=O) and thioacylium ions (**17**: X=S) with isocyanates (**18**: Y=O) and isothiocyanates (**18**: Y=S) has been investigated using tandem-in-space pentaquadrupole mass spectrometry (MS) <2005JAM1602>. The formation of single (**19**) and double (**20**) addition products in these reactions was observed to occur concurrently with proton transfer. The products of double addition have been observed to be favored in reactions with ethyl isocyanate, whereas the reactions with ethyl isothiocyanate formed preferentially either the single-addition product or proton-transfer products, or both. Furthermore, *ab initio* calculations at the Becke3LYP//6-311+G(dp) level indicate that cyclization of the double addition products is favored and 3,4-dihydro-2,4-dioxo-2*H*-1,3,5-oxadiazinium ions (**16**: X=Y=O) are formed (Scheme 2) <2005JAM1602>.



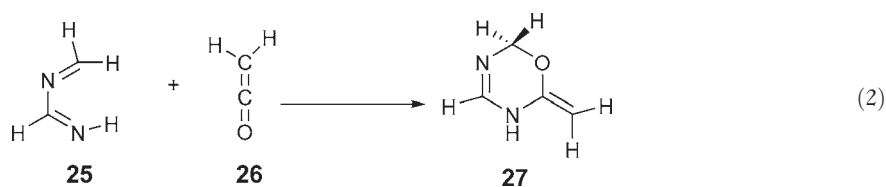
Scheme 2

The singly charged acylium thioacylium ion **21** represents a special case since the initial addition to ethyl isocyanate can occur either via its C=O or C=S charged sites <2005JAM1602>. The initial addition of ethyl isocyanate to the C=S charged site of **21** to give **22b** was found to be 29.7 kJ mol⁻¹ more exothermic than addition to the C=O charge site to yield **22a**. Calculations have also shown that the double-addition product **23a** is 30.5 kJ mol⁻¹ more stable than the single-addition product **22a**. Alternatively, the double-addition adduct **23b** was found to be unstable according to calculations. The cyclic addition products **24a** and **24b** were predicted to be only 7.9 kJ mol⁻¹ apart, indicating that both **24a** and **24b** are formed in the gas phase (Scheme 3) <2005JAM1602>.



Scheme 3

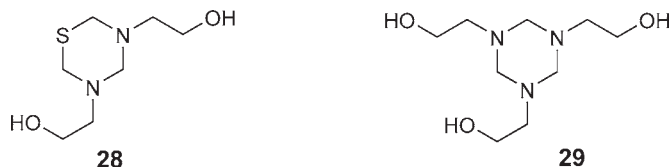
Ab initio MO and density functional theory (DFT) calculations on 1,3-diazabuta-1,3-diene **25** and its reaction with ketene **26** at HF/6-31G*, MP2/6-31G*, and B3LYP/6-311++G**//B3LYP/6-31G* levels using the Gaussian94W program have been presented <2000OL2725>. The oxadiazine **27**, a [4+2] cycloadduct of **25** and the C=O bond of ketene, has a small stabilization energy of -23.9 kcal mol⁻¹. The geometrical features of the transition state for this conversion suggest also that the reaction proceeds through an asynchronous cycloaddition process without any zwitterionic intermediates (Equation 2) <2000OL2725>.



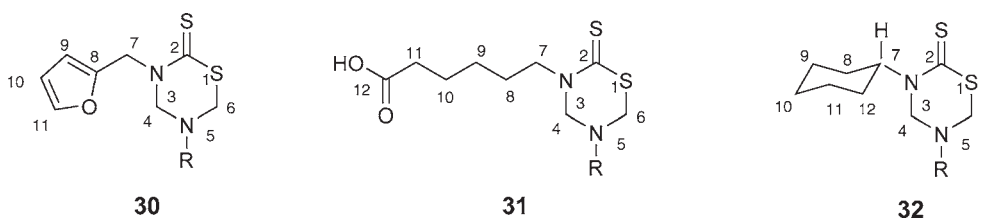
9.09.3 Experimental Structural Methods

9.09.3.1 NMR Spectra

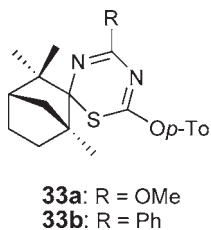
Proton magnetic resonance (PMR), ^{11}B , ^{13}C , two-dimensional (2-D), and variable-temperature nuclear magnetic resonance (NMR) spectroscopies have been used to study the conformational and structural characteristics of borane and chloroborane adducts of 1,3,5-thiadiazine and their rearranged products <1999EJI2063>. The conformational studies are discussed in Section 9.09.4.2. Extensive NMR experiments (correlation spectroscopy (COSY) and NOE) have been performed to identify the main component **28**, from a mixture formed by the reaction of triazine **29** with sulfide ions <2001IEC6051>. The ^{13}C NMR spectrum of the mixture is correlated with the PMR spectrum by proton-carbon COSY. The ^{13}C signals corresponding to the PMR signals tentatively assigned to **28** have been compared to calculated ^{13}C data for **28** and were found to be in good comparison <2001IEC6051>.



The complete PMR and ^{13}C assignments for a series of differently substituted thiadiazin-2*H*-thiones **30–32**, having different groups on the two heterocyclic nitrogen atoms, have been presented <2001MRC222>. To assign all of the NMR signals unequivocally, 1-D and 2-D techniques such as distortionless enhancement of polarization transfer (DEPT 135), heteronuclear multiple quantum correlation (HMQC), and heteronuclear multiple bond correlation (HMBC) were used.

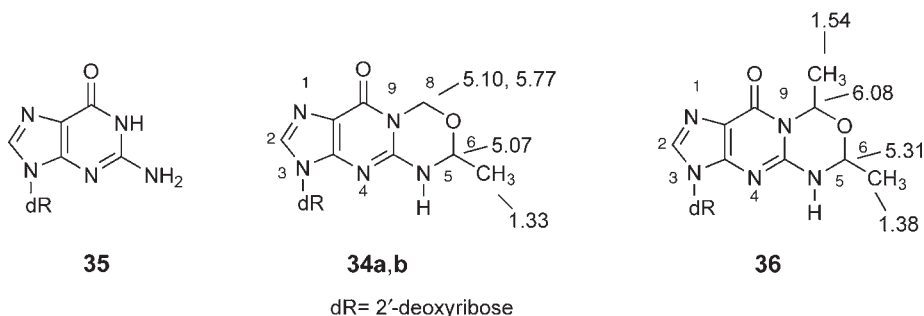


In general, the 300 MHz PMR spectra of thiadiazine-2-thiones show two singlets corresponding to ring protons H-4 and H-6. NOE experiments have been used to confirm the assignment of the singlets for compound **31**. The ^{13}C NMR spectra of the above compounds exhibit signals in the thiocarbonyl, carbonyl, aromatic, and aliphatic regions. The thiocarbonyl carbon (C-2) in these systems appears in the narrow range of δ 190.1–192.1 ppm and the COOH carbon appears at δ 170–174 ppm <2001MRC222>. The ^{13}C NMR spectra of 6*H*-1,3,5-thiadiazines **33a** and **33b**, taken at -15°C , show two closely related sets of singlets (δ = 157, 175 ppm) which are assigned to $-\text{O}-\text{C}=\text{N}$ units. At δ = 89 ppm, however, a signal of an sp^3 -hybridized carbon atom is observed. The two sets of signals are due to mixtures of diastereomers ((*R,R*) and (*R,S*)) with regard to the (*R*)-fenchon moiety and the stereogenic spiro carbon atom. At room temperature, some signals collapse to single lines <2001EJO83>.

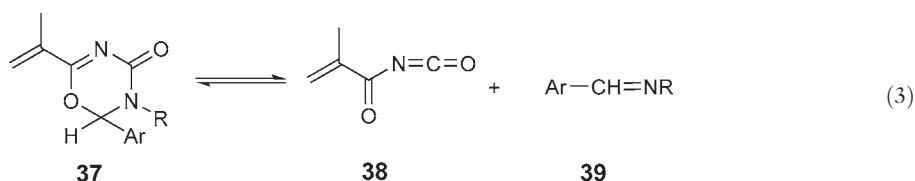


Previously unknown adducts **34a** and **34b** are formed in the reaction of deoxyguanosine (dGuo) **35** with acetaldehyde. PMR and carbon NMR data are fully consistent with the two diastereoisomers, **34a** and **34b**. There were no protons corresponding to N(1)–H or the NH_2 group of dGuo, indicating that substitutions had occurred at the 1 and N^2 positions. An exchangeable N(5)–H proton was observed. The methyl group protons on C-6 were found to be a doublet,

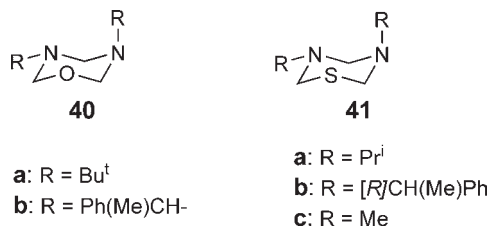
and coupling to the methine proton on C-6 has been confirmed by COSY. In addition, COSY and HMQC analysis confirmed coupling between protons on C-8. Chemical shift data favor structure **34** over **36** <2003CRT145>.



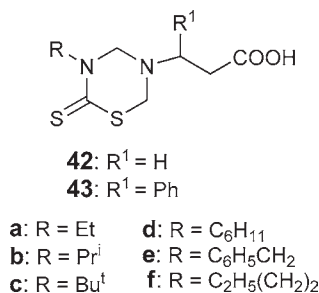
2*H*-1,3,5-Oxadiazin-4(3*H*)-ones **37**, [4+2] cycloadducts of aryldine amines **39** and methacryloyl isocyanate **38**, dissociate to the starting materials based on variable-temperature NMR (VT-NMR) spectroscopy. The study shows that equilibrium is set up between compounds **37**, **38**, and **39**. The ratios of these compounds have been found to depend on the temperature. At lower temperatures, the dissociation of **37** was lower and was observed even at -30°C (Equation 3) <1996H(42)533>.



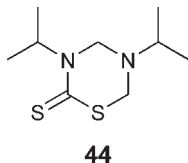
Structural characterization of 3,5-dialkyl-1,3,5-oxadiazines **40a** and **40b** and 3,5-dialkyl-1,3,5-thiadiazines **41a-c** has been investigated using variable-temperature PMR and ^{13}C NMR experiments <1999H(51)2079>. As the 1,3,5-oxadiazines **40a** and **40b** are in conformational equilibrium, their equatorial and axial groups are equivalent at room temperature <1999H(51)2079>.



The synthesis of two series of tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones (THTTs) by incorporation of β -alanine **42a-f** and β -phenylalanine **43a-f**, respectively, at the fifth position of the THTT moiety has been reported <2003AF526>. The PMR spectra, with the exception of the N-3 substituents, are nearly superimposable in each of the two series. The protons of the C-4 and C-6 methylenes of the THTT ring in compounds **42a-d** appear as one singlet integrating for four protons, while they are separated as two singlets, two protons each, in compounds bearing aralkyl groups at the third position, viz. **42e** and **42f**. In β -phenylalanine derivatives **43a-f**, the C-4 and C-6 methylene protons appear as two singlets for the two protons in all of the derivatives except **43a**, which bears an ethyl group in the third position. It is speculated that the presence of aromatic groups in these compounds perturbs the electronic configuration of the THTT ring, affecting the chemical shifts of these sets of protons <2003AF526>.

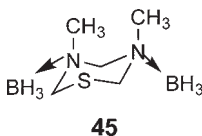


The PMR spectrum of 3,5-diisopropyltetrahydro-2*H*-1,3,5-thiadiazine-2-thione **44** has been reported <2000MI281>. Measured in DMSO-*d*₆, the interesting observation is the large difference in the shifts of the methine protons (δ 3.00, 1H, m (septet) for methine N5-CH(CH₃)₂ and 6.05, 1H, m (septet) for methine N3-CH(CH₃)₂) of the two isopropyl groups (DMSO = dimethyl sulfoxide). A high deshielding effect is seen for the methine attached to N-3 <2000MI281>.

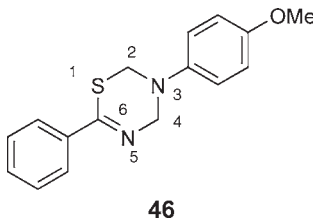


9.09.3.2 X-Ray Crystallography

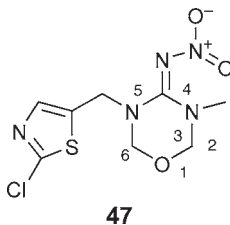
X-Ray diffraction studies for 3,5-bis(borane)-3,5-dimethyl-1-thia-3,5-diazacyclohexane **45** have been presented <1999EJI2069>.



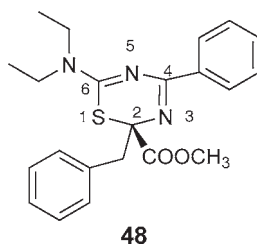
The C–S bonds are on average shorter than that of the free heterocycle as a consequence of the ammonium-type N atom. Compound **45** has a chair conformation with the two BH₃ groups in equatorial positions and the two methyl groups in axial positions. A dipolar interaction between the hydridic B–H and protic C–H groups is offered as the explanation for the frozen conformation <1999EJI2069>. Single crystal X-ray crystallographic studies of 3-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine **46** show that the thiadiazine ring exists in a half-chair conformation with S-1, C-2, C-4, N-5, and C-6 coplanar (mean deviation from the plane of 0.022 Å) and with N-3 lying 0.684 Å above the plane. The phenyl ring is inclined at an angle of 17° to the above plane and there are no unusually short intermolecular interactions <2002JOC4960>.



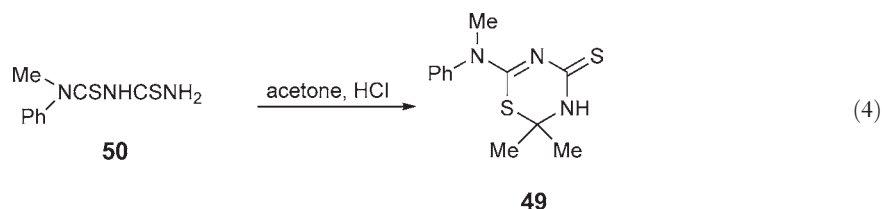
The crystal structure of the potent insecticide thiamethaxam **47** has been reported <2004AXE2413>. The 1,3,5-oxadiazine ring has a twist boat conformation. The oxygen atom in the 1-position and carbon atom in the 6-position are out of the plane formed by C-2, N-3, C-4, and N-5. The N nitro group is twisted away from the methyl group due to steric interaction <2004AXE2413>. C–H···N and C–H···O interactions account for the generation of dimers and molecular chains <2004AXE2413>.



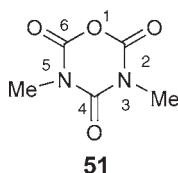
X-Ray analysis of the antifungal agent, methyl 2-benzyl-6-diethylamino-4-phenyl-2*H*-1,3,5-thiadiazine-2-carboxylate **48**, reveals that the central thiadiazine ring has a boat conformation <2004AXE713>. The two N=C bonds have characteristic bond lengths. The other N–C bond lengths are shorter than average C–N single bond lengths. While the phenyl ring is in the same plane as the C(4)=N(3), the benzyl ring is twisted out of the plane of the heterocyclic ring <2004AXE713>.



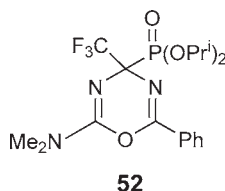
X-Ray analysis has been used to prove the structure of the keturet **49** formed by condensation of 1-methyl-1-phenyldithiobiuret **50** with acetone (Equation 4) <1999AXC434>.



X-Ray analysis showed that there are two molecules per asymmetric unit and the two molecules are mirror images of each other. The C=N bond in both molecules constrains the S-C=N-C(S) grouping to be almost planar. The other two atoms are displaced from the plane making the conformation a distorted chair <1999AXC434>. 3,5-Dimethyl-1,3,5-oxadiazine-2,4,6-trione **51**, a cyclic derivative of urea containing an anhydride moiety, does not differ in bond lengths from the standard values found in other anhydrides and urea derivatives according to X-ray investigation. The molecule lies across a crystallographic plane formed by O-1, C-4, and the oxygen attached to the C-4 carbon. The molecule lacks hydrogen-bond donors and hence the crystals are held together by unusual C=O...O, O...C, and weak C-H...O interactions, forming layers <2005AXCo545>.

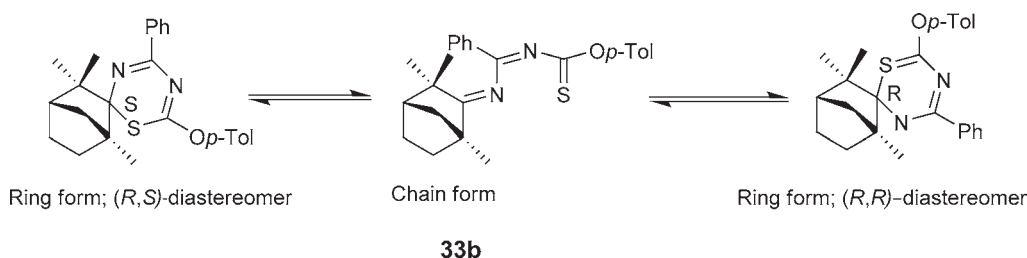


Single crystal X-ray diffraction analysis of 4-phosphorylated 1,3,5-oxadiazine **52** has been reported <2002HAC22>. The central heterocycle is planar and the dimethylamino group lies practically in the plane of the heterocycle. The lengths of the two C=N bonds in the heterocycle differ insignificantly <2002HAC22>.

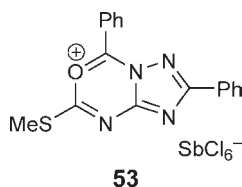


X-Ray analysis was performed on one of the products, **33b**, obtained by treatment of *N*-alkylideneisoureas with chlorothioformate. In the solid state, **33b** exists as a ring tautomer and the 1,3,5-thiadiazine ring adopts a boat conformation. The spiro carbon atom of the crystalline species has the (*R*)-configuration. PM3 calculations for both diastereomers of **33b** indicate an energetic preference of 0.44 kcal mol⁻¹ in favor of the observed (*R,R*)-diastereomer over the (*R,S*)-diastereomer. The Ph group is well in plane with the C=N bond but the *p*-tolylloxy group is twisted by 109.5° out of the plane of the heterocycle (Scheme 4) <2001EJO83>.

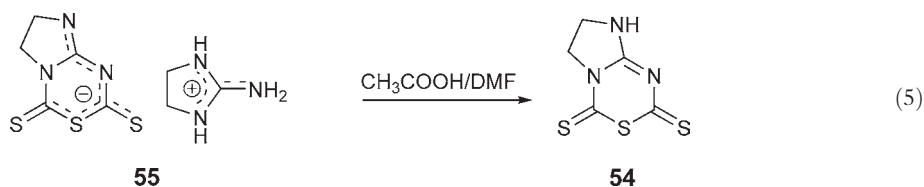
The crystal structure of the oxadiazinium compound **53** has been reported <1995JPR274>.



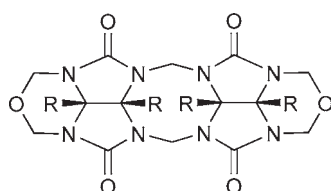
Scheme 4



The cation is almost planar, with only the methyl group slightly outside the plane. The presence of π -interaction between rings is observed [\[1995JPR274\]](#). The structure of 3-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine **46** has been confirmed by single X-ray crystallography. The bond lengths and bond angles are similar to structurally related compounds. The thiadiazine ring exists in a half-chair conformation and there are no unusually short intermolecular interactions [\[2002JOC4960\]](#). The structure of 7,8-dihydro[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)dithione **54**, isolated by treatment of the salt **55** with acetic acid in dimethylformamide (DMF), has been confirmed by X-ray crystallography (Equation 5) [\[2003JOC4791\]](#).

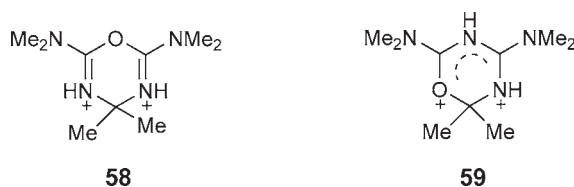


Compound **54** can exist in three possible tautomeric forms: **54**, **54a**, and **54b** (see Section 9.09.4.3, Scheme 6). X-Ray crystallographic analysis showed that the most stable form is **54** [\[2003JOC4791\]](#). In addition, X-ray crystal structure determination has been carried out on oxadiazines **56** and **57**, building blocks for cucurbit[6]uril analogs. Cucurbiturils are macrocyclic molecules consisting of glycouril repeat units. The name is derived from the resemblance of this molecule to a pumpkin of the family of Cucurbitaceae. Cucurbiturils are commonly written as cucurbit[#]uril (CB[#]), where the number of repeat units is indicated within the brackets [\[2003ACR621\]](#). The bond angles through the glycouril quaternary carbons of **56** and **57** are almost identical to those observed for CB[6]. The bond angles through the methylene bridges are somewhat smaller than the corresponding values for CB[5] and this is attributed to the presence of six-membered cyclic ether rings in **56** and **57**, while CB[5] has eight-membered rings. The X-ray analyses suggest that the building blocks **56** and **57** are preorganized to form CB[5] and/or CB[6] analogs [\[2005JOC10381\]](#).



56: R = COOH
57: R = (CO₂)NBu

The dication **58** formed by addition of 1,1-dimethyl cyanamide to acetone in the presence of acid has been subjected to X-ray analysis, which proved that the structure was **58** rather than **59**.



The X-ray structure of **58** reveals that the molecule is planar with the interatomic distances C(2)–N(3) and C(2)–N(7) suggesting double-bond character. The intermolecular distance between the heterocyclic cation and triflate anion N(3)–O = 2.79 Å (H(3)···O = 1.88 Å) suggests hydrogen-bond contact (**Figure 1**).

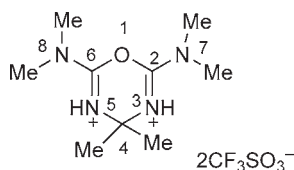
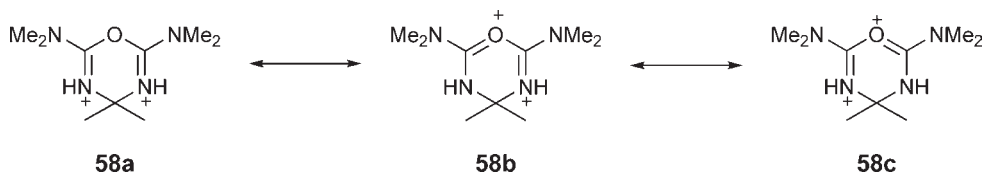


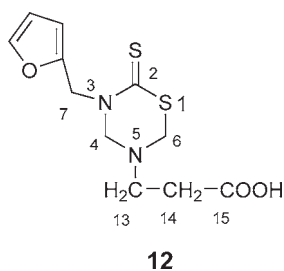
Figure 1

The structure **58** is not aromatic with one sp^3 carbon present. The O-1 and C-2 bond lengths suggest π -electron delocalization through resonance as shown in **Scheme 5** <1996CC1731>.

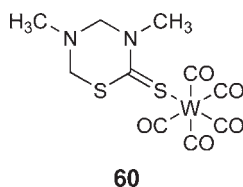


Scheme 5

The X-ray structure of compound **12** shows an envelope conformation for the thiadiazine-2-thione ring with a pseudo mirror plane through C-2. The C-13 atom is in an axial position with respect to N-5, whereas the S-2 and C-7 moieties are positioned in equatorial positions. The crystal structure is stabilized by formation of dimers and the short intramolecular interactions help keep the conformation of the molecule in the crystal <2001T7361>.

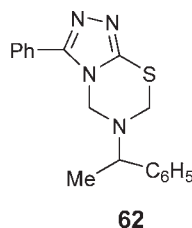
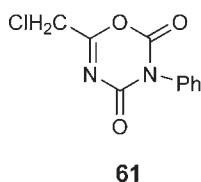


[W(CO)₅DTTT] **60**, synthesized by the photochemical reaction of W(CO)₆ with 3,5-dimethyltetrahydro-2*H*-1,3,5-thiadiazine-2-thione (DTTT), has been subjected to X-ray diffraction studies. The studies confirmed that the tungsten atom adopts a distorted octahedral geometry. The study also showed that the DTTT coordinates via the C–S sulfur atom to the metal center. The sulfur atom of the DTTT is bonded *trans* to the C=O group, with the remaining C=O groups occupying equatorial positions <2003POL1689>.



9.09.3.3 Mass Spectra

Mass spectral data for 1,3,5-oxadiazines and thiadiazines have been reported in a number of publications along with NMR and elemental analyses to assist with the identification of structures. In most of the cases M^+ and/or $M+1$ peaks are seen, though sometimes in low intensities. For the oxadiazine **61**, the most predominant peak is that of fragment $[M-\text{PhNCO}]^+$ at 119 <1996SC783>, while in the case of thiadiazine **62**, the M^+ peak at 322 is followed by a $[M-\text{CH}_3-\text{CH}-\text{Ph}]^+$ fragment at 217 <1999SC2027>.



Gas-phase reactions of acylium and thioacylium ions with isocyanate and isothiocyanate were investigated by MS <2005JAM1602>. The use of liquid chromatography/mass spectrometry (LC/MS) for the confirmation and quantification of thiomethoxam has been reported <2005ANA21>.

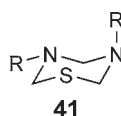
9.09.4 Thermodynamic Aspects

9.09.4.1 Aromaticity

A disodium salt of bisdithiocarbamate of urea (UBDT) cyclizes on heating to yield thiadiazine **69**, which is highly stabilized by resonance (see [Scheme 7](#)) <2004MI139>. A crystal structure analysis of cation **53** has been carried out. The cation is almost planar, with only the methyl group slightly outside the plane. The π -electrons in the triazole ring are localized; however, the coplanarity of the rings and the rather short bonds indicate π -interaction between rings <1995JPR274>.

9.09.4.2 Conformational Studies

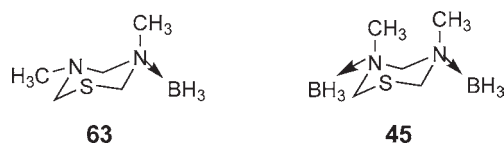
1,3,5-Thiadiazines **41** do not have preferred conformations. NMR data reveal that they are in ring and N-conformational equilibrium at room temperature. The NMR spectrum of compound **41c** at -90°C in $\text{THF}-d_8$ revealed no preferred conformation as the CH_3 and SCH_2N resonances were averaged (THF = tetrahydrofuran).



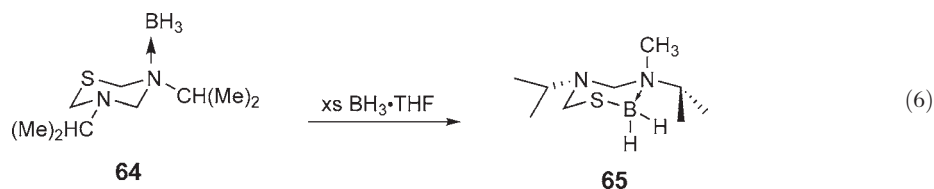
- a:** R = Prⁱ
b: R = CH(Me)Ph
c: R = Me

However, coordination of these systems with BH_3 , BHCl_2 , and BCl_3 forms adducts with frozen conformations. Reaction of **41c** with equimolar amounts of $\text{BH}_3 \cdot \text{THF}$ results in complex **63**, while with excess $\text{BH}_3 \cdot \text{THF}$ the bis-adduct **45**, with both N- BH_3 groups in the equatorial position, is formed. Geminal coupling patterns have been

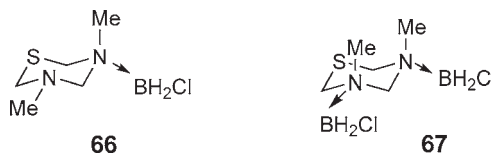
observed for the two CH₂ groups in the PMR spectra for these compounds. This is further supported by X-ray diffraction studies. The mono-adduct **63** in solution converts to **45** and the free heterocycle **41c** <1999EJI2063>.



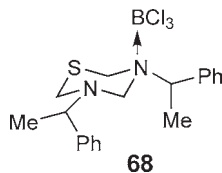
Interestingly, similar treatment of **41a** with equimolar amounts of BH₃·THF gives the mono-adduct **64**, which has a chair conformation, with the two isopropyl groups in the equatorial position. Compound **64** undergoes a rearrangement with excess BH₃ to furnish compound **65** (Equation 6) <1999EJI2063>.



The mono- and bis-monochloroborane adducts **66** and **67**, respectively, are formed readily from the thiadiazine **41c**. Both are stable adducts with *N*-chloroborane in an equatorial position <1999EJI2063>.



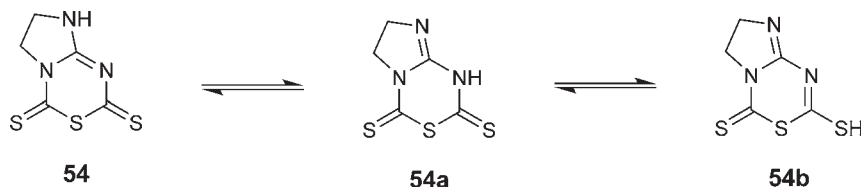
Only one example, **68**, of an N-BCl₃ adduct is known. It is not very stable and decomposes on vacuum evaporation of solvent <1999EJI2063>.



BCl₃ adducts are less stable than those with at least one B-H bond, due to stabilization resulting from interaction between the hydrides on boron and protons on carbon <1999EJI2063>. The conformation of 3,5-bis(borane)-3,5-dimethyl-1-thia-3,5-diazacyclohexane **45** has been determined by X-ray diffraction studies. The conformation is fixed at room temperature in solution and a dipolar interaction between the hydridic B-H and protic C-H has been used to explain the frozen conformation <1999EJI2069>. 1,3,5-Oxa and thiadiazines are in a ring conformational equilibrium with fast nitrogen inversion. In the preferred chair conformation, the smallest N-substituent is in the axial position. Energy associated with the N-atom inversion process (~15 kJ mol⁻¹) is less than that for ring inversion (45.1 kJ mol⁻¹). The effect of the nature of the heteroatoms on the energy barrier for ring inversion using variable-temperature PMR and ¹³C NMR experiments has been reported <1999H(51)2079>. Data indicate that 1,3-oxadiazine **40b** and thiadiazines **41a-c** have similar values, suggesting that the nature of the heteroatom does not have a profound effect on the inversion mechanism <1999H(51)2079>. The conformations of 1-oxa-3,5-diazacyclohexane **13**, 3-methyl-1-oxa-3,5-diazacyclohexane **14**, and 3,5-dimethyl-1-oxa-3,5-diazacyclohexane **15** were studied <1997JOC6144>. Both PMR and ¹³C NMR spectra have proved that the most stable conformer of **14** has the *N*-methyl group in the axial position. *Ab initio* calculations have shown that the axial preferences of the R-N-C-O unit are due to hyperconjugation, this contribution being more important than steric effects. N-Methylation reduces the preference for the axial forms by 3–3.5 kcal mol⁻¹ due to increased delocalization in the equatorial forms. The *N,N*-dimethyl derivative **15** contains one axial and one equatorial methyl group. The influence of water on conformational stability has been investigated <1997JOC6144>.

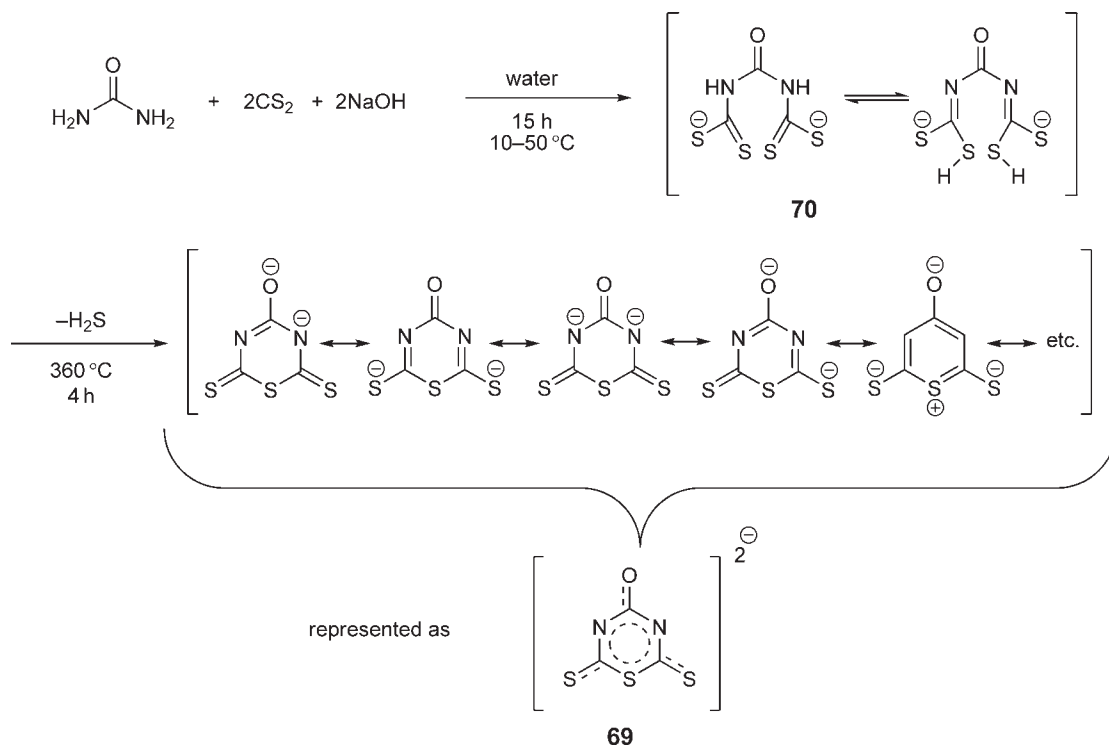
9.09.4.3 Tautomerism

The imidazothiadiazine-2,4-dithione **54** can exist in three possible tautomeric forms: **54**, **54a**, and **54b**. *Ab initio* computations have shown that tautomer **54** is the most stable among the three tautomers. It is favored over **54a** by 0.6 kcal mol⁻¹ while **54b** is disfavored by 12.9 kcal mol⁻¹. Due to the small energy difference between **54** and **54a**, it is presumed that both tautomers may occur in solution. Based on calculated dipole moments, **54** (9.2 D) is predicted to predominate over **54a** (4.7 D) in polar solvents (Scheme 6) <2003JOC4791>.



Scheme 6

A novel disodium salt of bisdithiocarbamate of urea **69** and its Cu(II) complex have been prepared and characterized. Thermal decomposition of **70** at 360 °C afforded **69** as a white crystalline residue, which was hygroscopic, water soluble, and still had good complexing ability for various metal ions. This material was found to be stable up to 800 °C, with the stability being attributed to the existence of several possible resonating structures (see Scheme 7) <2004MI139>.



Scheme 7

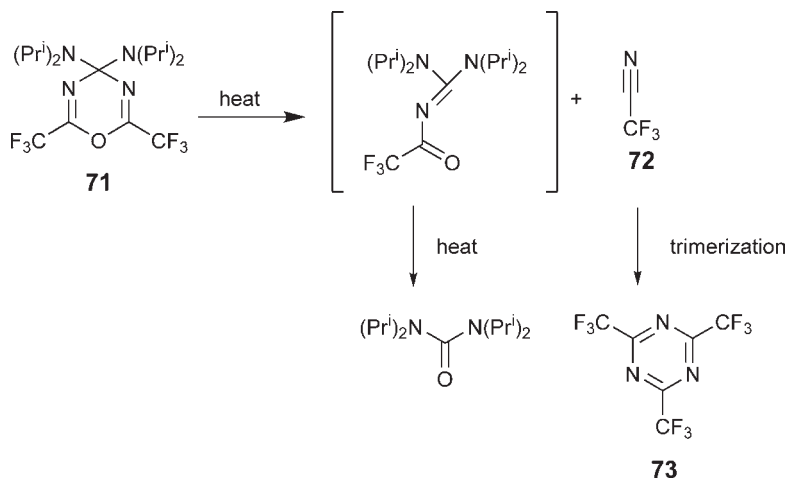
The MS and IR data are consistent with the proposed structures <2004MI139>. X-Ray analysis of the spiro thiadiazine **33b** reveals that the compound exists in the solid state as a ring tautomer with the 1,3,5-thiadiazine ring adopting a boat conformation. The spiro carbon atom of the crystalline species has the (*R*)-configuration. Theoretical

calculations on both diastereomers indicate an energetic preference of $0.44 \text{ kcal mol}^{-1}$ in favor of the observed (*R,R*)-diastereomer over the (*R,S*)-diastereomer. Equilibration of these diastereomers in solution probably takes place via an open-chain intermediate (see [Scheme 4](#) <2001EJO83>).

9.09.5 Reactivity of Fully Conjugated Rings

9.09.5.1 Thermal and Photochemical Unimolecular Reactions

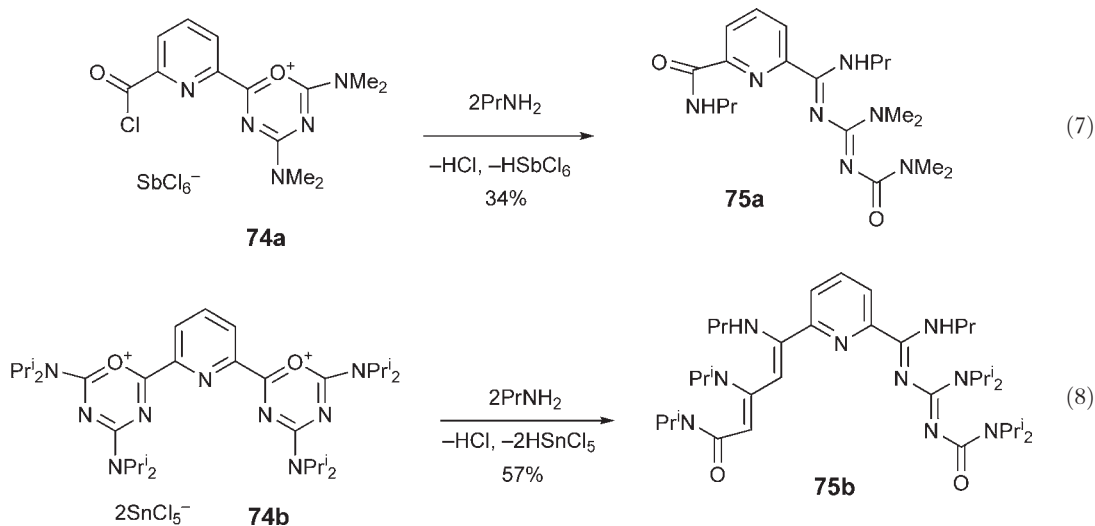
Thermal and photochemical reactions of 1,3,5-oxa and thiadiazines are uncommon; however, the thermolysis of 4,4-bis(diisopropylamino)-2,6-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine **71** has been reported ([Scheme 8](#) <1997JOC9070>). Compound **71** dissociates to tetraisopropylurea and trifluoroacetonitrile **72**, which trimerizes to give 2,4,6-tris-(trifluoromethyl)-1,3,5-triazine **73**. Monomeric **72** is never detected.

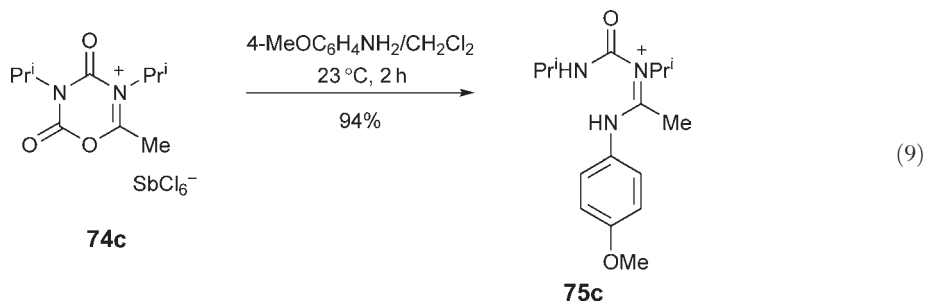


Scheme 8

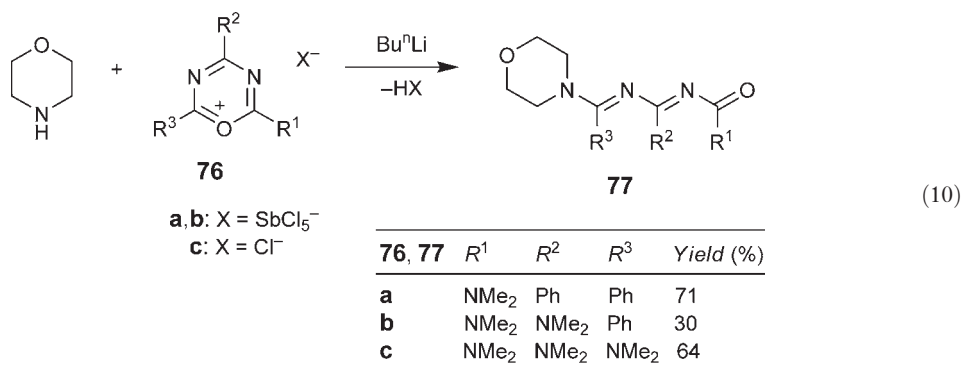
9.09.5.2 Reactions with Oxygen, Nitrogen, and Sulfur Nucleophiles

1,3,5-Oxadiazinium and 1,3,5-thiadiazinium salts are very susceptible to nucleophilic attack, giving a wide variety of products. The attack generally takes place at the C-2 and C-6 positions. Ring-opening reactions of 1,3,5-oxa- and thiadiazinium salts present a general and convenient access to oligonitriles. Thus, 1-oxa-3,5-diazinium salts **74** react with primary amines to give oligonitriles **75**, in modest to excellent yields ([Equations 7–9](#) <2005EJO3891, 1995JPR385>).

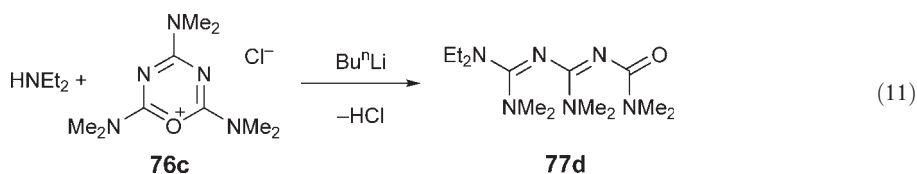




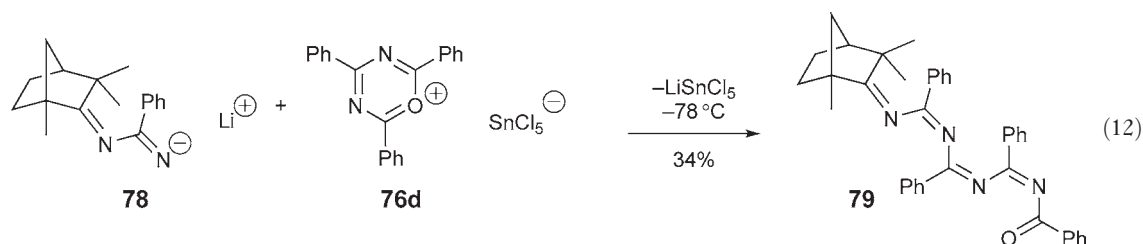
Secondary amines, likewise, open 1,3,5-oxadiazinium rings (Equations 10 and 11) <2003EJO1198>. The reactions are run in the presence of 1 equiv of *n*-butyllithium to increase the nucleophilicity of the secondary amines. In the case of **76a** and **76b**, nucleophilic attack generally takes place at the C-2/C-6 position, whichever does not carry the dimethylamino group. However, compound **76c**, with three dimethylamino groups, furnishes compound **77c** in 64% yield (Equation 10) <2003EJO1198>.



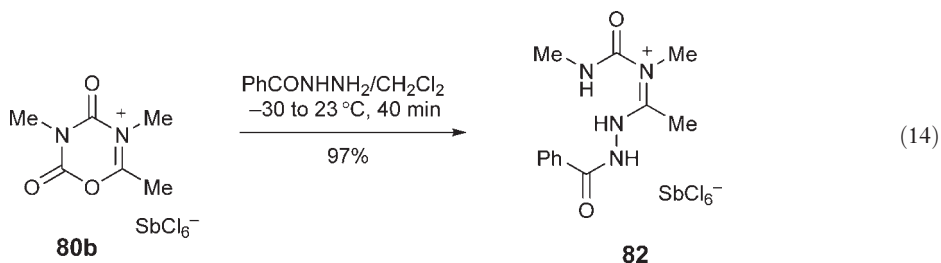
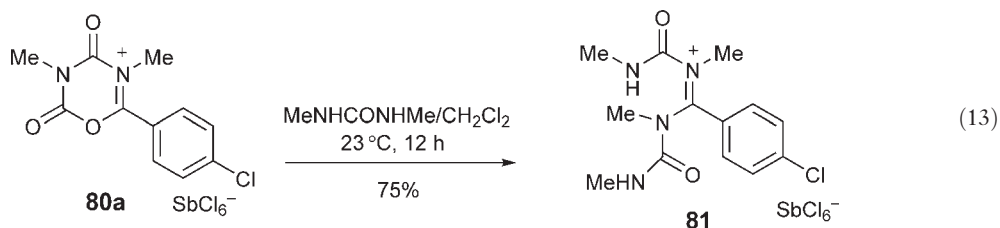
The *N*-acyldialkylcyanamide dimer **77d** is obtained in 50% yield as a result of addition of diethylamine to **76c** (Equation 11).



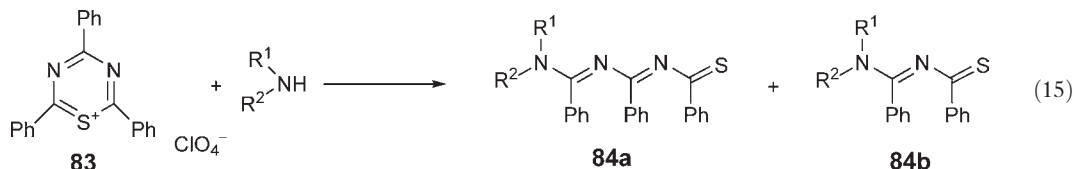
Lithiated 1,3-diazabutadiene **78** is known to react with 1,3,5-oxadiazinium salt **76d** to furnish the oligonitrile **79** (Equation 12) <1994AGE2337>.



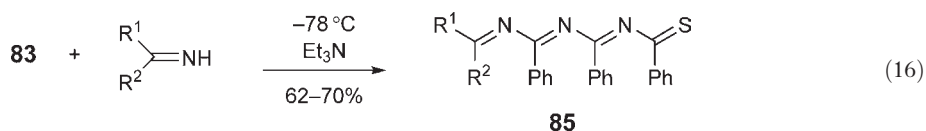
With 1,3-dimethylurea, the oxadiazinium salt **80a** affords the diacylated amidinium salt, **81** (Equation 13), while with **80b** and benzohydrazide, amidrazonium salt **82** is formed (Equation 14) <1995JPR385>.



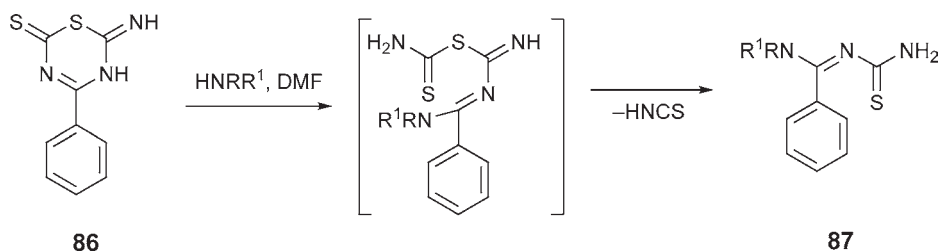
Secondary amines react with thiadiazinium salt **83** to furnish 1-thioacyl-substituted oligonitriles **84a** and **84b** (67–92%). At -78°C , the major product isolated is **84a**, while at 40°C , the product is primarily **84b** (Equation 15) <1997TL5481>.



Similarly, imines react with diazinium salt **83** to furnish the corresponding chain-elongated products **85** bearing an imine function in the ω -position (Equation 16) <1997TL5481>.

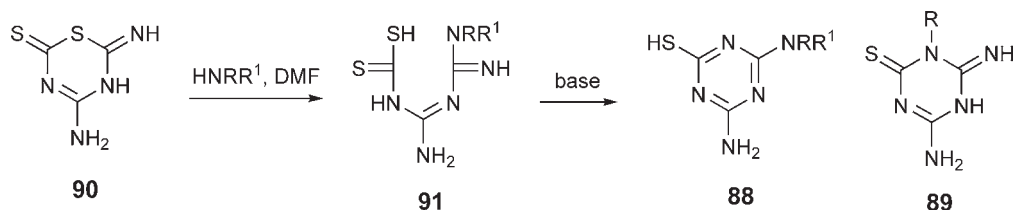


Reaction of thiadiazine **86** with primary or secondary amines in DMF proceeds smoothly to give N^1 -substituted N^2 -thiocarbamoylbenzamides **87**. It has been found that the amidino group of **86** is the most reactive site and nucleophiles attack the 4-position of the 1,3,5-thiadiazine ring (Scheme 9) <2000NKK859>.



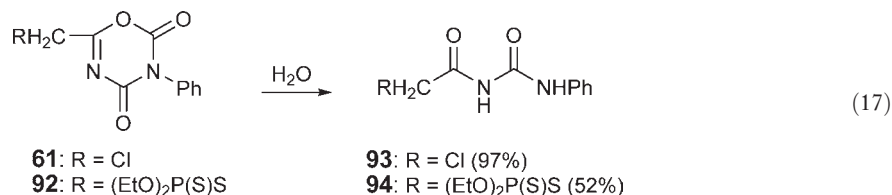
Scheme 9

When the phenyl ring in thiadiazine **86** is replaced with an NH_2 group (as in **90**), the product of reaction with a secondary amine is **88**. However, if the ring is attacked by a primary amine, the product is found to be **89** (Scheme 10) <2000NKK859>.

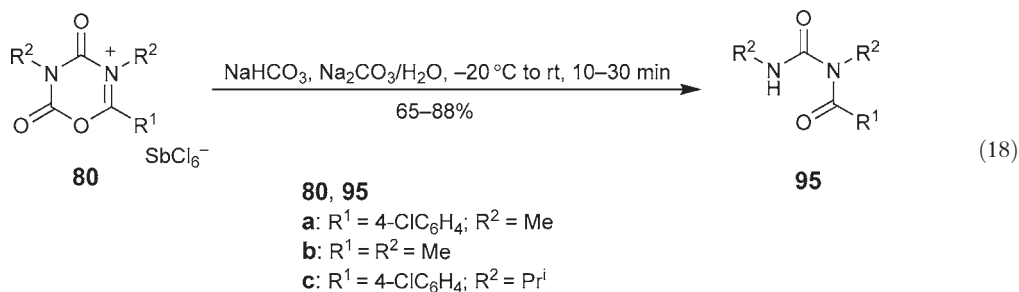


Scheme 10

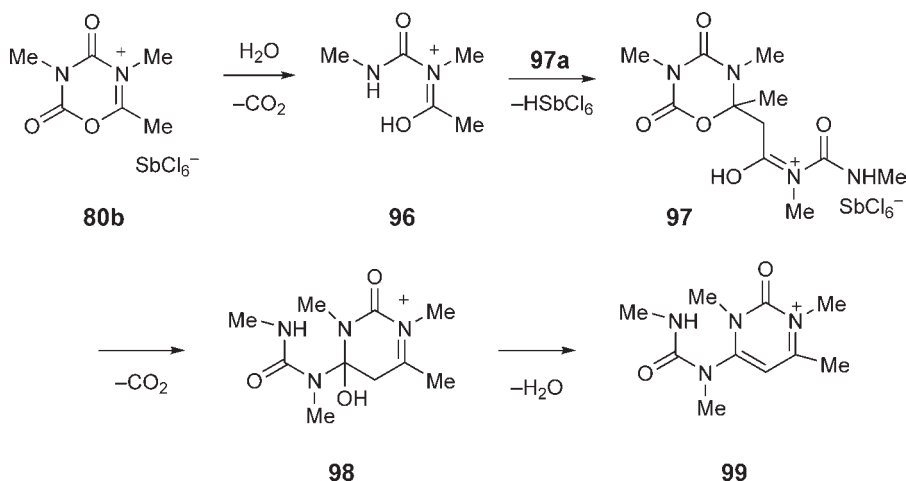
Oxadiazines **61** and **92** are very unstable in the presence of water, the main products of decomposition being the corresponding acylureas **93** and **94** resulting from the hydrolysis of the heterocyclic unit (Equation 17) <1996SC783>.



Hydrolysis of compounds **80** in the presence of base afforded the acyl ureas **95** (Equation 18) <1995JPR385>.

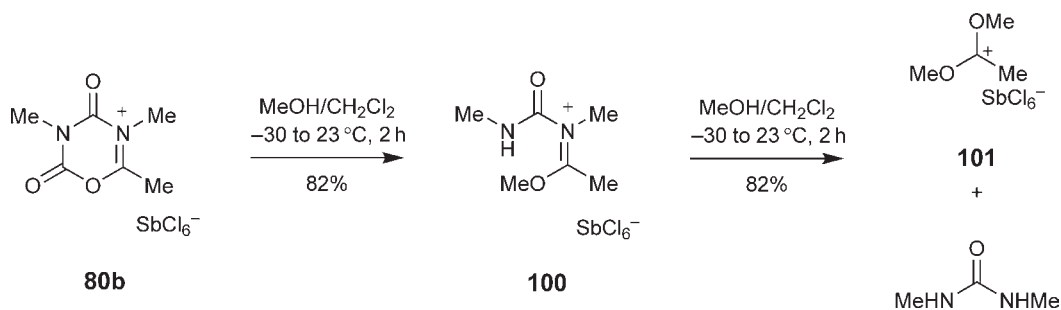


No reaction occurred between **80b** and DMF or dimethyl cyanamide; however, a water-catalyzed decomposition of **80b** was found to occur, resulting in the pyrimidinium salt, **99** (Scheme 11) <1995JPR385>.



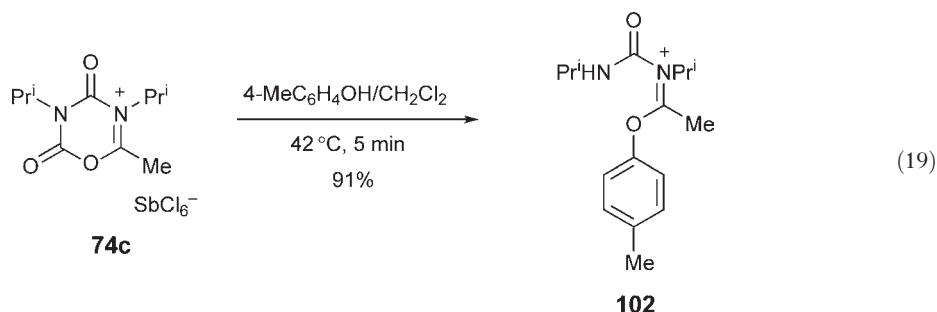
Scheme 11

With 1 equiv of methanol, compound **80b** gives the *N*-acyliminium salt **100**. With 2 equiv of methanol, the carbenium salt **101** is formed (Scheme 12) <1995JPR385>.

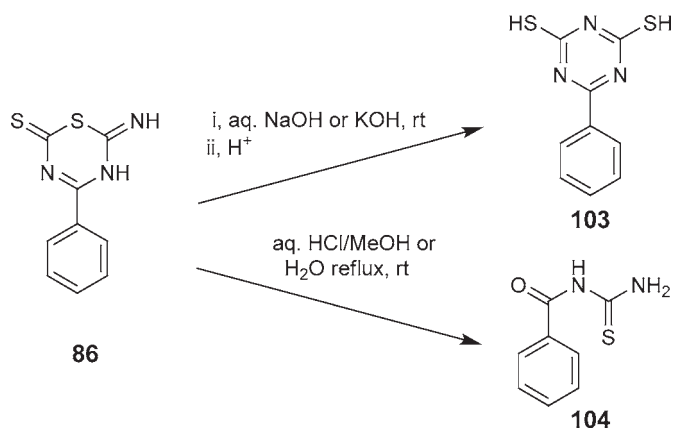


Scheme 12

With *p*-cresol, the oxadiazinium salt **74c** yields the *N*-acyliminium salt **102** (Equation 19) <1995JPR385>.



Treatment of 6-amino-4-phenyl-2*H*-1,3,5-thiadiazine-2-thione **86** with aqueous NaOH or KOH, at room temperature, furnishes the 1,3,5-triazine **103**, while reaction with aqueous HCl in methanol or reflux with water yields the *N*-benzoylthiourea derivative **104** (Scheme 13) <2000NKK859>.

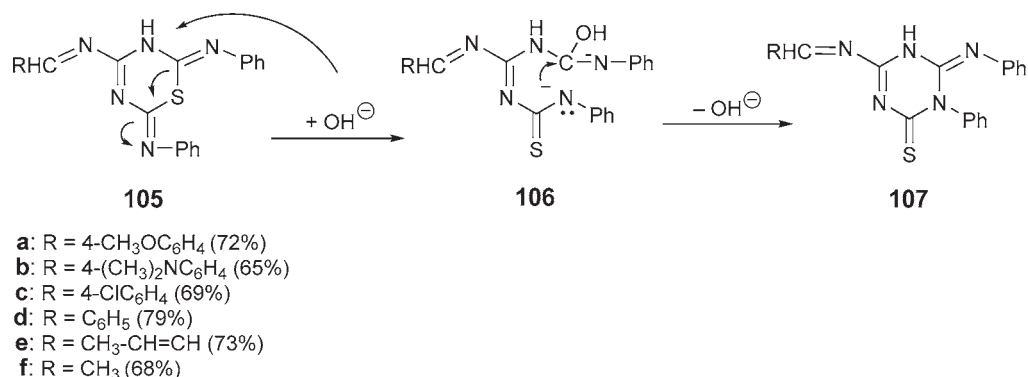


Scheme 13

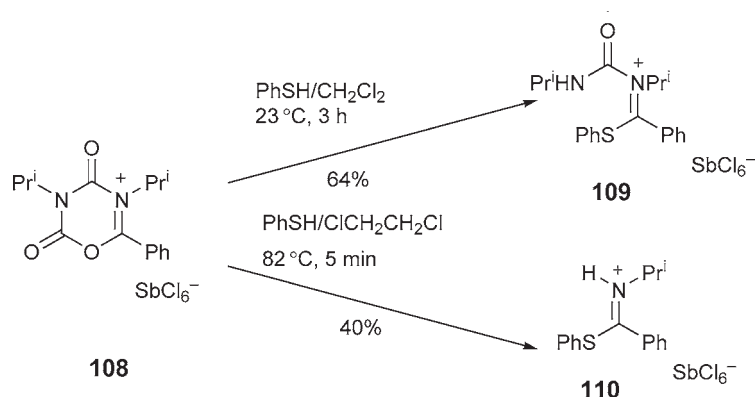
The thiadiazines **105**, on boiling with aqueous ethanolic (1:1) sodium hydroxide solution, are found to isomerize into the corresponding 1-phenyl-2-phenylamino-4-(substituted) benzyldene amino-6-thio-1,3,5-triazines, **107** (Scheme 14) <2005IJB638>.

Reaction of **108** with thiophenol at low temperature affords the thio-substituted *N*-acyliminium salt **109**, while in refluxing 1,2-dichloroethane the iminium salt **110** is formed (Scheme 15) <1995JPR385>.

No reactions of oxa- or thiadiazines with carbon or phosphorus nucleophiles or with electrophiles at nitrogen were reported during the time period of this review.



Scheme 14



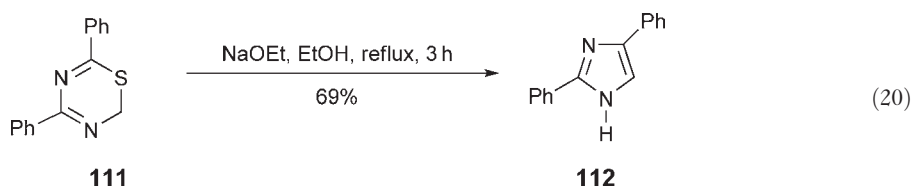
Scheme 15

9.09.6 Reactivity of Nonconjugated Rings

9.09.6.1 Thermal and Photochemical Unimolecular Reactions

Heating of substituted 2*H*-1,3,5-thiadiazines with ethanolic sodium hydroxide has been found to cause sulfur extrusion and ring contraction to 2,4-disubstituted imidazoles.

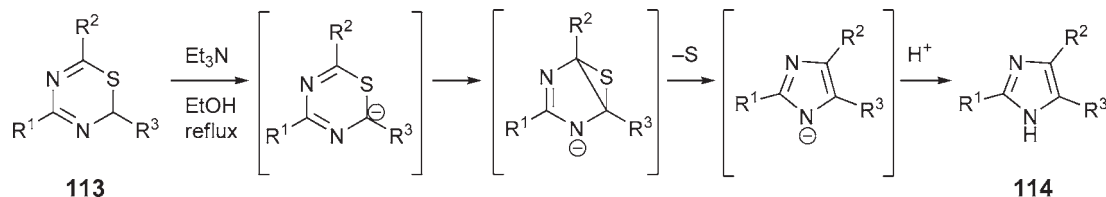
Thus, 4,6-diphenyl-2*H*-1,3,5-thiadiazine **111**, on treatment with ethanolic sodium ethoxide under reflux, is found to yield 2,4-diphenyl-1*H*-imidazole **112** in 69% yield as a result of sulfur extrusion and ring contraction (Equation 20) <1999J(P1)1709>.



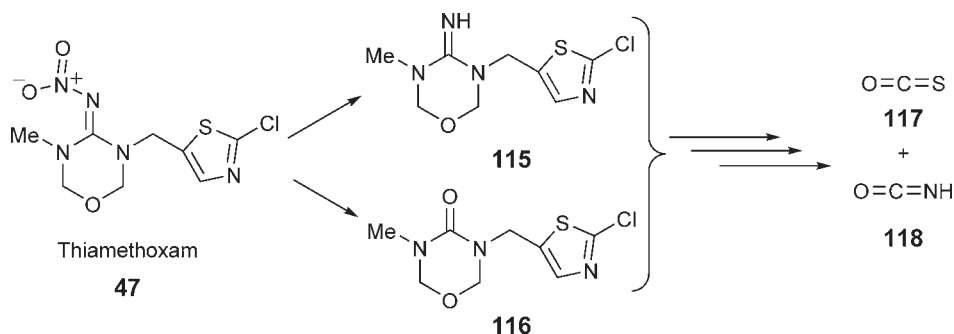
The mechanism for the conversion of thiadiazine **113** to **114** is similar to that reported previously (Scheme 16) <1977JOC3480>.

Aqueous photolysis of thiamethoxam **47** has been investigated (Scheme 17) <2000JFA4671>. The study showed that the by-products of the irradiation, on a 12 hours-on and 12 hours-off light cycle, are volatile products, which are trapped by cyclohexylamine. These fractions, trapped as thiocarbamate and isocyanic acid derivatives, have been

shown to be carbonyl sulfide **117** and isocyanic acid **118** as revealed by MS data. Further, the study indicated that thiamethoxam degrades significantly under photolytic conditions (Scheme 17) <2000JFA4671>.



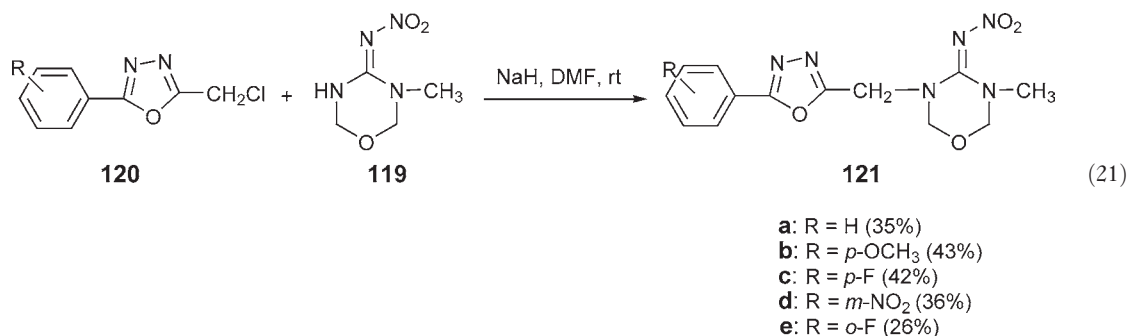
Scheme 16



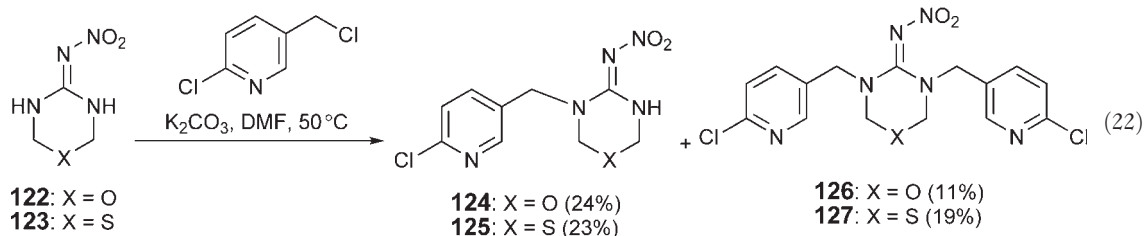
Scheme 17

9.09.6.2 Electrophilic Attack at Sulfur, Nitrogen, or Oxygen

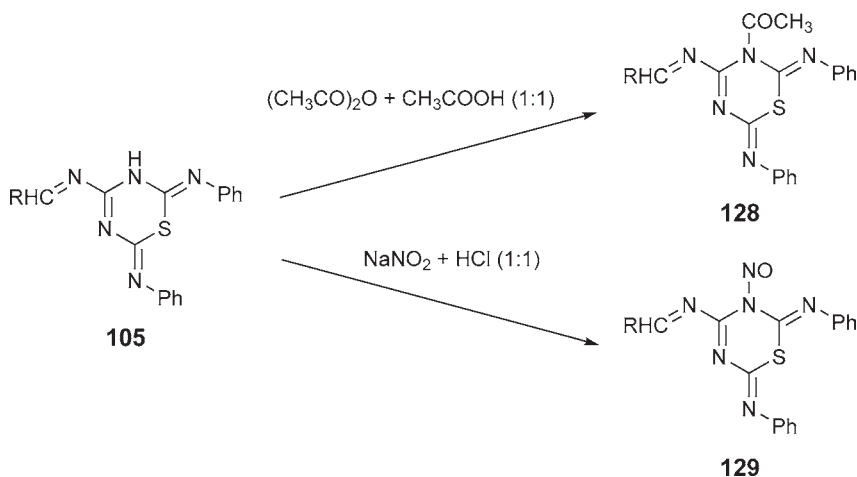
The reaction of 3,5-dimethyl-1-thia-3,5-diazacyclohexane **41c** with 1 or 2 equiv of $\text{BH}_3 \cdot \text{THF}$ initially gives the monoadduct **63**, which further disproportionates to the bis-adduct **45** as shown by their NMR spectra. In both adducts, the N-BH₃ groups are in the equatorial positions, as indicated by the ¹³C NMR chemical shifts of the N-CH₃ groups <1999EJI2069>. The nitroimino[1,3,5]oxadiazinane **119** reacts with 2-chloromethyl-5-aryl-1,3,4-oxadiazoles **120** in DMSO in the presence of NaH to give oxadiazine derivatives **121** in 26–43% yield (Equation 21) <2002HCO601>.



4-Nitroimino-1,3,5-oxa- and thiadiazinanes **122** and **123** undergo alkylation with 6-chloropyridin-3-ylmethyl chloride in the presence of potassium carbonate in DMF, resulting in a mixture of mono- and dialkylated oxa- and thiadiazines **124–127** (Equation 22) <2001MI165>.



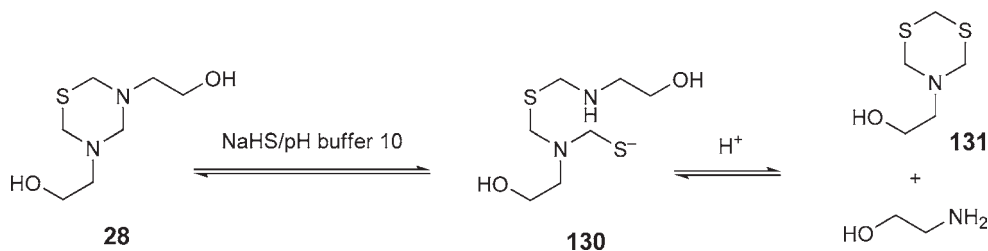
2,6-Diphenylimino-4-(substituted)-benzylideneamino-1,3,5-thiadiazines **105** react with a mixture of acetic anhydride and acetic acid to afford monoacetyl derivatives **128** in 70–80% yield. When **105** is treated with sodium nitrite in an acidic medium, the mono-nitroso derivatives **129** are obtained in 68–80% yield (Scheme 18) <2005IJB638>.



Scheme 18

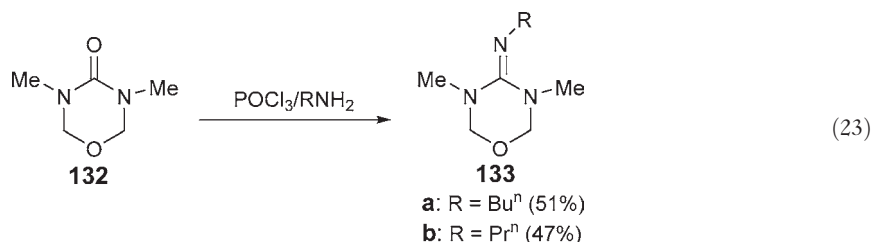
9.09.6.3 Nucleophilic Attack at Carbon

Reaction of thiadiazine **28** with NaHS at pH 10 gave one product **131**, in addition to hydroxyethylamine (Scheme 19). The structure of the product was elucidated by NMR spectroscopy and elemental analysis to be 5-(2-hydroxyethyl)-hexahydro-1,3,5-dithiazine **131**. Compound **131** did not undergo hydrolysis and did not react with $\text{S}^{2-}/\text{HS}^-$ at pH values from 10 to 2 <2001IEC6051>.

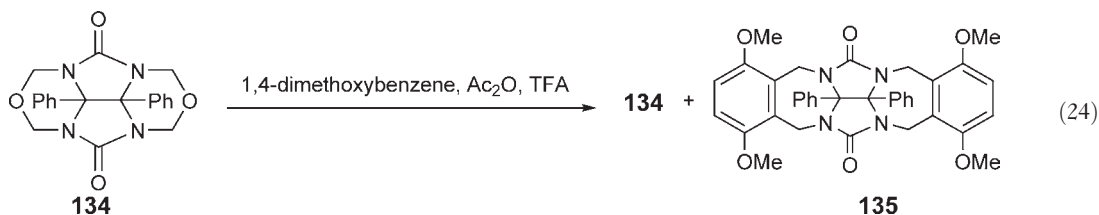


Scheme 19

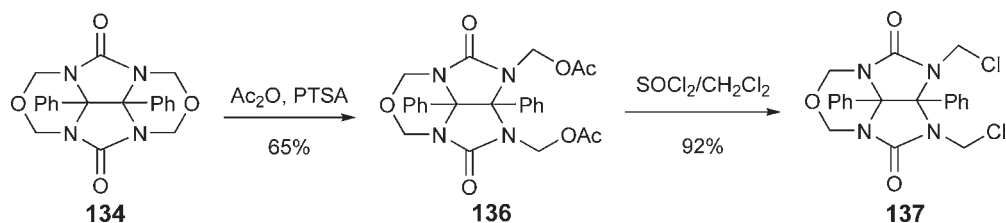
The conversion of tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one **132** into the corresponding imine **133** (**a**: R = Buⁿ; **b**: R = Prⁿ) is accomplished with POCl₃ and a primary amine (Equation 23) <2005IC1704>.



Treatment of cyclic ether **134** with 1 equiv of 1,4-dimethoxybenzene in a mixture of acetic anhydride and trifluoroacetic acid (TFA) under a variety of different conditions is found to result in a 1:1 mixture of **134** and **135** (Equation 24) <1997JOC2234, 1997JA9956>.

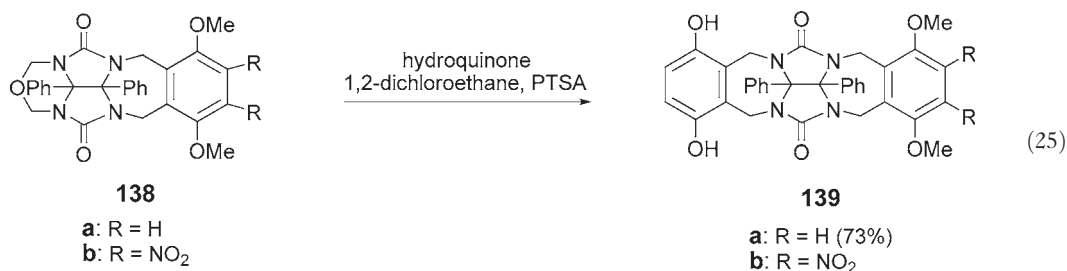


Partial reaction of **134** with acetic anhydride using *p*-toluenesulfonic acid (PTSA) as a catalyst gives a mixture of starting material, **134**, and diacetyl compound **136**. The acetyl compound **136** is separated from the mixture by column chromatography in 65% yield. Treatment of **136** with thionyl chloride in dichloromethane furnishes the dichloro compound **137** in 92% yield (Scheme 20) <1997JOC2234>.

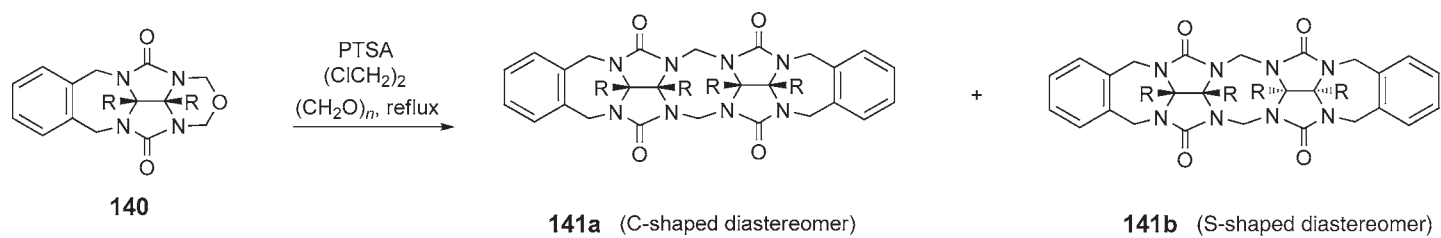


Scheme 20

Heating a mixture of **138** with hydroquinone in 1,2-dichloroethane with PTSA as catalyst yields compound **139** in 73% yield (Equation 25) <1997JOC2234, 1999JOC6653>.



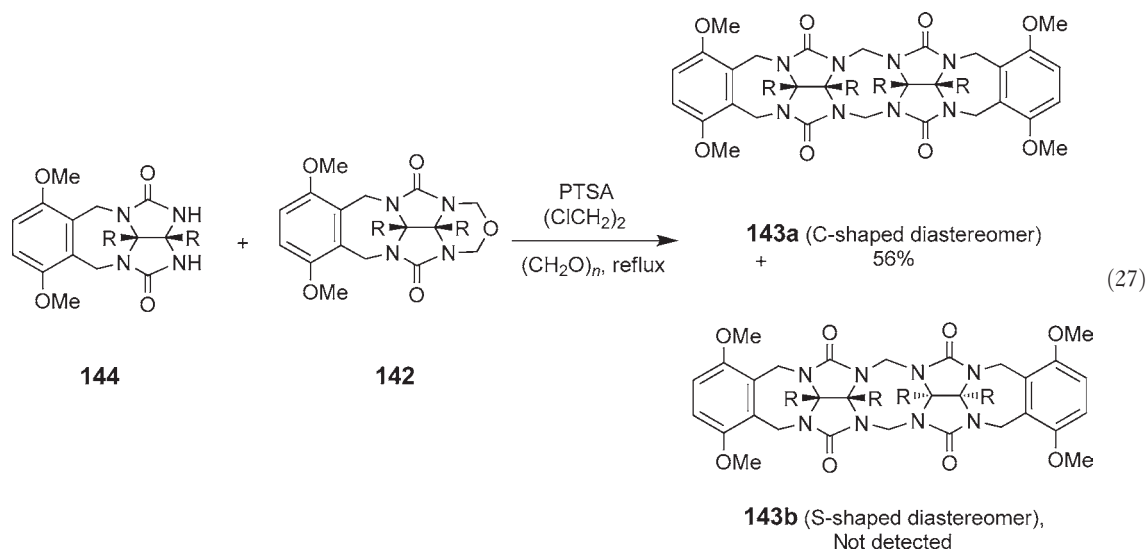
Cyclic ethers such as **140** undergo homodimerization reactions in the presence of PTSA and paraformaldehyde (Equation 26). The reaction yields two sets of diastereomers: one is the C-shaped diastereomer **141a** and other is the S-shaped diastereomer **141b**. Substrates that bear electron-withdrawing carboxylic acid derivatives on their convex face are efficient substrates, yielding only a C-shaped diastereomer in high yield <2002JOC5817>. On the other hand, for substrates where R=Ph, fused cyclohexyl, or 2-pyridyl groups, poor results have been obtained <2002JOC5817, 2000OL755>.



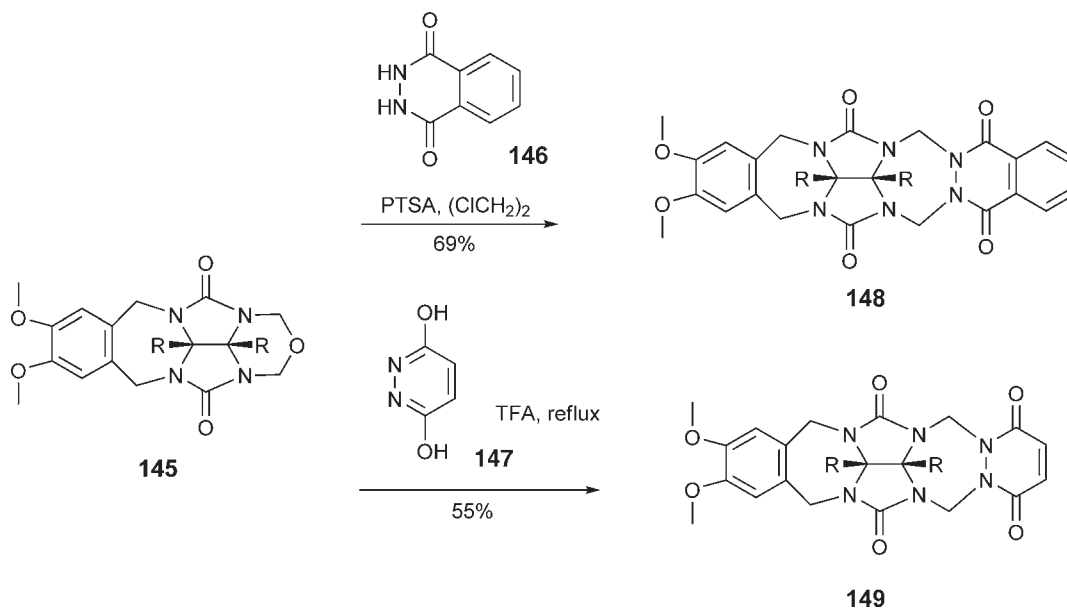
(26)

	<i>C-shaped diastereomer</i>	<i>S-shaped diastereomer</i>
R = COOEt	92%	Not detected
R = CO ₂ Li	85%	Not detected
R = Ph	Not detected	Not detected

Cyclic ethers also undergo heterodimerization reactions with ureidyl NH compounds. As seen with homodimerization, glycouril derivatives bearing electron-withdrawing groups such as ethoxycarbonyl dimerize much more readily than those bearing phenyl or fused cyclohexyl groups. However, there are instances where heterodimerization is preferred to homodimerization. For example, compound **142** did not afford **143a** or **143b** on homodimerization, while heterodimerization of **142** with **144** yields **143a** in 56% yield (Equation 27) <2002JOC5817, 2002JA8297, 2003MOL74>.

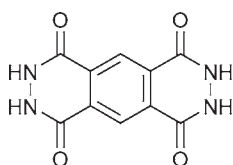
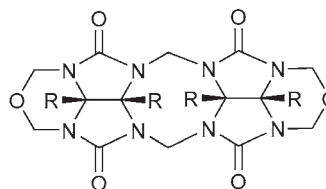


Cyclic ether **145** undergoes highly selective heterodimerization with hydrazides **146** and **147**, as shown in Scheme 21 <2005JOC10381>:

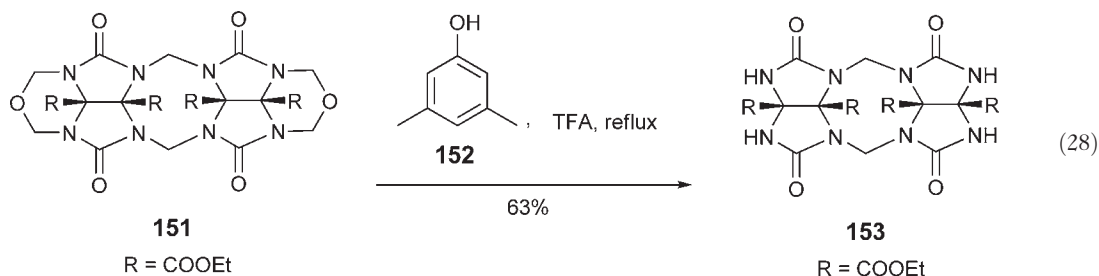


Scheme 21

Similarly, bis(phthalhydrazide) **150** undergoes a smooth reaction with glycouril cyclic ether **151** in hot anhydrous methane sulfonic acid yielding the curcurbit[*n*]uril analog, CB[6], in 78% yield <2003OL3745>.

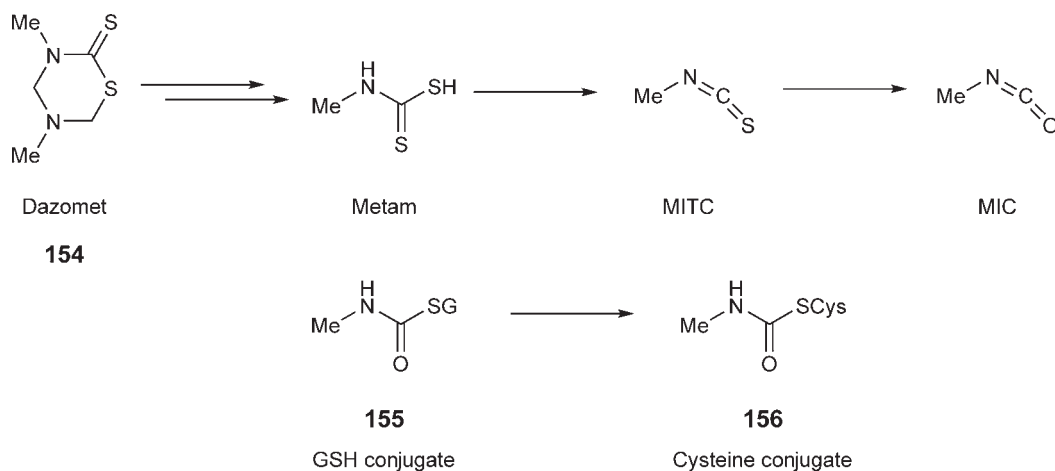
**150****151**R = CO₂Et

Glycouril cyclic ethers **151** undergo a deprotection reaction with 3,5-dimethylphenol **152** in TFA (Equation 28). 3,5-Dimethylphenol was chosen as the reagent for deprotection because the *meta*-positions on the aromatic ring are blocked and hence prevent seven-membered ring formation and promote the removal of methylene bridges <2005JOC10381>.

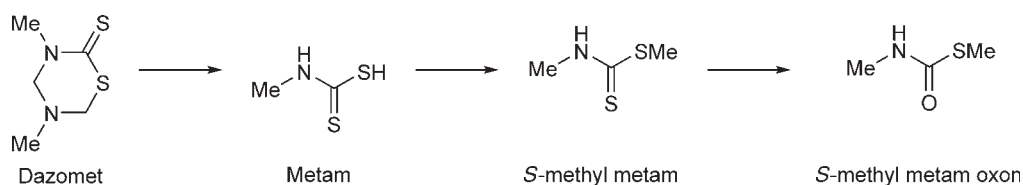


9.09.6.4 Degradation

Dazomet **154** is known as a major soil fumigant <1994JFA2019> with high application rates (~320 lb per acre). Proposed metabolic pathways and mode of action in mice and rats for dazomet have been reported <1995CRT1063>. The molecule is metabolized to a mercapturate, *N*-acyl-*S*-(*N*-methylthiocarbamoyl)cysteine **156** via a GSH conjugate **155** (see Scheme 22).

**Scheme 22**

Alternative paths have also been provided where the bioactivation product is very prone to oxidation, forming sulfenic and sulfinic acids, *S*-methylation, and ultimate metabolism to *S*-methyl metam oxon as a potential aldehyde dehydrogenase (ALDH) inhibitor (Scheme 23) <1995CRT1063>.

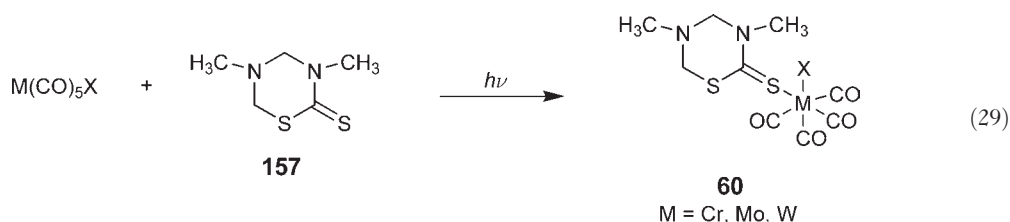


Scheme 23

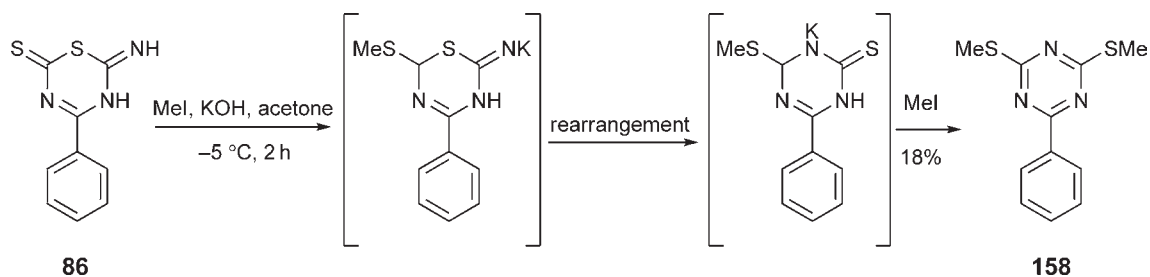
9.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

9.09.7.1 Sulfur-Linked Groups

The syntheses of new metal complexes of DTTF **60** have been reported. They are prepared in 80% yield by the photochemical reactions of metal complexes $M(CO)_6$ ($M = Cr, Mo, W$), $Re(CO)_5Br$, and $Mn(CO)_3Cp$ with DTTF **157** (Equation 29) <2003POL1689>.

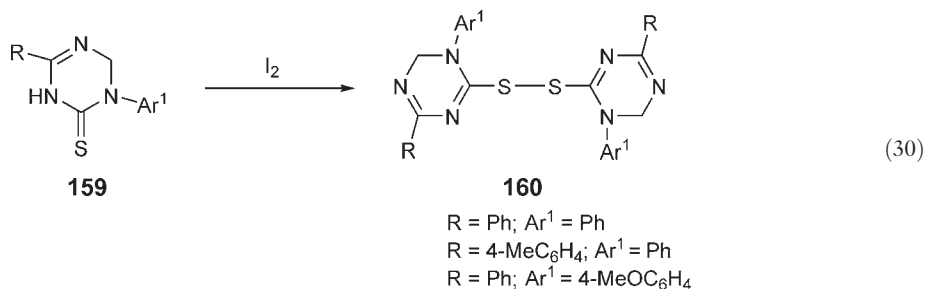


Treatment of the 6-amino-4-phenyl-2*H*-1,3,5-thiadiazine-2-thione **86** with methyl iodide in the presence of base at -5°C gave the 2,4-bis(methylthio)-1,3,5-triazine **158** in low yield (**Scheme 24**) [<2000NKK859>](#).



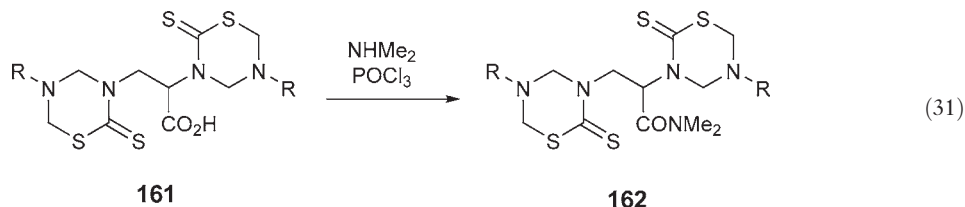
Scheme 24

1,2-Dihydro-1,3,5-triazine derivatives **159** are oxidized with iodine in an alkaline medium to the corresponding disulfides **160** (Equation 30) <1995RJO462>.

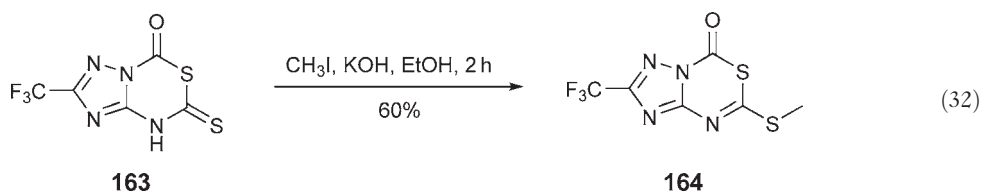


9.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

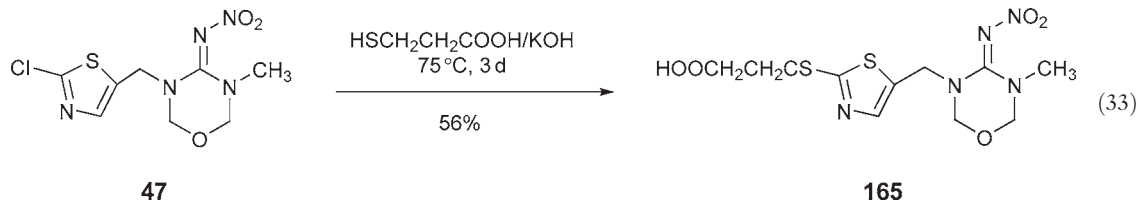
The reaction of 2,3-bis(2-thiono-1,3,5-thiadiazinan-3-yl)propionic acid derivatives **161** with dimethylamine, in the presence of POCl₃, gives the corresponding propionamide derivatives **162** in high yield (Equation 31) <2005MI38>.



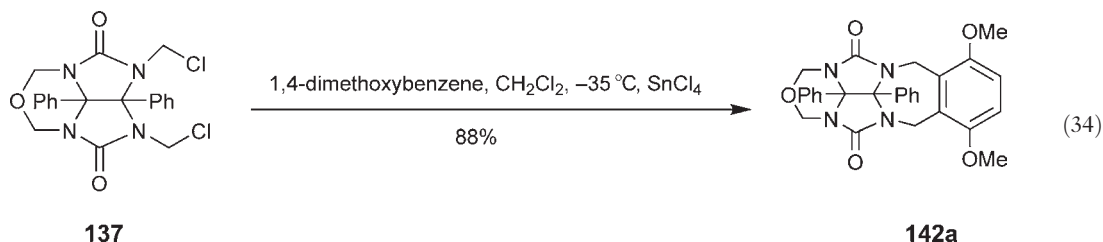
7-Thioxo-2-trifluoromethyl-7,8-dihydro[1,2,4]triazolo[1,5-*c*][1,3,5]thiadiazin-5-one **163** reacts with methyl iodide, in the presence of KOH, to yield the methylthio derivative **164** in 60% yield (Equation 32) <1998JCM536, 1998JCM2126>.



Thiamethoxam **47** reacts with 3-mercaptopropionic acid in DMSO at 75 °C in the presence of 85% KOH for 3 days to give the thiomethaxam hapten, 3-[2-(2-carboxyethylthio)-5-ylmethyl]-5-methyl-4-nitroimino-1,3,5-oxadiazinane **165** in 56% yield (Equation 33) <2003JFA1823>.



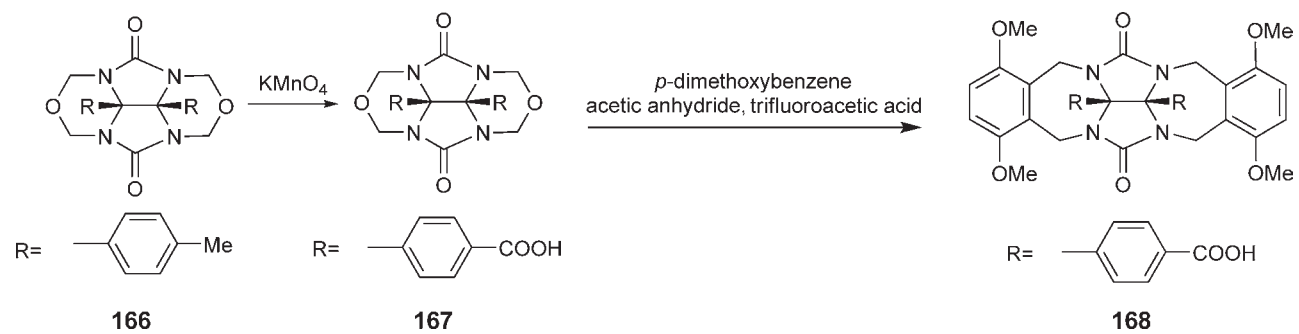
The dichloro compound **137** undergoes Friedel–Crafts alkylation with 1,4-dimethoxybenzene in the presence of a catalytic amount of SnCl₄, to give 88% of **142a** (Equation 34) <1997JOC2234>.



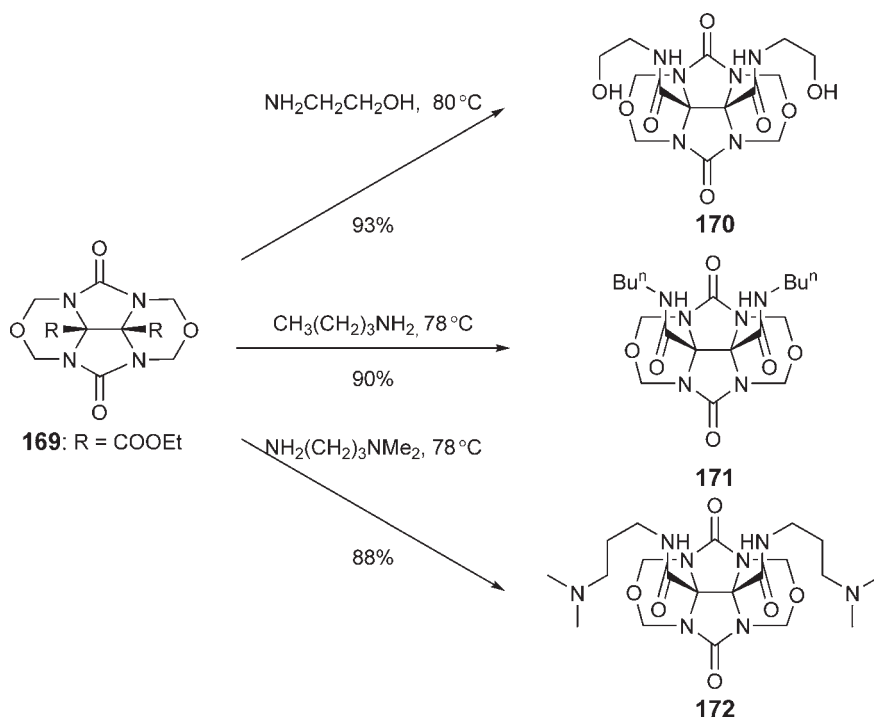
The tolyl group in glycouril cyclic ether **166** is oxidized with KMnO₄ in water to give the dibenzoic acid compound **167**. Ureidoalkylation of **167** with *para*-methoxybenzene affords the dibenzoic acid-functionalized compound **168** in 81% yield (Scheme 25) <2003JOC9040>.

Cyclic ethers such as **169** react with primary amines to give the corresponding amides **170–172** (Scheme 26).

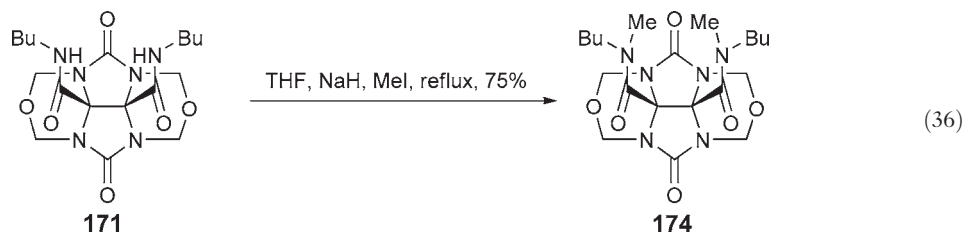
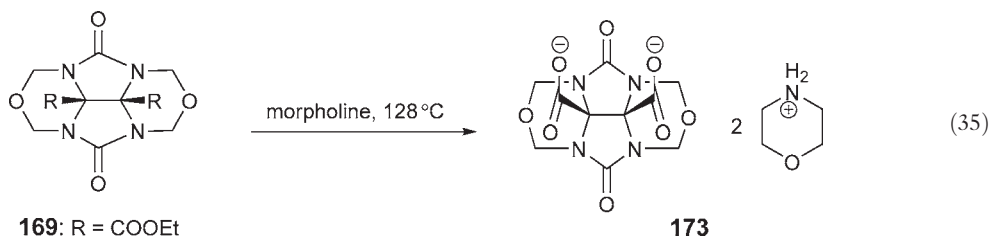
However, treatment of **169** with the secondary amine, morpholine, did not result in the tertiary amide as expected, but yielded the ammonium salt **173** (Equation 35) <2003T1961>. Instead, the desired tertiary amide **174** was obtained in 75% yield by the alkylation of **171** (Equation 36) <2003T1961>.



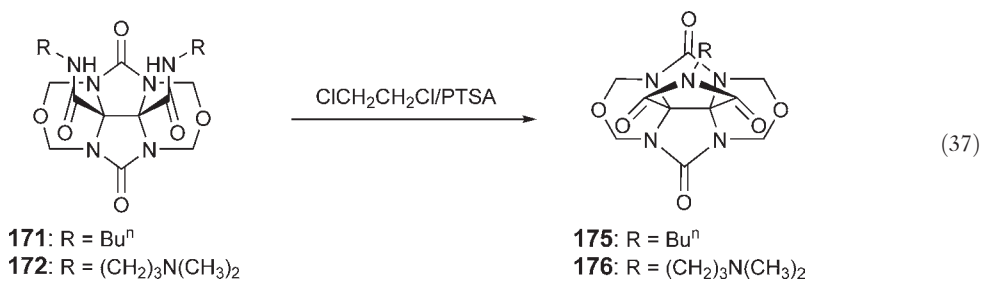
Scheme 25



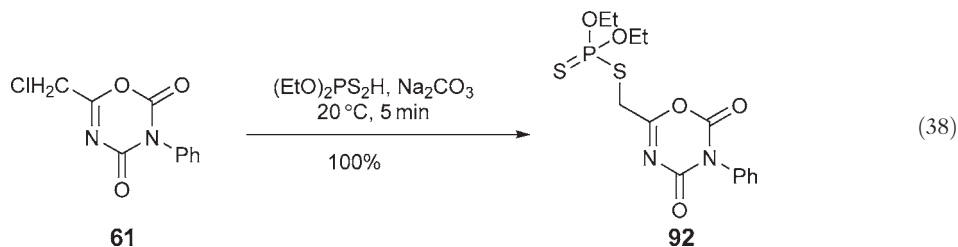
Scheme 26



Conversion of the amides **171** and **172** into the imides **175** and **176** (66% yield) by treatment with PTSA in 1,2-dichloroethane was reported (Equation 37) <2003T1961>.



The water-sensitive 1,3,5-oxadiazine **61** condensed with *O,O*-diethyl dithiophosphate to afford the oxadiazine **92** (Equation 38) <1996SC783>. These oxadiazines are difficult to isolate as they undergo rapid decomposition.



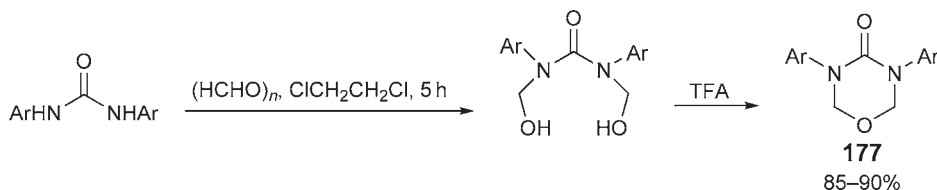
9.09.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

9.09.9.1 Formation of One Bond

9.09.9.1.1 Between carbon and oxygen

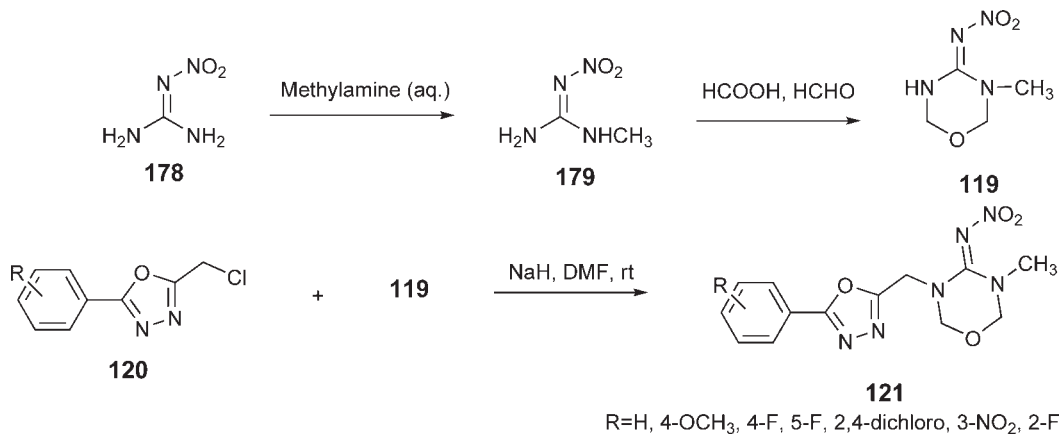
Several cyclization approaches to afford oxadiazine substructures have been reported via a carbon–oxygen bond-formation step. In the examples presented here, at least one sp^2 carbon is present in the ring, which is involved in a double bond in either endo- or exocyclic fashion. Several examples where the oxadiazine moiety is a part of a polycyclic system are presented in this chapter.

Treatment of *N,N'*-diaryl ureas (without activating groups on the aromatic ring), with paraformaldehyde, in 1,2-dichloroethane in the presence of TFA, for 5 h at room temperature furnishes the corresponding 3,5-diaryl-5,6-dihydro-2*H*-1,3,5-oxadiazin-4(3*H*)-ones **177** in 85–90% yields (Scheme 27) <1996SC3217>.



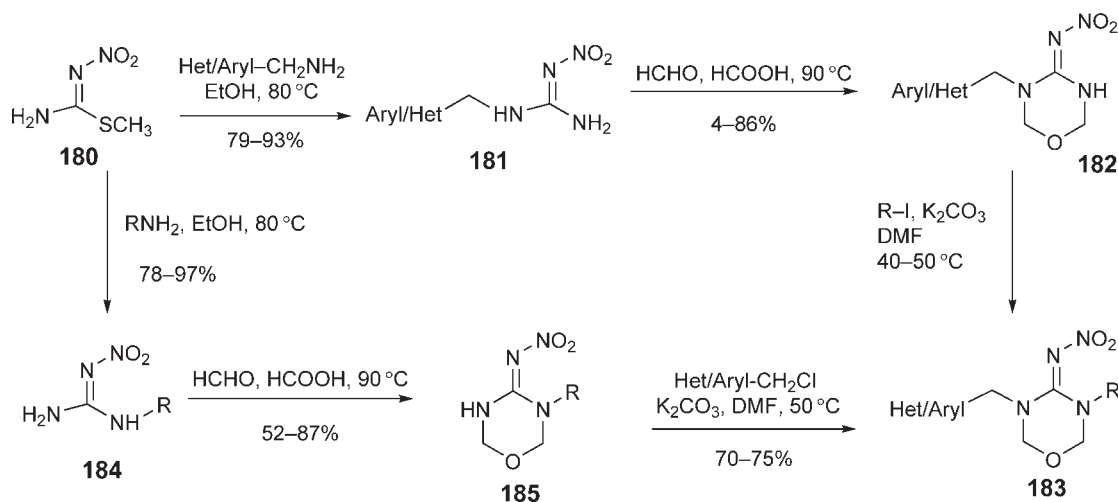
Scheme 27

A similar approach has been utilized for the syntheses of 1,3,4-oxadiazolynitroimino 1,3,5-oxadiazines **121** starting from nitroguanidine **178** (Scheme 28) <2002HCO601>.



Scheme 28

A more general synthetic method has been reported for the preparation of 3-heterocyclylmethyl-5-alkyl-4-nitroimino-1,3,5-oxadiazines **183**, which allows introduction of the heterocyclylmethyl or arylmethyl group, either using a heterocyclylmethyl or arylmethyl amine or a heterocyclylmethyl or arylmethyl chloride (**Scheme 29**) <2001MI165>. Treatment of *S*-methyl-*N*-nitroisothiourea **180** with amines affords *N*-alkyl-*N'*-nitroguanidines **181**, which undergo cyclization to **182** using a 1:1 mixture of formaldehyde and formic acid. Alkylation with alkyl halides gives the 4-nitroimino-1,3,5-oxadiazines **183** in good yields. Alternatively, compounds **183** can be prepared from *N*-alkyl-*N'*-nitroguanidines **184**, which are obtained from *S*-methyl-*N*-nitroisothiourea **180** and alkylamines. The intermediate **184** is cyclized to **185** using formaldehyde and formic acid. All such oxadiazine ring formation reactions are performed with a 1:1 mixture of HCHO and HCOOH at 80 °C and the best yields for the alkylation reactions are obtained using 2.5 equiv of K₂CO₃ as a base, in DMF. In general, the route via **185** more consistently gives higher overall yields of **183**, as opposed to the highly variable yields obtained via **181** (**Scheme 29**) <2001MI165>.



Scheme 29

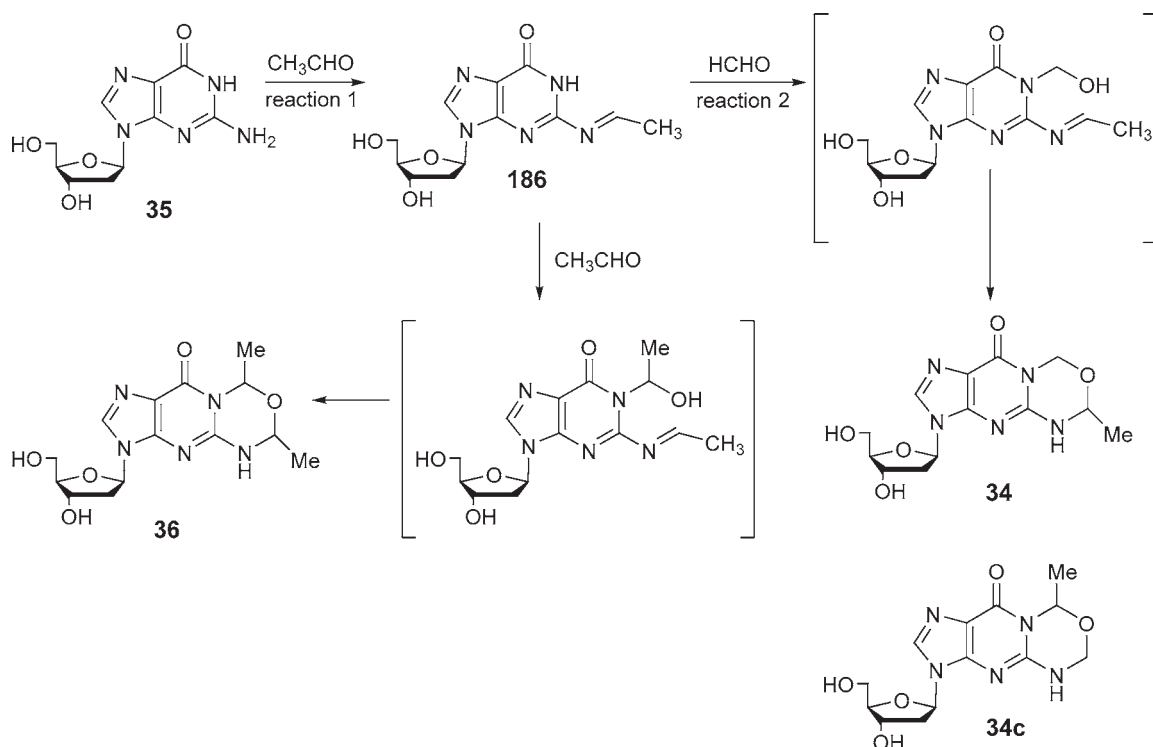
Thiomethaxam hapten, 3-[2-(2-carboxyethylthio)-5-ylmethyl]-5-methyl-4-nitroimino-1,3,5-oxadiazinane **165**, is synthesized in 56% yield by treatment of thiamethoxam **47** with 3-mercaptopropionic acid in DMSO at 75 °C in the presence of 85% KOH (see **Equation 33**) <2003JFA1823>. The reaction of formaldehyde and acetaldehyde with dGuo **35** has been reported <2003CRT145>. Sequential reactions of acetaldehyde, to form the Schiff base **186**, followed by treatment with formaldehyde produced substantial amounts of 6-methyl-1,3,5-diazinan[4,5-a]purin-10(3*H*)-one **34**. A reverse sequence of addition did not give the corresponding cyclized product **34c** but an analogous diastereomeric mixture **36** was formed by reaction of acetaldehyde with dGuo (**Scheme 30**) <2003CRT145>.

Synthesis of 1,3,5-oxadiazines from acyl azides consists of treatment of the acyl azides **187** with urea or thiourea at 170 °C to afford the 1,3,5-oxadiazin-4-ones **188a** and **188b** by diazido displacement with subsequent cyclization (**Scheme 31**) <1998MI91>.

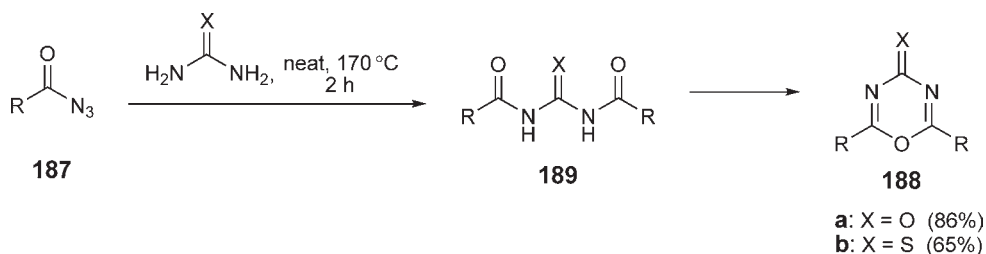
Treatment of *N*-2-benzimidazolylethylimidates **190** with 1 equiv of ethyl chloroformate in the presence of excess triethylamine or pyridine, as shown in **Scheme 32**, affords the corresponding *N*-2-(1-carbethoxy)benzimidazolylimidates **191**. Compounds **191** transform into substituted oxadiazinobenzimidazoles **194** in 55–75% yields, when treated with Grignard reagents <1997SC3039>. If ethyl chloroformate is replaced with an acyl chloride, more variability can be introduced into the oxadiazinobenzimidazole ring system, where the two R² substituents on C-2 are dissimilar.

Cumulenes **195** react readily with 2 equiv of an alkyl or aryl isocyanate to yield nitrilium salts **198**, with either allophanoyl chlorides **199** or carbamoyl chlorides **200** as side products. Allophanoyl chlorides **199**, when treated with antimony pentachloride, cyclize to crystalline oxadiazinium salts **201**, which were found to be unstable (**Scheme 33**) <1995S820>.

1-*H*-Pyrazolo-1-[*N,N'*-bis(*tert*-butoxycarbonyl)amidine] **202** is reported to react with amines and amino acids to give the protected guanidines **203**. With secondary amines also the reaction proceeded smoothly to give the corresponding derivatives of **203**, except for diisopropylamine, in which case the oxadiazine **204** was isolated in 52% yield (**Scheme 34**) <1994S579>.



Scheme 30



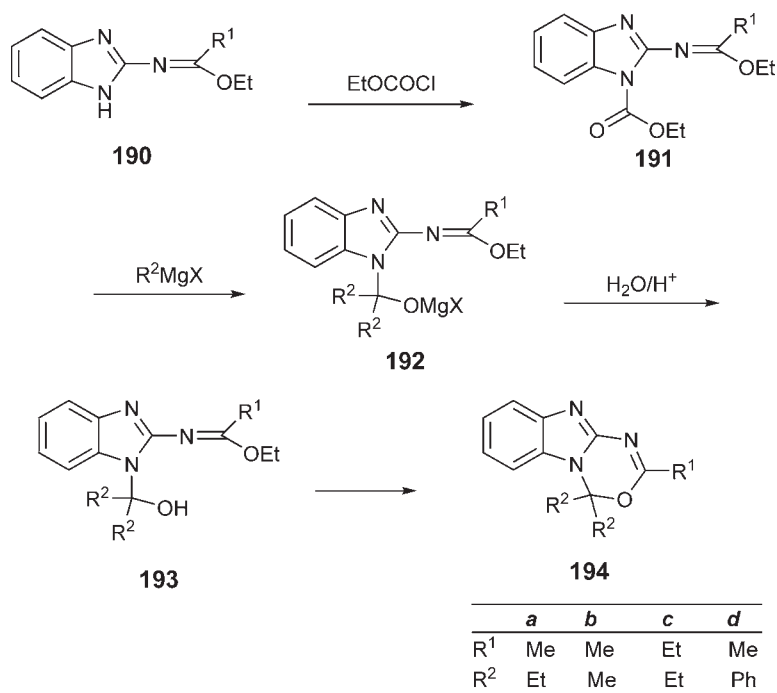
Scheme 31

Two equivalents of 1,1-dimethyl cyanamide add to acetone in the presence of 2 equiv of trifluoromethanesulfonic acid to furnish the oxadiazine **58**, shown in [Scheme 35](#). The proposed mechanism involves initial addition of dimethyl cyanamide to acidified acetone followed by a 1,3-hydroxyl shift and subsequent attack by a second molecule of 1,1-dimethyl cyanamide at the tertiary carbocation. The ultimate cyclization affords the 1,3,5-oxadiazine **58**. X-Ray analysis, discussed in [Section 9.09.3.2 <1996CC1731>](#), confirmed the structure of the obtained product to be that of **58** and not the expected **59**, as depicted in [Scheme 35](#).

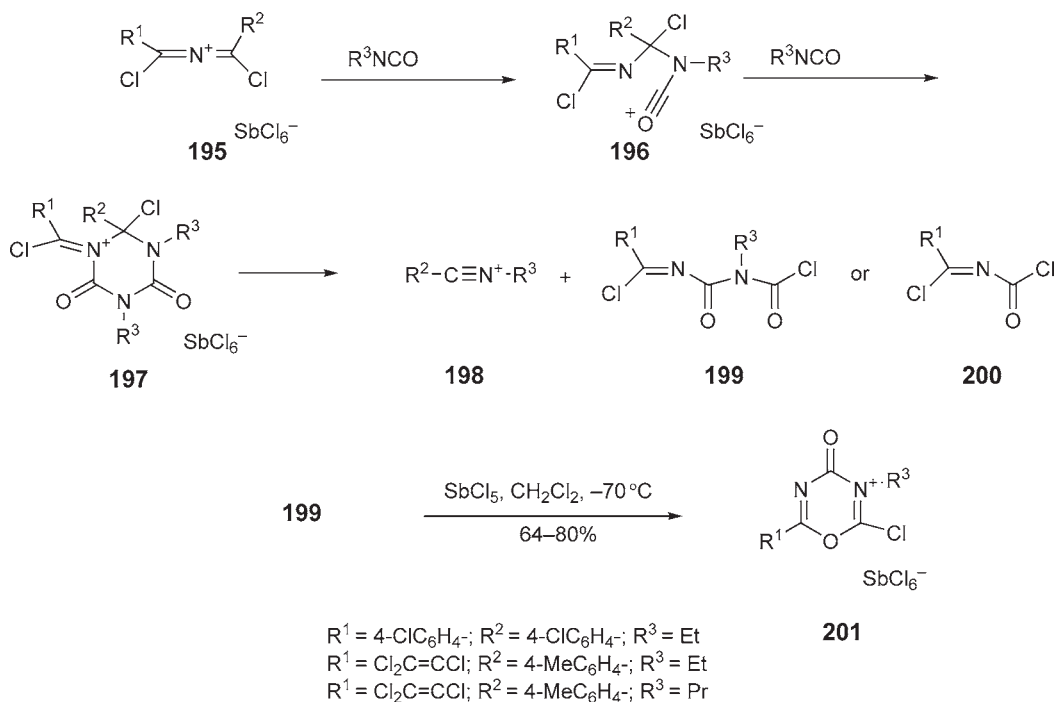
1,3,5-Oxadiazine **209** is formed as a major by-product when a 2,4-dimethoxybenzaldehyde (DMB) derivative of 4-aminobutanal diethylacetal, viz. **210**, is treated with the N,N' -di-BOC-protected compound **211** (BOC = *t*-butoxy-carbonyl; [Equation 39](#) <2002SL2003>).

9.09.9.1.2 Between carbon and sulfur

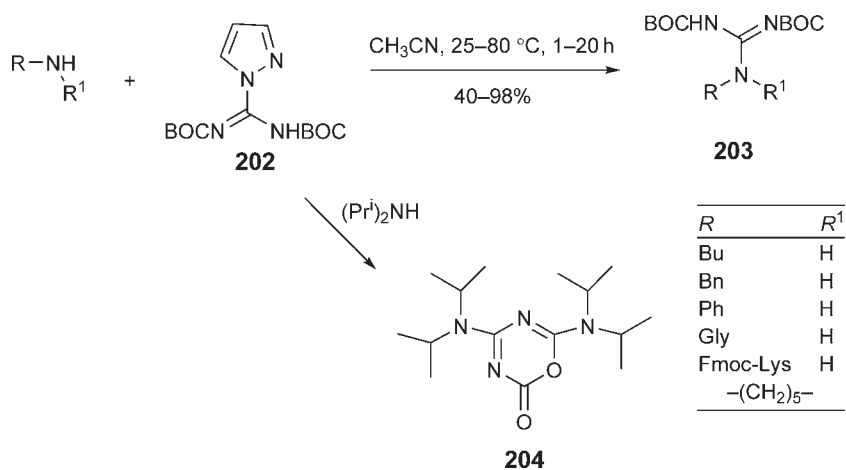
4,5-Dihydroimidazol-2-yl isothiocyanate **212**, formed from 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate **213** ([Scheme 36](#)), reacts further with a second molecule of carbon disulfide to give compound **215**, which after cyclization affords the 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithiane anion **55** ([Scheme 37](#) <2003JOC4791>).



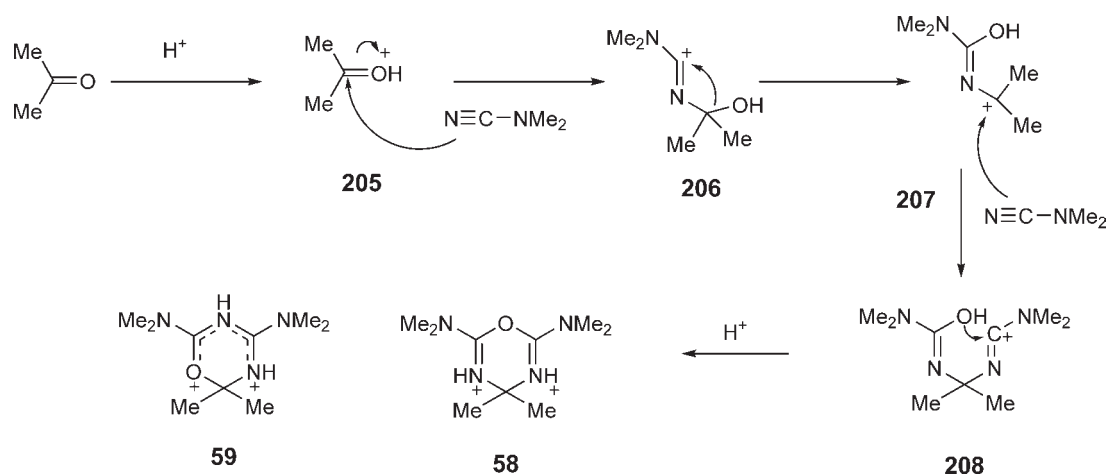
Scheme 32



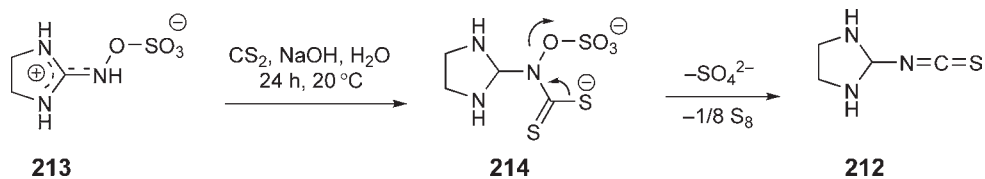
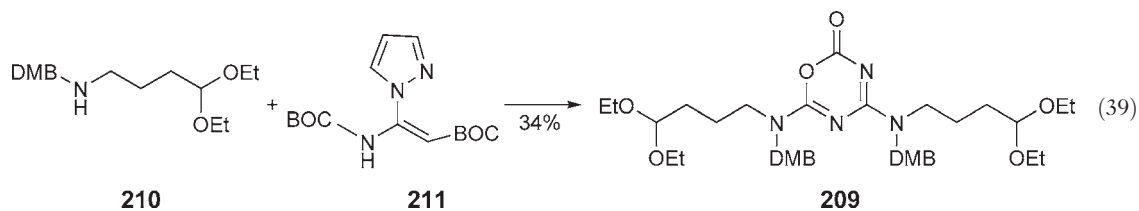
Scheme 33



Scheme 34

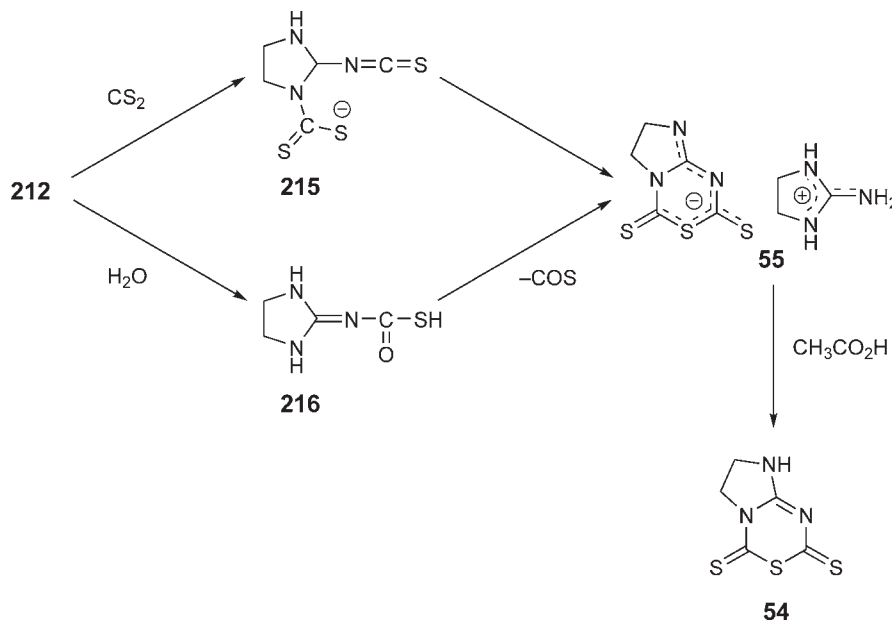


Scheme 35



Scheme 36

The remaining intermediate, 4,5-dihydroimidazol-2-yl isothiocyanate **212**, decomposes hydrolytically to generate the counteraction 2-iminoimidazoline for compound **55** via intermediate **216**. The salt intermediate is isolated and recrystallized before liberating the free form of 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithiane **54** (Scheme 37) <2003JOC4791>.



Scheme 37

Similar to the preparation of some of the oxygen analogs discussed in Section 9.09.9.1.1, thiadiazine **125** is synthesized in low yield starting from *N*-nitroguanidine **217** with formaldehyde and sodium sulfide in the presence of HCl. Alternatively, **125** is synthesized in two steps from **178** via the cyclic intermediate **123**. Alkylation of **123** with 6-chloropyridine-3-ylmethyl chloride gave **125** in 23% yield and the dialkylated thiadiazinane **127** as a by-product in 19% yield (Scheme 38) <2001MI165>.

Treatment of *N*-alkylideneisoureas **218** with chlorothioformate **219** in hexane, in the presence of a base such as *n*-butyllithium or 2,4,6-collidine, furnishes the thiadiazines **33a** and **33b** in 54% and 46% yield, respectively (Scheme 39) <2001EJO83>.

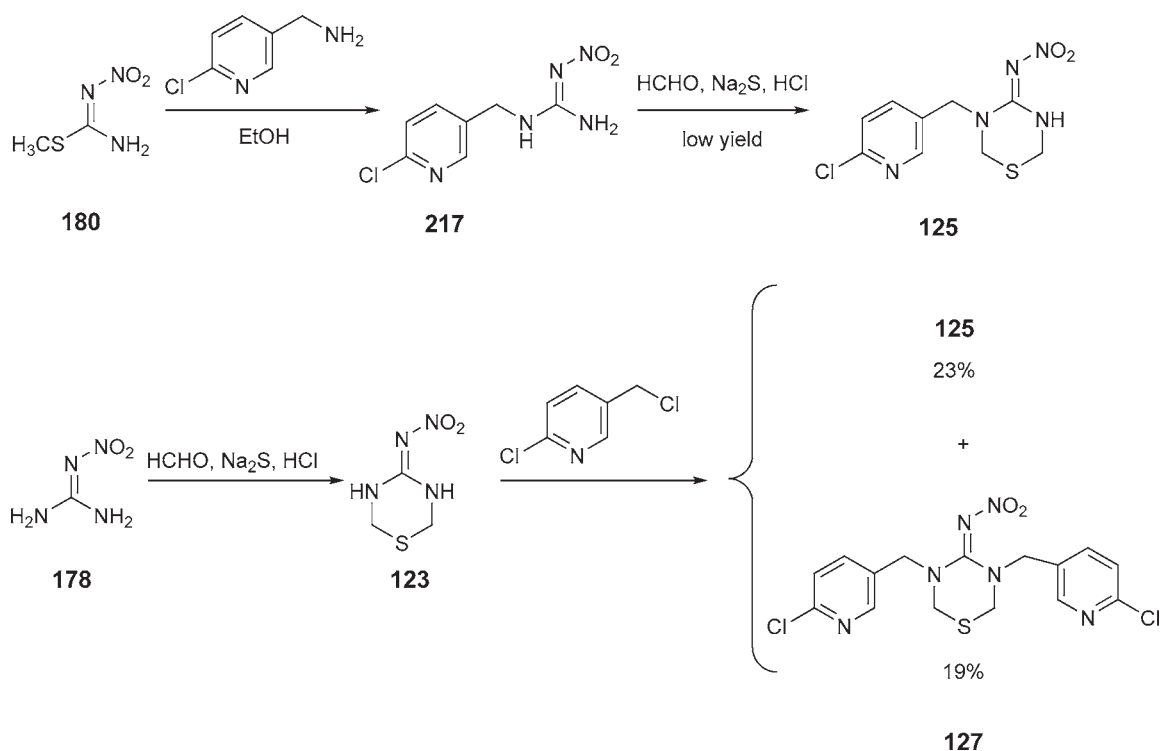
6-Amino-4-aryl-2*H*-1,3,5-thiadiazine-2-thione **86** is prepared from the reaction of *N*-cyanobenzamidine **220** with carbon disulfide in the presence of potassium hydroxide (Scheme 40) <2000NKK859>.

The 1,3,5-thiadiazine **48**, a new thiourea derivative of phenylalanine, is synthesized by the treatment of 3-(chlorophenylmethylene)-1,1-diethylthiourea **223** with DL-phenylalanine methyl ester **224** in acetone in the presence of triethylamine (Scheme 41) <2004AXE713>.

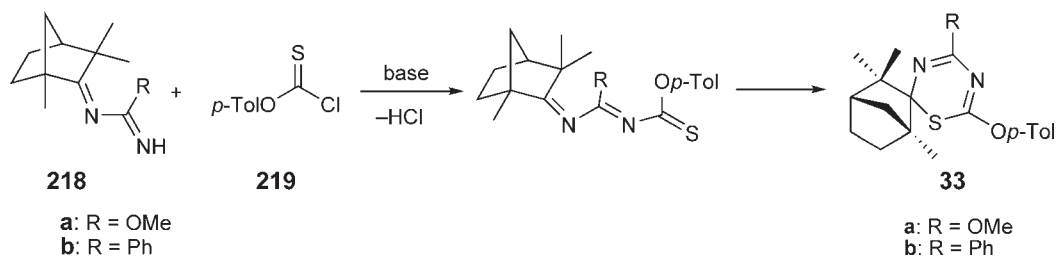
9.09.9.1.3 Between carbon and nitrogen

3-Substituted-6-methyltriazolo[3,4-*b*][1,3,5]thiadiazines **229** are obtained in 18–88% yield by the bis-Mannich reaction of 3-substituted-5-mercapto-1,2,4-triazoles **226** and formaldehyde in the presence of acid (Scheme 42) <1999SC2027, 2001SC2841>. It has been found that the pH of the reaction mixture plays an important role and the optimum pH is in the range 5–6. Addition of a catalytic amount of potassium fluoride to the reaction further enhanced the overall yield <2001JHC929>. Chiral 1,3,5-thiadiazines are obtained when a chiral amine such as *S*(–)- α -phenylethylamine is used.

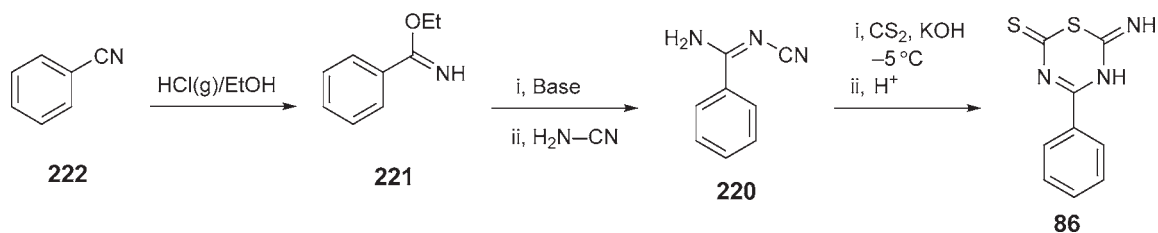
Ethyl 2,3-diaminopropionate **230** is shown to react with 2 equiv of carbon disulfide in the presence of aqueous KOH solution. The corresponding bis(dithiocarbamate) formed is treated with HCl to afford the free bis(dithiocarbamic acid) **231**. Upon addition of 4 equiv of formaldehyde as an aqueous solution, and 2.1 equiv of a primary amine as the HCl salt at ambient temperature, 2,3-bis(5-alkyl-2-thiono-1,3,5-thiadiazine-3-yl)propionic acid derivatives **233** are obtained (Scheme 43) <2005MI38>.



Scheme 38

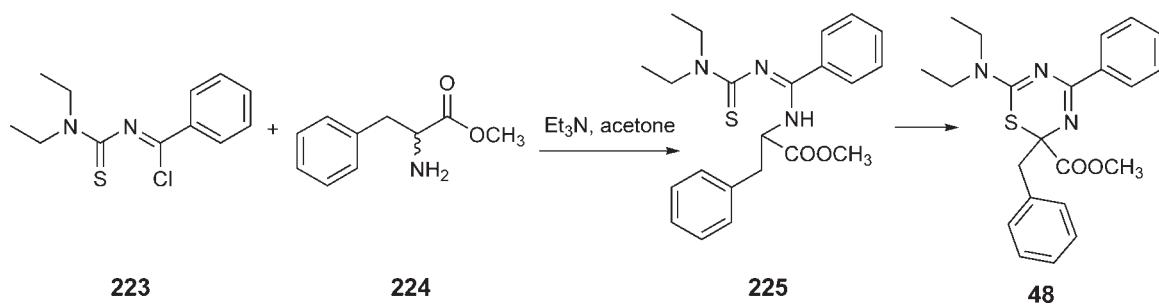


Scheme 39

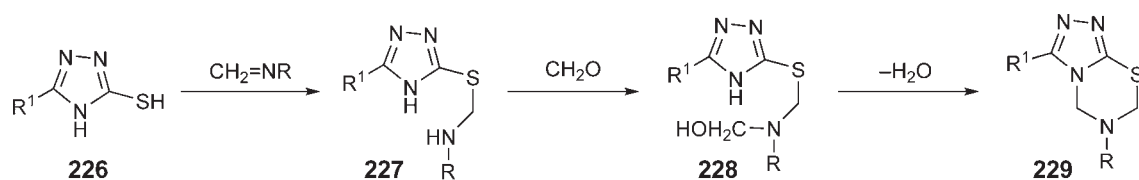


Scheme 40

7-Aryl-2-(carboxymethyl)(or carboxyethyl)thiazolo[3',4':2,3]-1,2,4-triazolo[5,4-*b*]-1,3,3-thiadiazines **234** are obtained from 2-aryl-3-thioureido-4-thiazolidinones **235**, which are formed by the addition-condensation of aldehyde thiosemicarbazones **237** and mercaptoacetic acid. Compounds **235** undergo chemoselective intramolecular heterocyclizations to 5-aryl-2-mercapto-1,5-dihydrothiazolo[3,4-*b*]-1,2,4-triazoles **236**, which in turn undergo condensation with α -amino acids to yield 1,3,5-thiadiazines **234** (Scheme 44) <1994JFA811>.



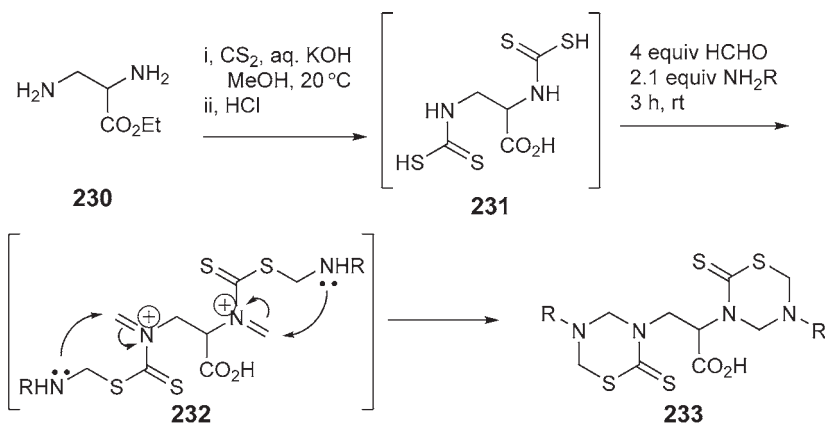
Scheme 41



$\text{R}^1 = p\text{-NO}_2\text{C}_6\text{H}_4^-$; $\text{R} = \text{CH}_3$ (82%)
 $\text{R}^1 = \text{C}_6\text{H}_5$; $\text{R} = \text{CH}_3$ (56%)
 $\text{R}^1 = 3\text{-pyridinyl}$; $\text{R} = \text{CH}_3$ (85%)
 $\text{R}^1 = o\text{-CH}_3\text{OC}_6\text{H}_4^-$; $\text{R} = \text{CH}_3$ (48%)
 $\text{R}^1 = p\text{-CH}_3\text{OC}_6\text{H}_4^-$; $\text{R} = \text{CH}_3$ (88%)
 $\text{R}^1 = \text{Ph}$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (77%)
 $\text{R}^1 = \text{Py}$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (85%)

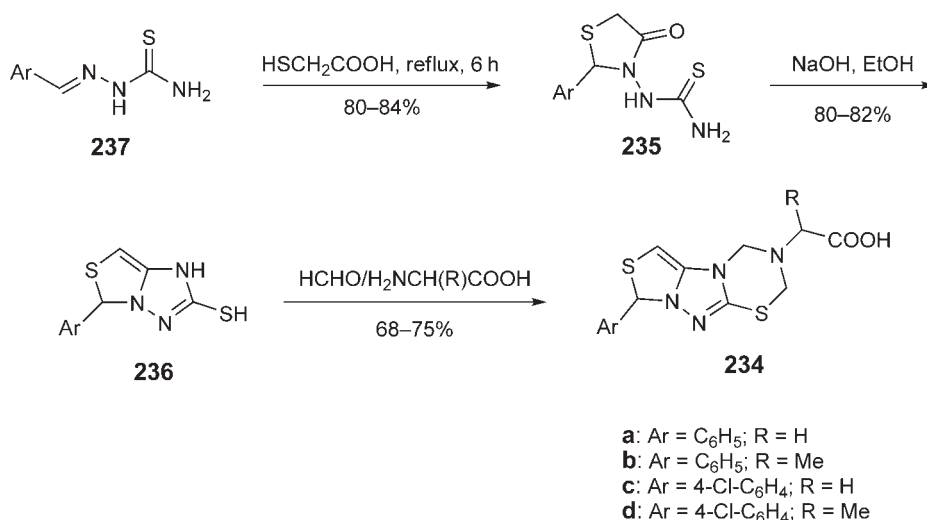
$\text{R}^1 = m\text{-NO}_2\text{C}_6\text{H}_4^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (69.2%)
 $\text{R}^1 = p\text{-NO}_2\text{C}_6\text{H}_4^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (76.3%)
 $\text{R}^1 = o\text{-CH}_3\text{OC}_6\text{H}_4^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (89%)
 $\text{R}^1 = p\text{-CH}_3\text{OC}_6\text{H}_4^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (23.7%)
 $\text{R}^1 = p\text{-EtOC}_6\text{H}_4^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (18.2%)
 $\text{R}^1 = \text{PhOCH}_2^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (75.6%)
 $\text{R}^1 = o\text{-ClPhOCH}_2^-$; $\text{R} = \text{CH}_3(\text{Ph})\text{CH}-$ (56.1%)

Scheme 42



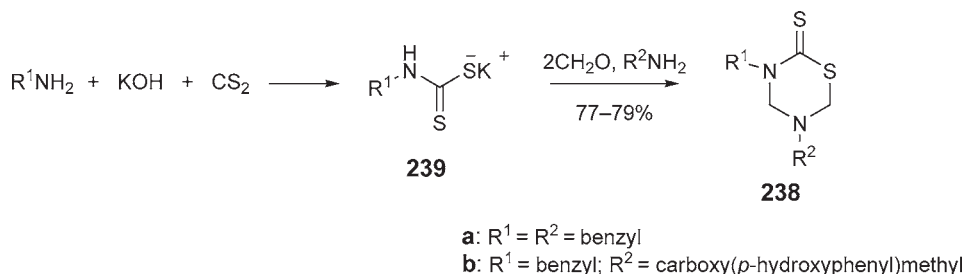
$\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{C}_4\text{H}_9, \text{cyclo-C}_6\text{H}_{11}, \text{C}_6\text{H}_5\text{CH}_2, 4\text{-FC}_6\text{H}_4\text{CH}_2, \text{C}_6\text{H}_5(\text{CH}_2)_2$

Scheme 43



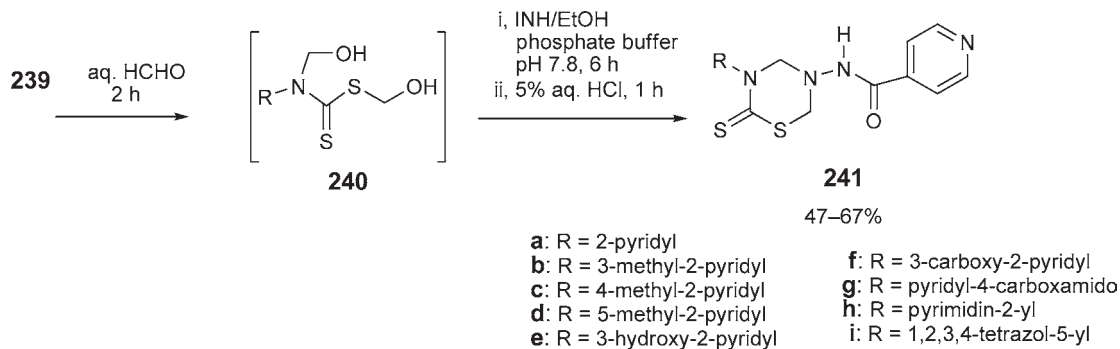
Scheme 44

Thiadiazines **238a** and **238b** are prepared from primary amines and carbon disulfide under basic conditions. The potassium dithiocarbamate salts **239** formed react with 2 equiv of formaldehyde and the corresponding primary amine/amino acid to furnish the desired thiadiazines **238** (Scheme 45) <1999JME5359>.



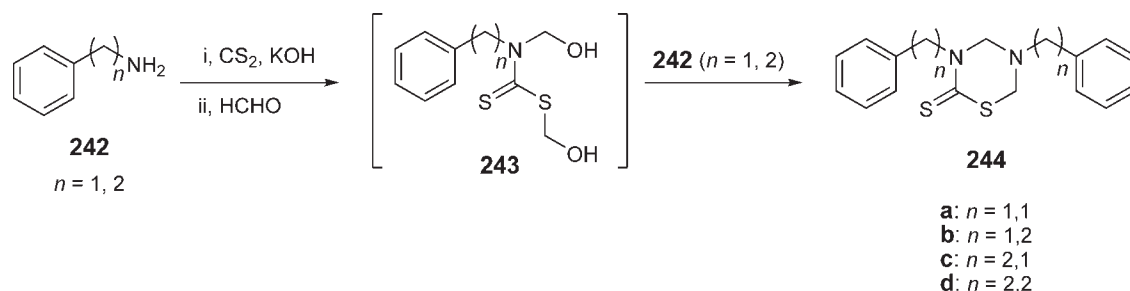
Scheme 45

Attachment of isoniazid (INH) to a tetrahydro-2*H*-[1,3,5]thiadiazine-2-thione moiety has been carried out via the dithiocarbamate salt **239** using a similar approach (see Scheme 46) <2004MI35>.



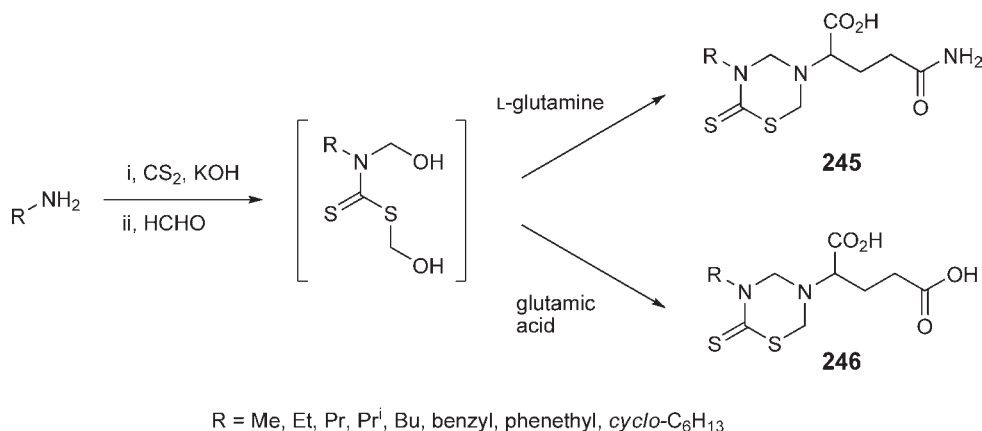
Scheme 46

Delivery of amines through incorporation into tetrahydro-2*H*-1,3,5-thiadiazine-2-thione (THTT) structures has been demonstrated for two classes of pharmaceutically important molecules. As excellent substrates for the enzyme, monoamine oxidase, phenethylamine **242** ($n = 2$), and benzylamine **242** ($n = 1$) are known to be potent vasopressors. These two compounds were incorporated in highly lipid soluble and hydrolytically vulnerable THTT structures in order to modify their pharmacokinetics (Scheme 47) <1994EJM11>.



Scheme 47

L-Glutamine and glutamic acid were incorporated into a THTT skeleton containing different groups at N-3. These derivatives, for example **245** and **246**, were found to be highly lipophilic when compared to L-glutamine and glutamic acid (Scheme 48) <2000MI31>.

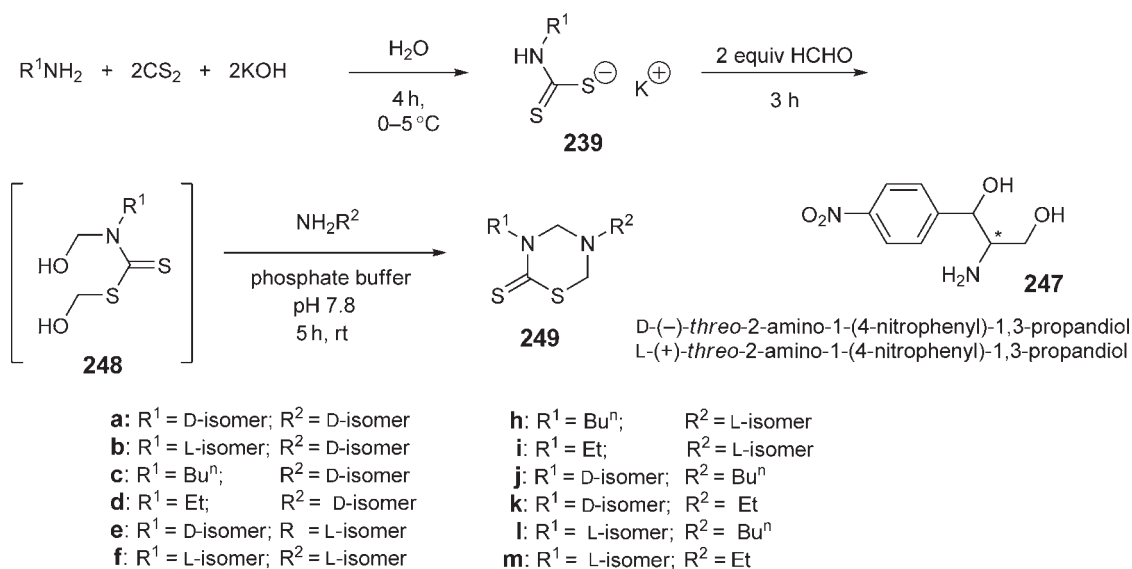


Scheme 48

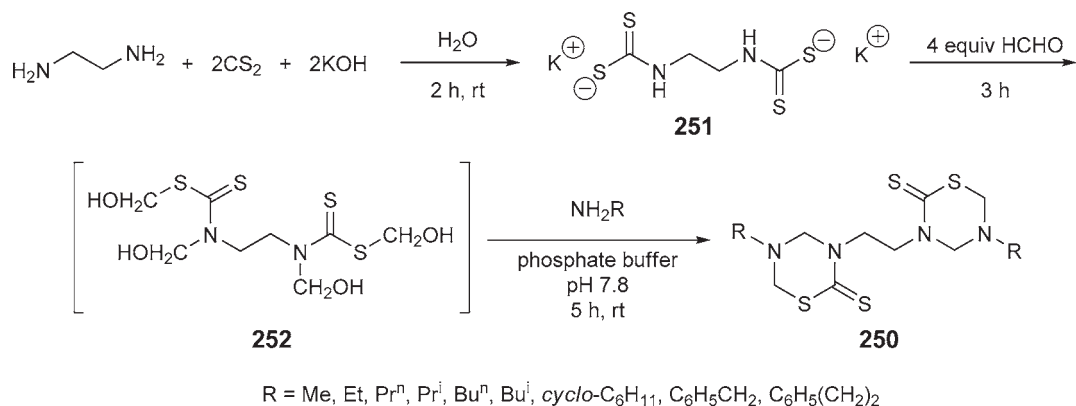
In an attempt to suppress the toxic side effects of the antimicrobial drug, but retain or enhance the activity, the deacylated chloramphenicol amine D-(−)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-diol (D-amine, **247-D**) and its enantiomer, the L-(+)-*threo*-form (L-amine, **247-L**) are introduced into a tetrahydro-2*H*-1,3,5-thiadiazine-2-thione skeleton (Scheme 49). Coupling between the D-amine and the diol **248** affords tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives **249** of moderate to good antibacterial activity <2000MI281>.

A number of new 3,3'-ethylenebis(5-alkyl-1,3,5-thiadiazine-2-thiones) **250** have been synthesized via the dithiocarbamate route starting from ethylene diamine, as shown in Scheme 50 <2001MI305>.

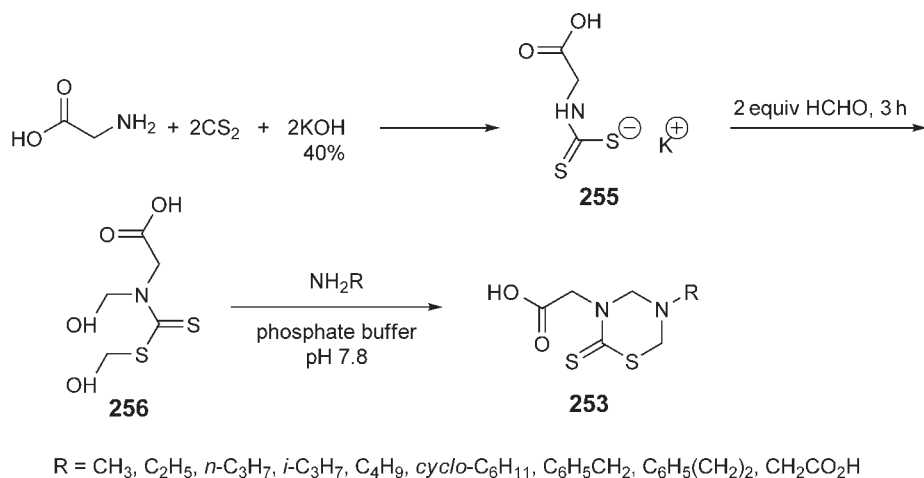
Similar chemistry has been utilized to further elicit new derivatives as medicinal chemistry targets. Thus, preparation of new thiadiazine derivatives **253** and **254** has been accomplished via the incorporation of glycine and glycnamide at the N³, N⁵, or at both positions of the thiadiazine ring structure (Schemes 51 and 52) <2002MI438>.



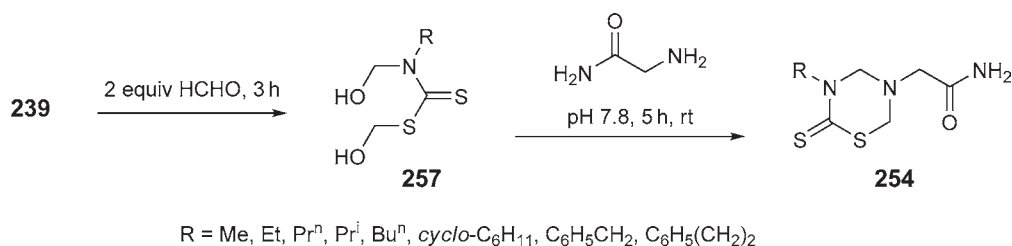
Scheme 49



Scheme 50

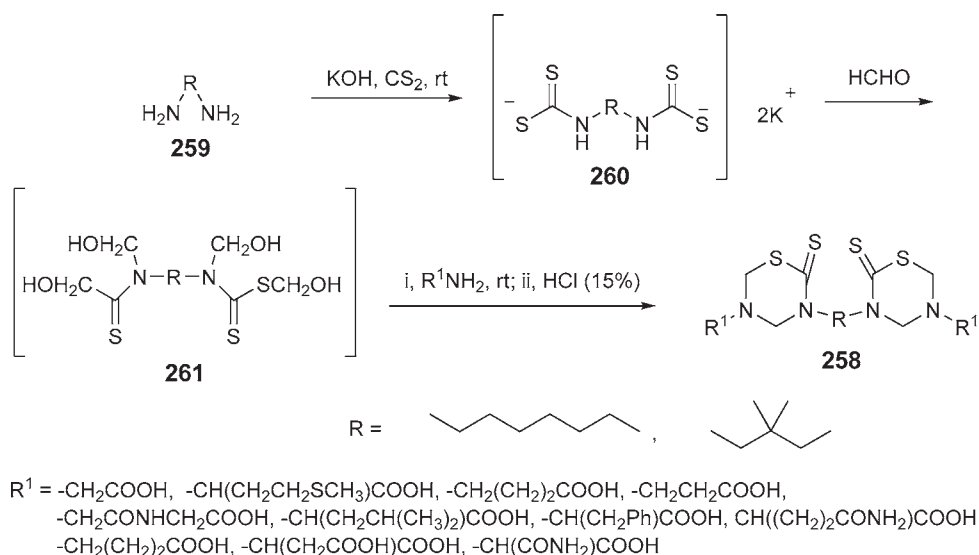


Scheme 51



Scheme 52

Similarly, alkyl-linked bis(2-thioxo-[1,3,5]thiadiazinan-3-yl) carboxylic acids **258** can be synthesized starting from diamines **259** in 35–66% yield (Scheme 53) <2005BMC3413>. The yield of compounds made from the bulky diamine 2,2-dimethyl-1,3-propanediamine is low due to steric hindrance at the cyclization stage <2005BMC3413>.

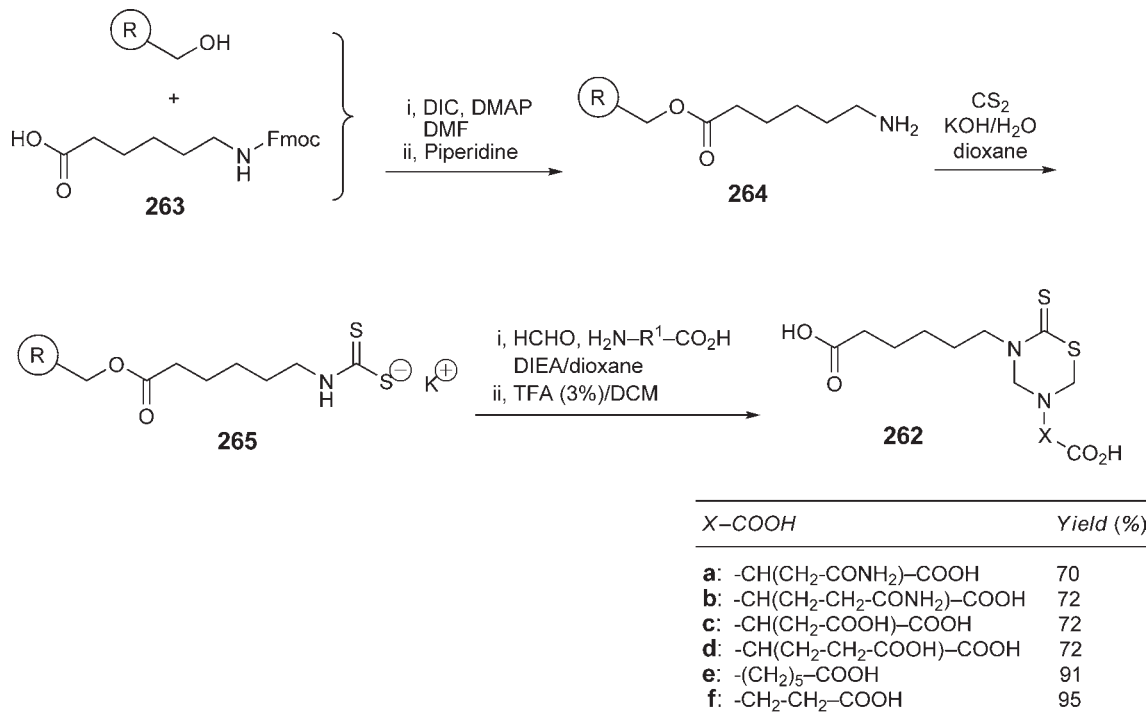


Scheme 53

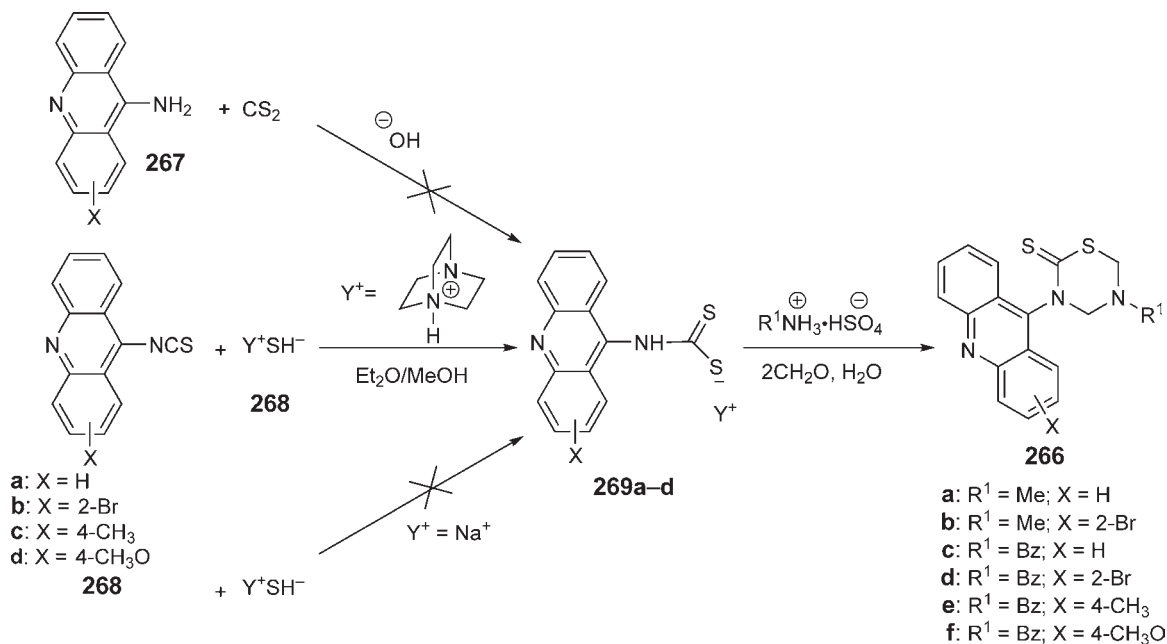
Based on an analogous approach, the synthesis of 3-(5'-carboxypentyl)-5-substituted tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives **262** has been carried out on a solid support in 30–81% yield. Wang resin as the solid support failed, since the extremely acidic conditions required for cleavage caused hydrolysis of the thiadiazine ring. Accordingly, Wang resin was substituted by SASRIN resin, which could be cleaved under milder conditions. Thus, Fmoc-protected 6-amino hexanoic acid **263** was coupled via the C-terminus to hydroxymethyl polystyrene using SARIN linker (Fmoc = 9-fluorenylmethyloxycarbonyl group). Following deprotection, the bound amino acid was converted to the corresponding dithiocarbamate **265**, followed by cyclization in the presence of formaldehyde and the corresponding amino acid to afford 3-(5'-carboxypentyl)-5-substituted tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones **262**. Cleavage of the final products from the resin was performed under mild acidic conditions, as shown in Scheme 54 <2000TL613>.

Synthesis of 1,3,5-thiadiazine-2-thiones, starting from amines R-NH₂ and carbon disulfide in an alkaline medium, involves the dithiocarbamate intermediate, which cyclizes subsequently with another molecule of the ammonium salt R¹NH₃⁺A⁻ (A = HSO₄, Cl). This is not successful in the case of 3-(9'-acridinyl)-5-substituted tetrahydro-1,3,5-thiadiazine-2-thiones **266** due to amino-imino tautomerism of the starting 9-aminoacridines **267**. Addition of the amino group to CS₂ did not proceed and attempts to add H₂S to 9-isothiocyanatoacridines **268** also failed due to the instability and low purity of the sodium 9-acridinyldithiocarbamates **269**. However, relatively stable dithiocarbamates **269** have been obtained in high yield (90–94%) by the reaction of 9-isothiocyanatoacridines **268a–d** with a

methanolic solution of 1-azonium-4-azabicyclo[2.2.2]octane hydrogen sulfide (DABCO·H₂S). Though the dithiocarbamates decompose on standing, immediate treatment of **269a–d** with alkyl ammonium sulfates and formaldehyde in water resulted in the corresponding thiadiazone-2-thione derivatives **266a–f** in good yield (Scheme 55) <1996SC4343>.

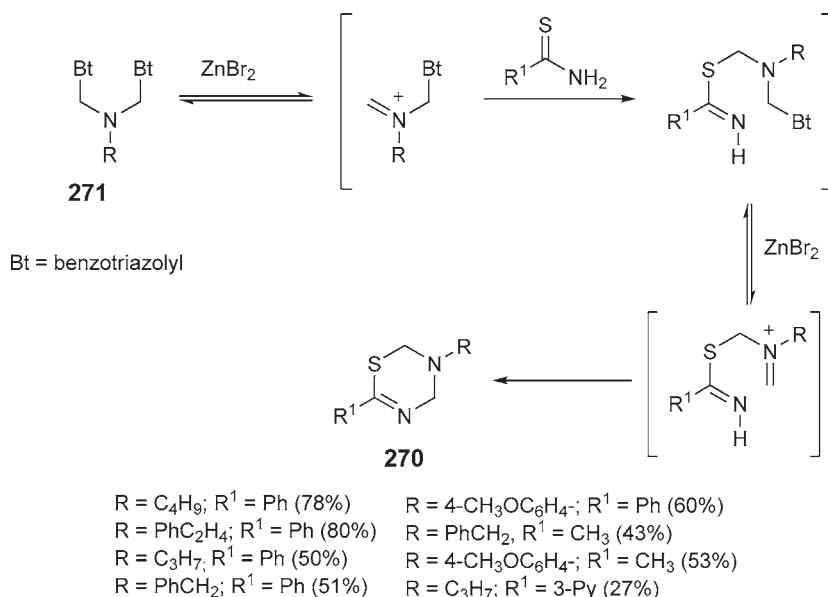


Scheme 54



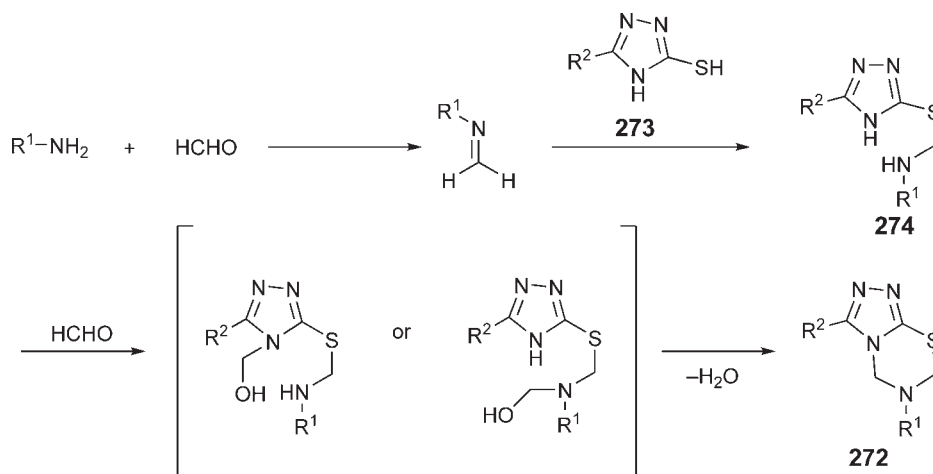
Scheme 55

3,4-Dihydro-2*H*-1,3,5-thiadiazines **270** can be synthesized via [3+3] cycloaddition reactions. Thus, starting from *N*-substituted *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)amines **271** containing two leaving groups, as the equivalent of 1,3-bielectrophiles, and thioamides as 1,3-binucleophiles, these components undergo a Lewis acid-promoted condensation to afford 3,4-dihydro-2*H*-1,3,5-thiadiazines **270** (Scheme 56) <2002JOC4960>.



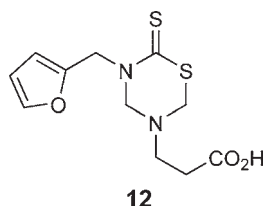
Scheme 56

3,6-Disubstituted tetrahydro-*s*-triazolo[3,4-*b*][1,3,5]thiadiazines **272** have been synthesized in 50–85% yield by the double Mannich reaction of 3-aryl-5-mercapto-1,2,4-triazoles **273** with various aromatic amines and formaldehyde in the presence of ethanolic HCl, as shown in Scheme 57 <1996MOL89>.

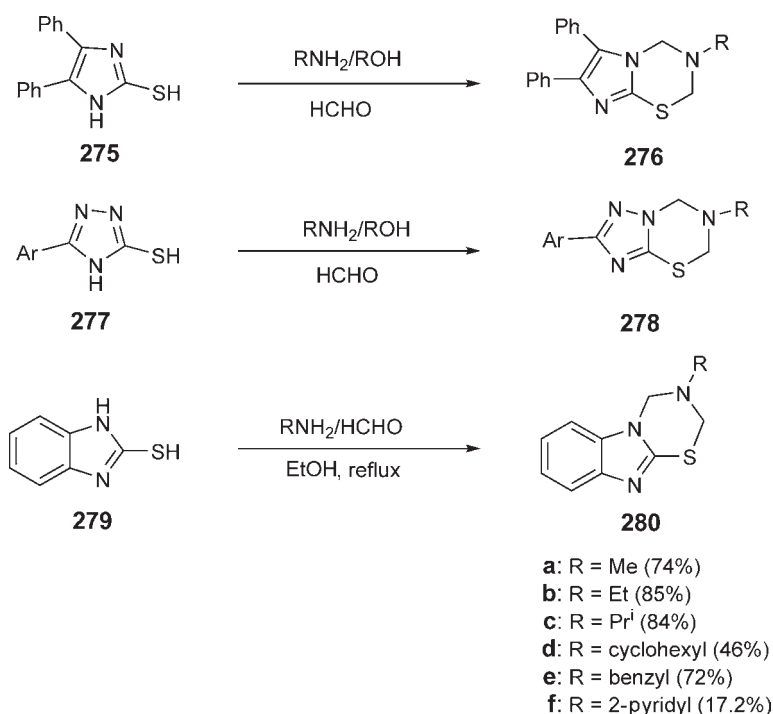


Scheme 57

Compound **12** is synthesized by the reaction of furfurylamine with CS₂ and KOH to give the dithiocarbamate potassium salt, followed by cyclocondensation with formaldehyde and β-alanine <2001T7361>.



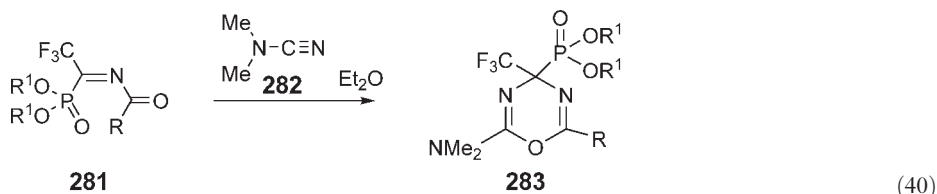
4,5-Diphenylimidazole-2-thiol **275** undergoes the Mannich reaction with aliphatic or aromatic amines and formaldehyde to furnish the corresponding thiadiazinoimidazole derivatives **276** in good yields. Likewise, 2-aryltriazole-5-thiols **277** afford *s*-triazolo[3,4-*b*]thiadiazine derivatives **278** in good yields. The Mannich reaction approach is applied also for the synthesis of compounds **280a–f** starting from 2-mercapto-benzimidazole **279** and primary, aliphatic, and aromatic amines. In a neutral or acidic medium, the reaction affords the cyclized thiadiazino[1,3,5][3,2-*a*]benzimidazoles **280a–f** in good yields (Scheme 58) <2006SC987>.



Scheme 58

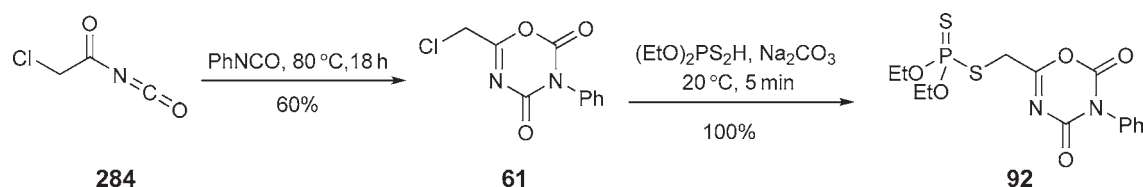
9.09.9.2 Formation of Two Bonds

N-Substituted trifluoroacetamidoylphosphonates **281** react with dimethylcyanamide in a [4+2] cycloaddition fashion to give 1,3,5-oxadiazines **283**, as exemplified in Equation (40) <2002HAC22>. The reactivity of the imines declines as the electron-withdrawing power of the substituent at the nitrogen atom decreases (COPh > COOMe) or as the steric volume of the phosphoryl group increases [P(O)(OMe)₂ > P(O)(Prⁱ)₂]. Thus, **283b** is formed at room temperature while **283a** and **283c** require reflux conditions in diethyl ether to form the respective oxadiazines. Less-nucleophilic nitriles, such as benzonitrile and acetonitrile, are unreactive in this reaction, suggesting that the cycloaddition proceeds through an interaction of the acceptor, four-center lowest unoccupied molecular orbital (LUMO) of the heterodiene with the donor highest occupied molecular orbital (HOMO) in the cyanamide.



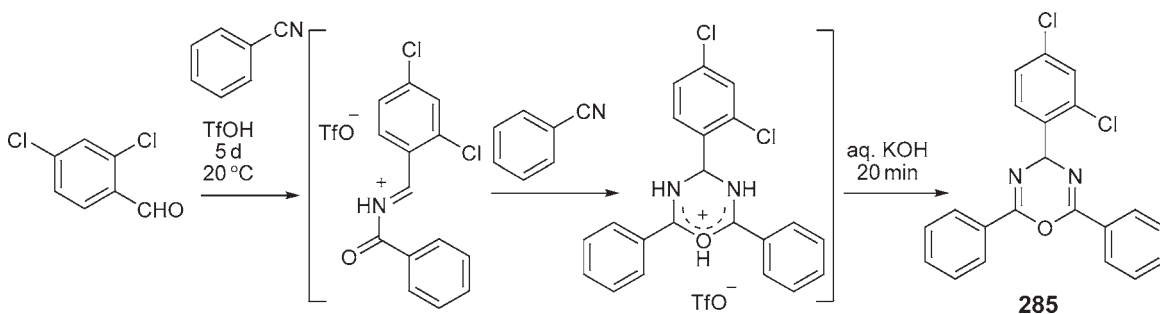
- a: R = Ph; R¹ = Prⁱ; reflux
 b: R = Ph; R¹ = Me; 20 °C, 20 h
 c: R = Ph; R¹ = Et; 20 °C, 20 h
 d: R = Ph; R¹ = Pr; reflux
 e: R = OMe; R¹ = Prⁱ; reflux

The [4+2] cycloaddition of acylisocyanates to isocyanates to give 2,4-dioxo-2,4-*H*-1,3,5-oxadiazines is well established <1981BSF28, 1970ZNB1180>. Thus, the water-sensitive 1,3,5-oxadiazine **61**, formed from acylisocyanate **284** and phenyl isocyanate, reacts with *O,O*-diethyl dithiophosphate to afford the oxadiazine **92** (Scheme 59) <1996SC783>. However, these oxadiazines are difficult to isolate as they undergo rapid decomposition.



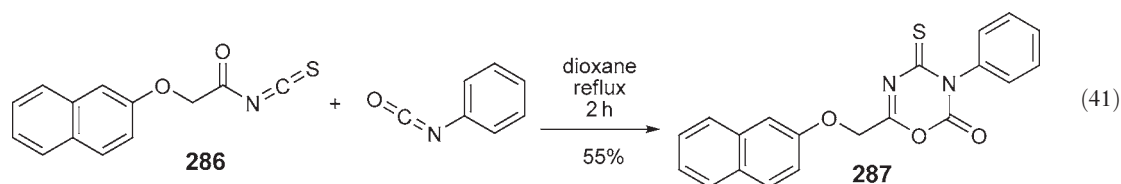
Scheme 59

Trifluoromethanesulfonic acid is found to be the most effective acid catalyst for the condensation of aldehydes with nitriles leading to 1,3,5-oxadiazines. Thus, a stoichiometric mixture of 2,4-dichlorobenzaldehyde and trifluoromethanesulfonic acid is treated with 5 equiv of benzonitrile at ambient temperature for 5 days (Scheme 60). After treating the precipitate with a 10% aqueous solution of KOH, and recrystallizing the crude product, the purified 4-(2,4-dichlorophenyl)-2,6-diphenyl-4*H*-1,3,5-oxadiazine **285** is isolated in 66% yield. All attempts to carry out the transformation in the presence of other strong acids (e.g., sulfuric, perchloric) were unsuccessful <1997RJO91>.

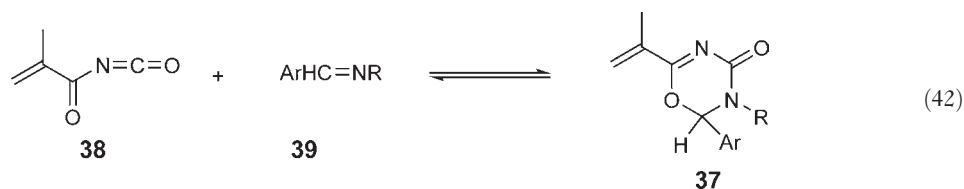


Scheme 60

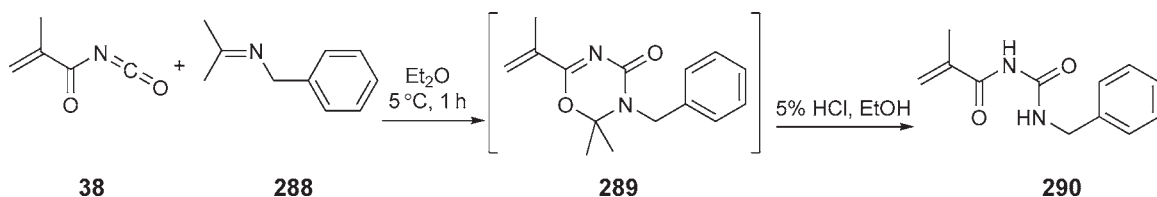
Reaction of β -naphthoxyacetyl isothiocyanate **286** and phenyl isocyanate gives the cycloaddition product **287** (Equation 41). *In vitro* testing of this molecule for biological activity against a variety of bacteria confirmed its potential use <1997IJH43>.



Cycloaddition reactions of methacryloyl isocyanate with arylideneamines [<1996H\(42\)533>](#) and with imines derived from ketones and alkylamines [<1996H\(43\)2083>](#) have been reported. However, the adducts formed by the cycloaddition between compounds **38** and **39** dissociate into the two original substrates (Equation 42). Compounds **37** could not be isolated and were confirmed only by NMR spectroscopy. The VT-NMR spectra show that the ratios of substrates to adducts are temperature dependent and that the lower the temperature, the lower the dissociation of the cycloadducts.

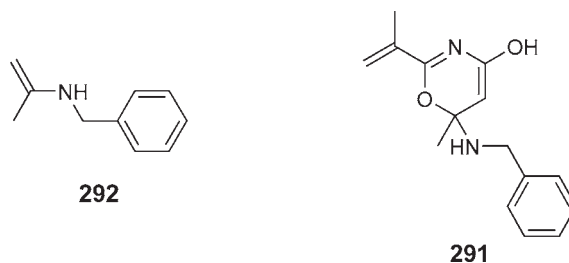


Cycloaddition products are isolated with arylidenealkylamines bearing both electron-donating or electron-withdrawing substituents on the aromatic ring [<1996H\(42\)533>](#). Reaction of methacryloyl isocyanate **38** with imines derived from acetone, for example, isopropylidenebenzylamine **288**, in diethyl ether at 5 °C for 1 h gives high yields of 1,3,5-oxadiazinones such as 3-benzyl-2,2-dimethyl-6-isopropenyl-2*H*-1,3,5-oxadiazin-4(3*H*)-one **289**. The latter, due to extreme moisture sensitivity, is difficult to isolate and the intermediate hydrolyzes quickly to 1-benzyl-3-methacryloyl-urea **290** by treatment with 5% ethanolic hydrochloric acid (Scheme 61) [<1996H\(42\)533, 1996H\(43\)2083>](#).

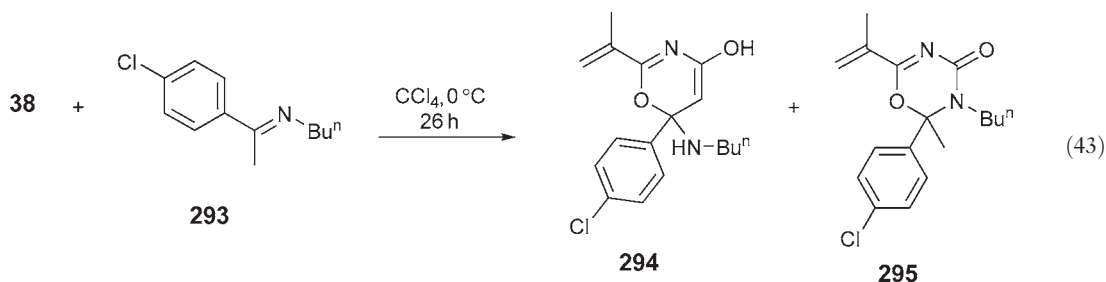


Scheme 61

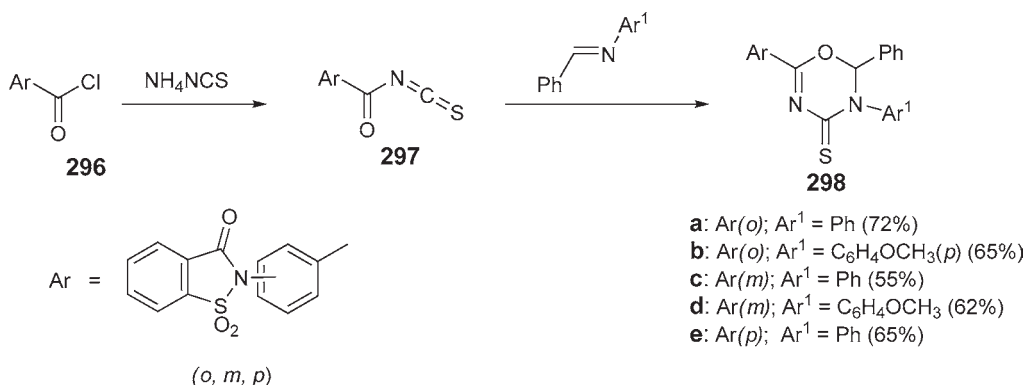
Reaction of **38** and **288** in benzene under reflux for 2 h, however, affords 6-benzylamino-4-hydroxy-2-isopropenyl-6-methyl-1,3-oxazine **291** in 45% yield along with 43% of the urea **290**. Formation of compound **291** is due to the cycloaddition reaction of methacryloyl isocyanate **38** with the enamine tautomer of isopropylidenebenzylamine **292** [<1996H\(42\)533, 1996H\(43\)2083>](#).



Further corroborating the understanding of these reactions, treatment of methacryloyl isocyanate **38** with α -methyl-*p*-chlorobenzylidene-*n*-butylamine **293** in carbon tetrachloride at 0 °C for 26 h analogously gives a nearly 1:1 mixture of two [4+2] cycloadduct products, 1,3,5-oxadiazinone **294** and 1,3-oxazine **295** (Equation 43) [<1996H\(43\)2083>](#).

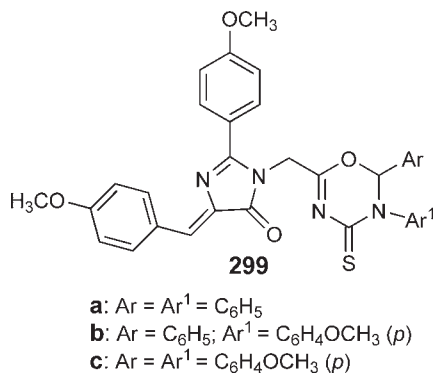


ortho-, *para*-, and *meta*-(*N*-Saccharinyl)benzoyl isothiocyanates **297**, obtained by treating the corresponding acid chlorides **296** with ammonium thiocyanate in acetone, react with benzylidene aryl amines to furnish the corresponding 1,3,5-oxadiazine-4-thiones **298** in moderate to good yields via [4+2] cycloaddition (Scheme 62) <1999EJC563, 1998IJB135>.

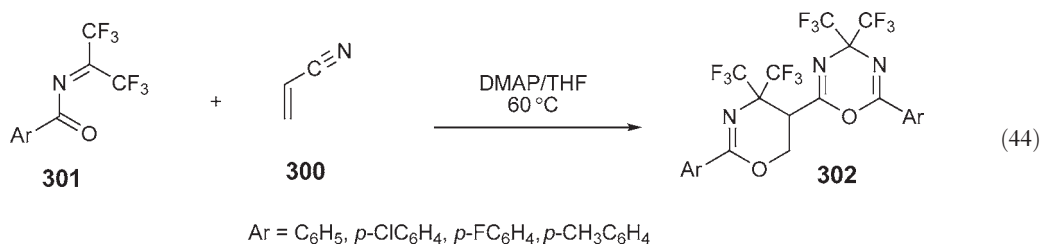


Scheme 62

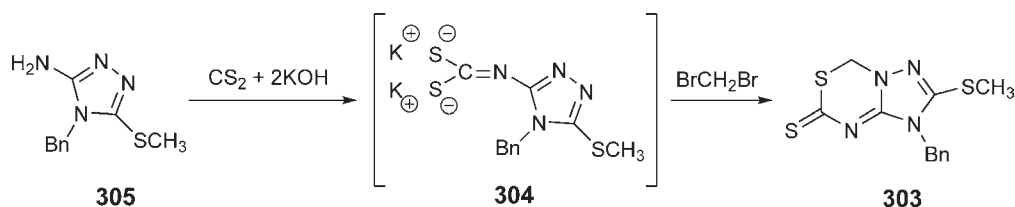
A similar approach is adopted for the synthesis of imidazolone derivatives of 1,3,5-oxadiazines **299** in 58–67% yield <2000EJC389>.



A sequential [4+2] cycloaddition reaction takes place when acrylonitrile **300** reacts with 4,4-bis(trifluoromethyl)-1-oxa-3-azabuta-1,3-dienes **301** in the presence of equimolar amounts of 4-dimethylaminopyridine to afford 2-aryl-6-[2-aryl-4,4-bis(trifluoromethyl)-5,6-dihydro-4*H*-1,3-oxazin-5-yl]-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazines **302** (Equation 44) <1995M1383>.

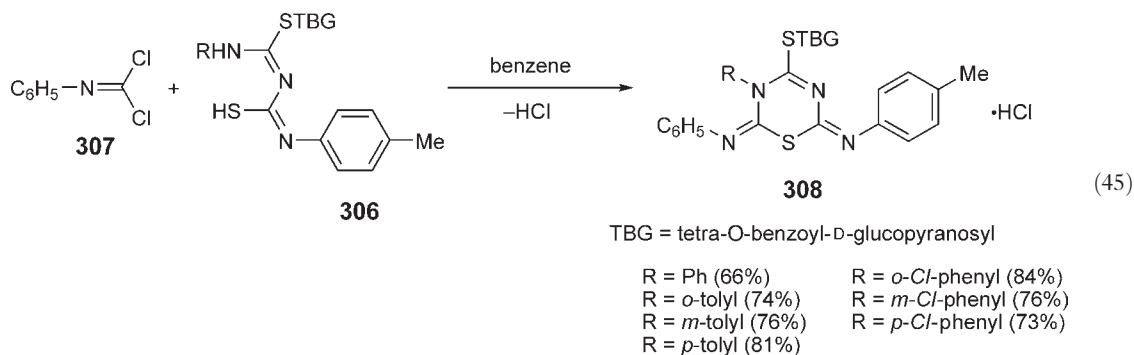


1-Benzyl-1,7-dihydro-2-methylthio-1,2,4-triazolo[1,5-*c*][1,3,5]thiadiazine-5-thione **303** is obtained as a by-product in the reaction of triazole **304** (prepared *in situ* from compound **305** with carbon disulfide and KOH) with dibromomethane (Scheme 63) <1994JHC997>.

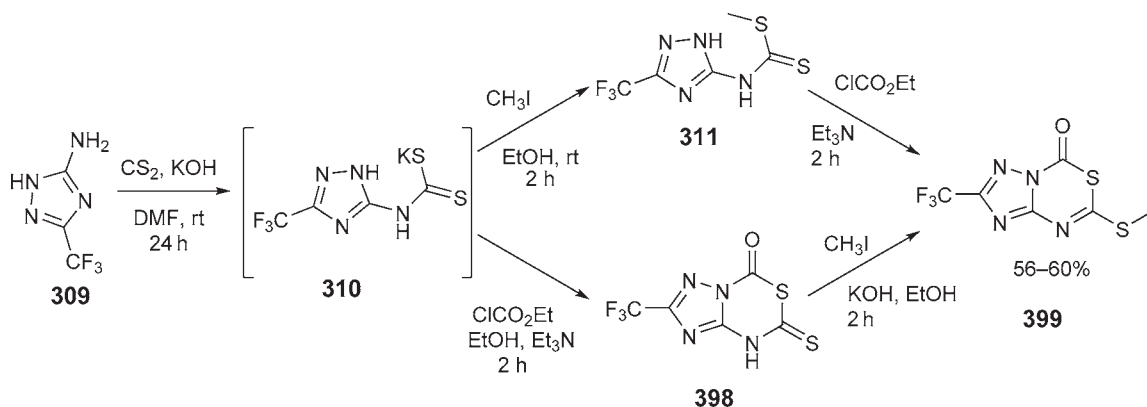


Scheme 63

Treatment of 2-*S*-tetra-*O*-benzoyl-D-glucopyranosyl-1-aryl-5-*p*-tolyl-2,4-isodithiobiuret **306** with phenyl isocyanodichloride **307** results in 1,3,5-thiadiazines **308** by nucleophilic displacement of both chlorines in compound **307** (Equation 45) <2003JIC654>.

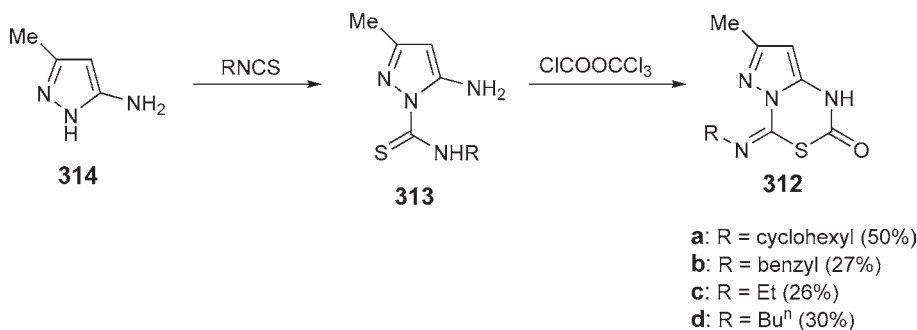


On account of the excellent pharmacological activity of heterocyclic compounds containing a trifluoromethyl group, the reaction of 3-amino-5-trifluoromethyl[1,2,4]triazole (**309**) with carbon disulfide, and *in situ* treatment of the intermediate salt **310** with methyl iodide, followed by cyclization with ethyl chloroformate, is reported as an avenue to thiadiazinone product **399** (Scheme 64). The intermediate **310** is treated with methyl iodide to afford methyl 5-trifluoromethyl[1,2,4]triazol-3-ylthiocarbamate **311** in 56% yield. Intermediate **311** was then cyclized by treatment with ethyl chloroformate in the presence of triethylamine in ethanol to afford 7-methylthio-2-trifluoromethyl[1,2,4]triazolo[1,5-*c*][1,3,5]thiadiazin-5-one **399**. Alternatively, the cyclization can be performed prior to treatment with methyl iodide and KOH, to obtain the same thiadiazinone product **399** in 60% yield <1998JCM2126>.



Scheme 64

The preparative route to [1,5-*c*][1,3,5]thiadiazine-2-ones **312** is outlined in Scheme 65. Thus, 5-amino-3-methylpyrazole-1-carbothioamides **313**, obtained from the reaction of 5-amino-3-methylpyrazole (**314**) with isothiocyanates, react smoothly with trichloromethyl chloroformate to afford **312** (Scheme 65) <2004JFA1898>.



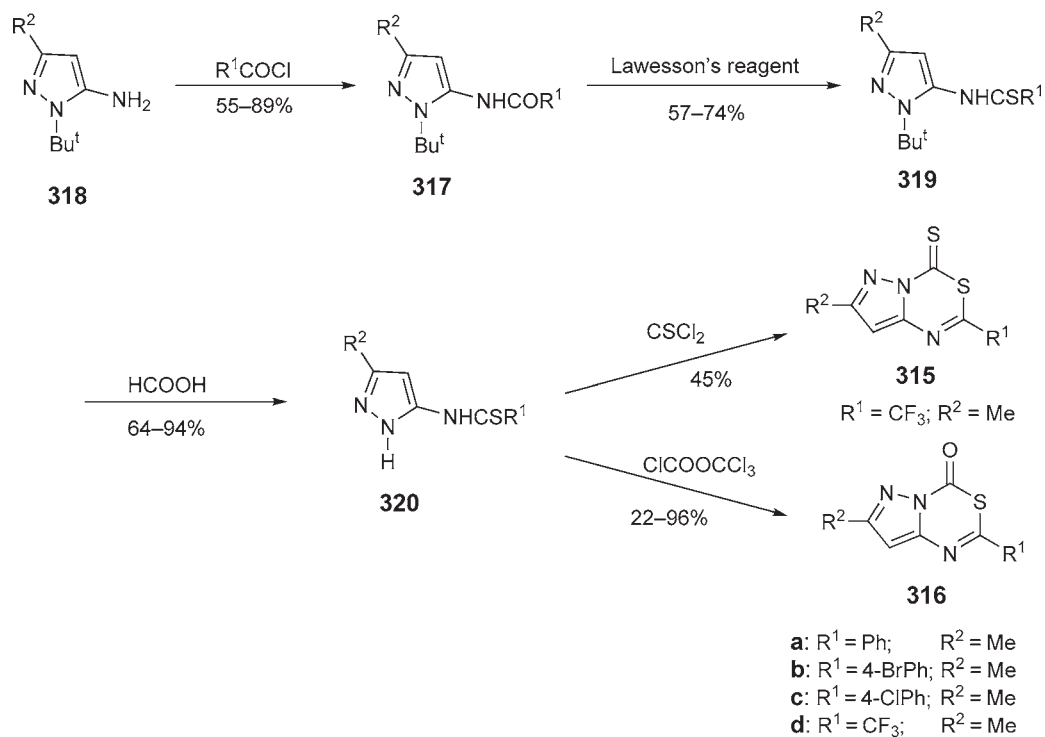
Scheme 65

Pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-ones/thione **315/316** are synthesized starting from *N*-(5-pyrazolyl)carboxamides **317**, which in turn are obtained by the acylation of the corresponding 5-aminopyrazoles **318**. Thiation of **317** with Lawesson's reagent provides the thiocarboxamide **319**. Compound **319** is converted to the dealkylated derivative **320** by heating with formic acid. Reaction of **320** with thiophosgene affords pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thiones **315**, while treatment with trichloromethyl chloroformate furnishes the oxadiazines **316** (Scheme 66) <2002JFA4839, 1993H(36)2291, 1994JHC1477>.

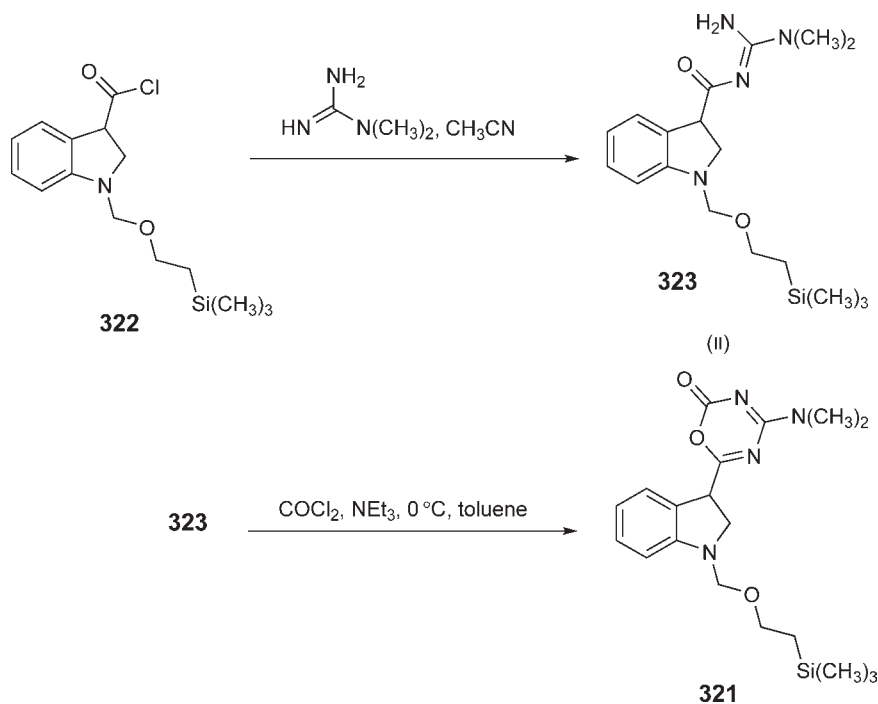
Synthesis of β -trimethylsilylethoxymethyl (SEM)-protected oxadiazinones **321** is accomplished by the treatment of acid chloride **322** with *N,N*-dimethylguanidine, followed by treatment of the intermediate **323** with phosgene in toluene (Scheme 67) <1997T2055>.

When the approach in Scheme 67 was attempted for the synthesis of alboinon **381** (a natural product from marine organism *Dendrodoa grossularia*), it was discovered that the oxadiazine system does not survive even the mildest of the SEM deprotection conditions. Therefore, an alternative method, starting from imidazole, via a Baeyer–Villiger approach was improvised <1997T2055> (see Section 9.09.9.4).

Heterocycles containing nitrogen and sulfur are synthesized by reaction of activated acetylenes with polyfunctional systems bearing mesomeric interaction between reaction centers. The 1,3,5-thiadiazine **326** is obtained from the reaction of benzoylacetylene **324** and 1,5-diphenyldithioobisurea **325**. Different products are obtained depending on the solvents, time, temperature, and stoichiometry of the two starting materials. Reaction of **324** with **325** in AcOH , benzene, or CH_3CN at 20°C and in CH_3OH at 0°C proceeds nonselectively to afford varying mixtures of products **326–329** (see Table 1; Equation 46) <2002CHE74>.



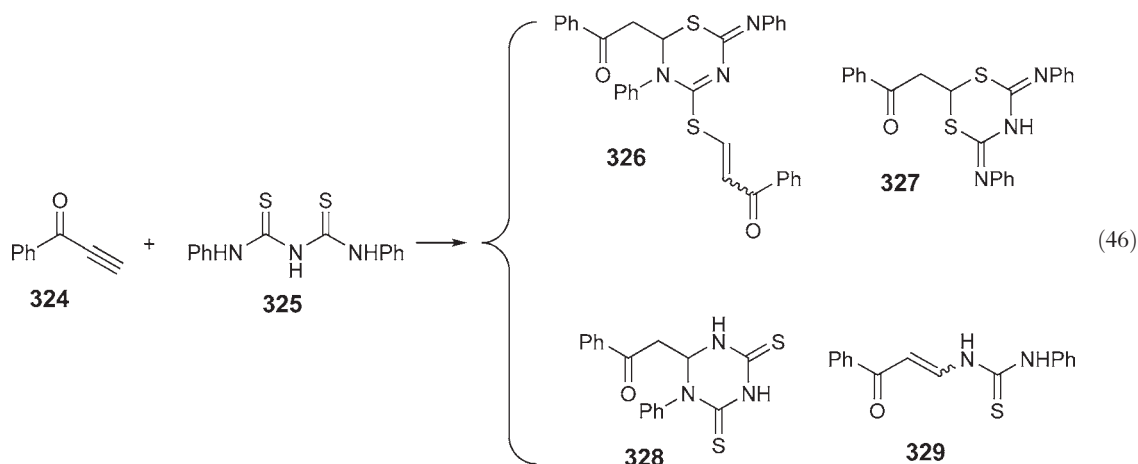
Scheme 66



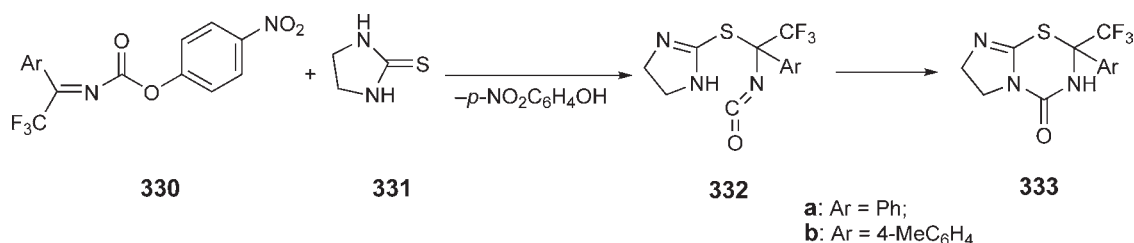
Scheme 67

Table 1 Reaction conditions for 1,3,5-thiadiazine **326** formation

324 (mmol)	325 (mmol)	<i>Solvent</i>	<i>Reaction time</i>	<i>Temperature (°C)</i>	<i>Yield of 326 (%)</i>
5	2.5	Benzene	2 h	5–8	53
5	5	Benzene	2 h, 2 d	20	32
5	5	CH ₃ CN	2 h, 2 d	20	33
5	5	MeOH	24 h	–8 to 0	30



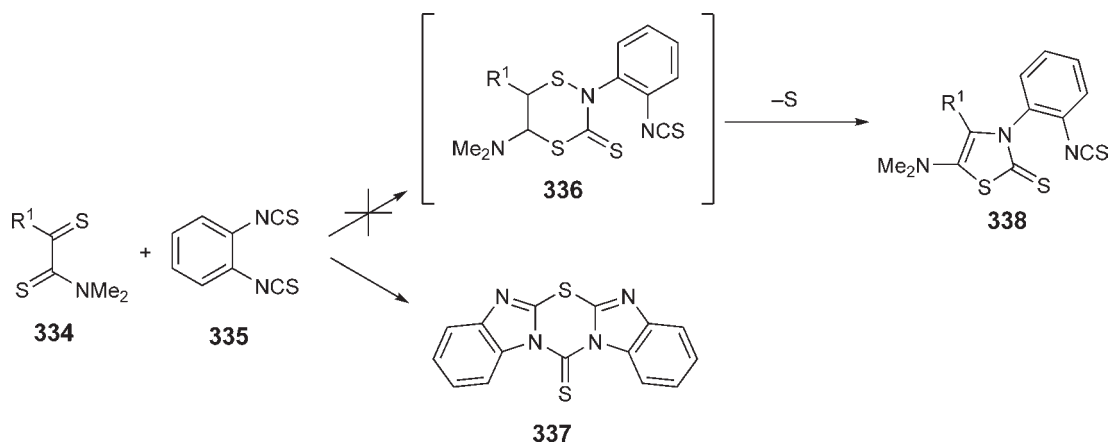
3-Aryl-5-oxo-3-trifluoromethyl-6,7-dihydroimidazo[2,3-*b*]1,3,5-thiadiazines **333** are formed by addition of 2-imidazoline thione **331** to 4-nitrophenyl-*N*-alkylideneurethane **330**. A requirement for the heterocyclization is the ability of the urethanes to generate intermediates **332** (Scheme 68) <2004CHE241>.

**Scheme 68**

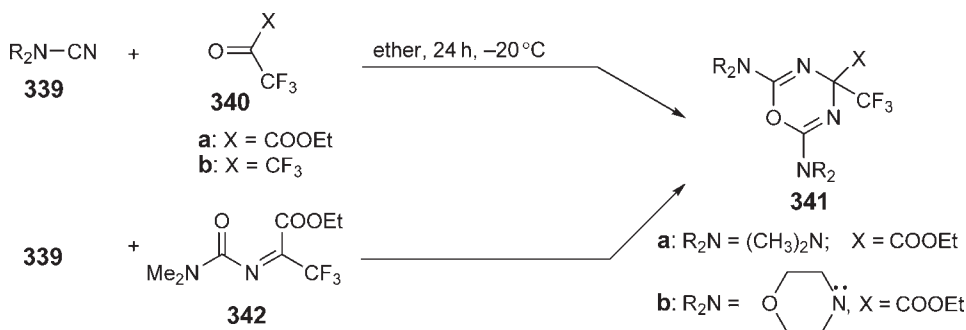
Regioselective [4+2] cycloaddition of α -thioxothioamides **334** to the C=N bond of heterocumulenes, followed by S[–] extrusion, typically affords 2-thioxothiazoles. However, attempts at using the phenylene-1,2-diisothiocyanate **335** as the heterocumulene did not give the expected mono- or bis-thioxothiazoles **338**. Instead, the reaction afforded primarily the pentacyclic thiadiazine derivative **337**, which is formed by the rapid cyclization/dimerization of the diisothiocyanate, and precipitates out of the reaction mixture (Scheme 69) <2001HAC617>.

N-Cyanoamines **339** react with 3,3,3-trifluoropyruvate **340a** and hexafluoroacetone **340b** to afford the 1,3,5-oxadiazines **341a** and **341b** in excellent yields. Additionally, the structure of **341a** is confirmed by its alternative synthesis by the [4+2] cycloaddition reaction of **339** and 2-*N*-(*N*,*N*-dimethylcarbamoyl)imino-3,3,3-trifluoropropionate **342** (Scheme 70) <1998RCB727>.

Reactions of the *N*-chloromethyl carbamoyl chlorides **343** and **346** with benzimidazole-2-thiol **344** or 3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole-2-thiol **347** for preparation of fused thiadiazines **345** and **348** have been reported.



Scheme 69



Scheme 70

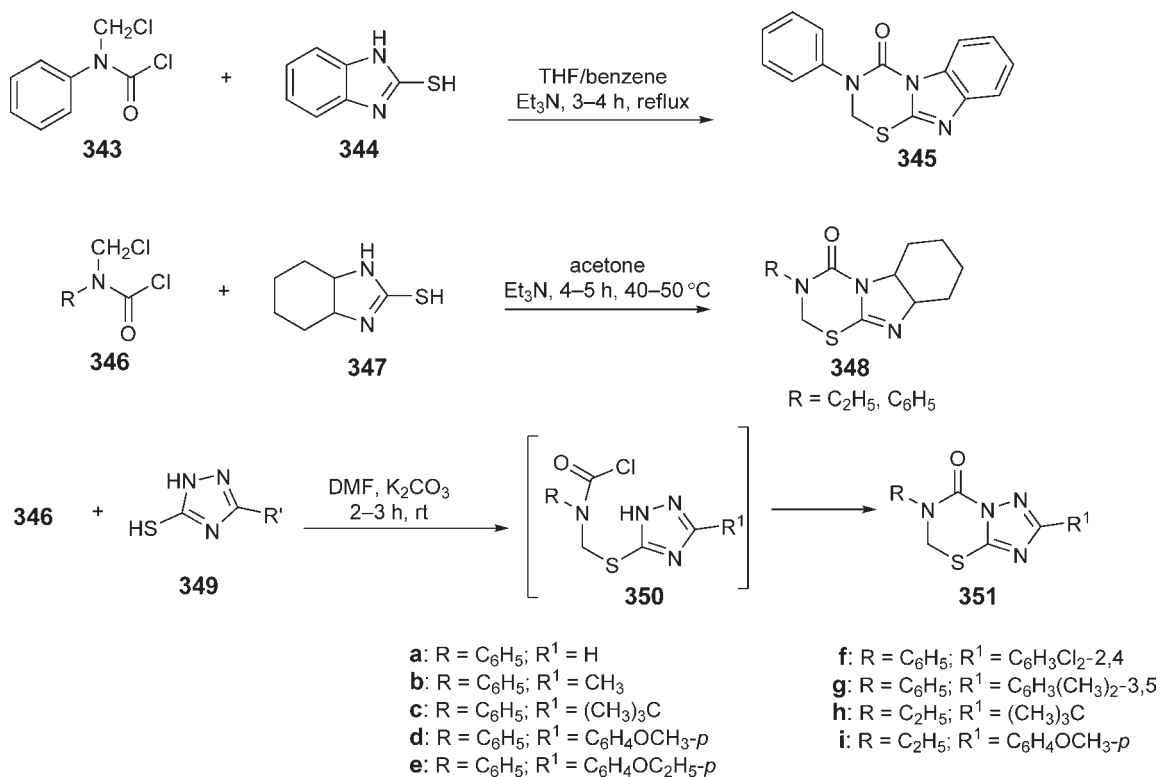
Similarly, 3-substituted 1,2,4-triazole-5-thiols **349** react with *N*-chloromethyl carbamoyl chlorides **346** to afford 5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-ones **351**. The N-1 and N-2 positions of *s*-triazoles are more nucleophilic than the N-4 position. The nucleophilic thiol group of **349** attacks the chloromethyl group of *N*-chloromethyl carbamoyl chloride **346** in preference to the carbamoyl chloride moiety. After the initial attack, the carbamoyl group reacts with N-1 of the triazole to afford the corresponding 5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one **351** (Scheme 71) <2000M953>.

9.09.9.3 Formation of Three Bonds

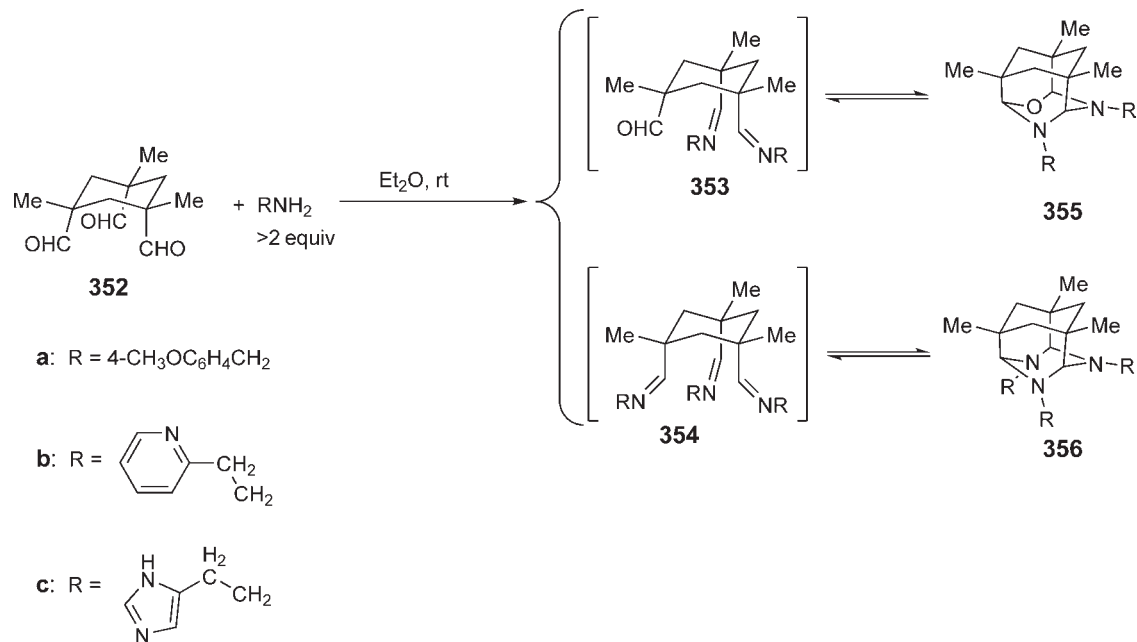
Treatment of trialdehyde **352** with a large excess of 2-(2-aminoethyl)pyridine in diethyl ether at room temperature gives a 1:1 mixture of oxadiazawurtzitane **355** and triazawurtzitane **356**. A plausible mechanism for the reaction is proposed to be via intermediates **353** and **354**, as shown in Scheme 72 <1998J(P1)1925>.

1-Oxa-3,5-diazonium salts **74a** and **74b** are synthesized *in situ* by Lewis acid- (SbCl_5 , SnCl_4) promoted cyclization from pyridine-2,6-dicarbonyl dichloride **357** and dimethyl cyanamide and diisopropyl cyanamide, respectively. In this reaction, depending on the reaction conditions, choice of the Lewis acid, stoichiometry, reaction time, etc., either one or both chlorocarbonyl functions can be converted into the 1-oxa-3,5-diazinium ring (Scheme 73) <2005EJO3891>.

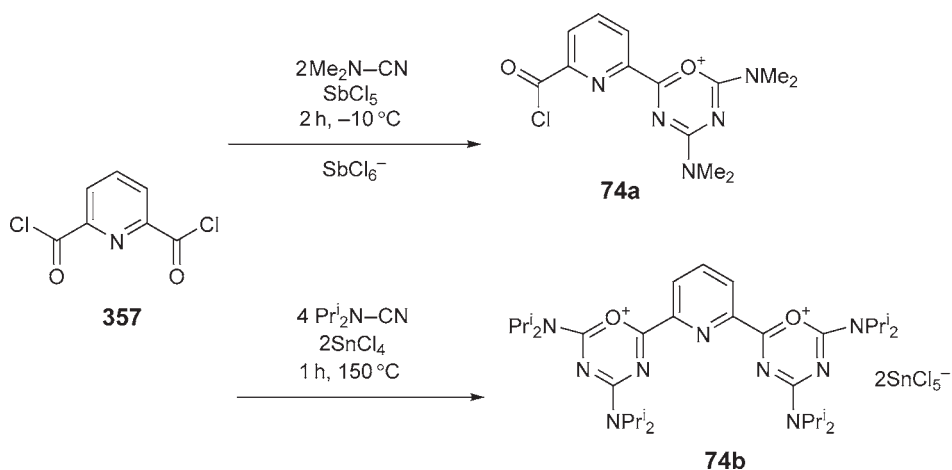
Relatively little-known 3,4-dihydro-2,4-dioxo-2*H*-1,3,5-oxadiazinium salts **358** are obtained by the acylation of 2 mol of alkyl isocyanate with 1 mol of acylium salt **359** (Equation 47) <1995JPR385>. Other reports of similar compounds are known in the literature <1993CB2069, 1980S112, 1977S753>.



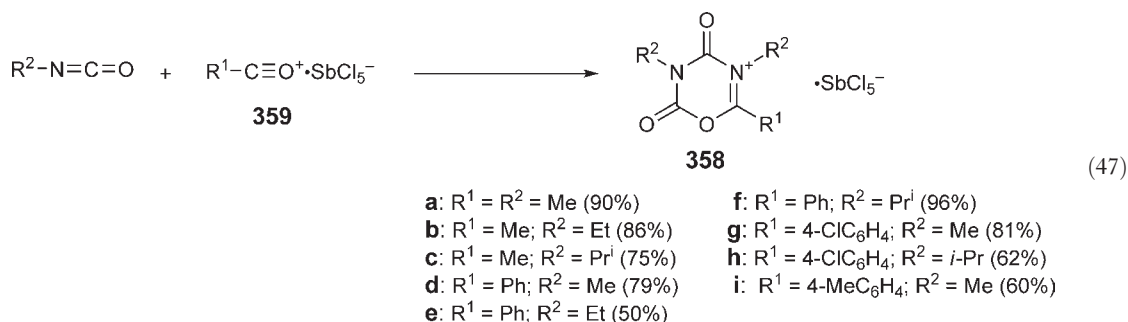
Scheme 71



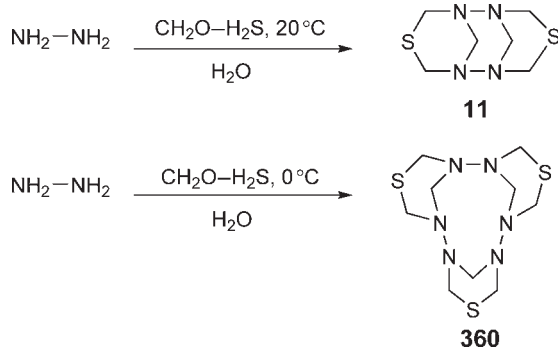
Scheme 72



Scheme 73



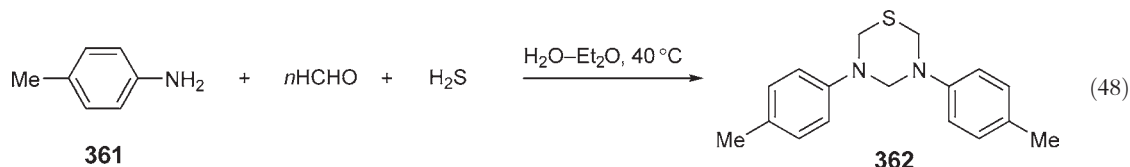
The effect of temperature and stoichiometry on the thiomethylation of hydrazine has been reported <2004RCB1717>. Heterocyclization of hydrazine with an excess of a CH₂O–H₂S mixture (1:6:4), in the temperature range from 0 to 20 °C, gives the tricyclic **11** and tetracyclic **360** nitrogen-and-sulfur-containing heterocycles. The nature of the product is affected substantially by the reaction temperature. At 20 °C, compound **11** is obtained in 30% yield and **360** in 18% yield. With a ratio of hydrazine:CH₂O:H₂S of 1:6:4, and a 0 °C reaction temperature, an increased yield of **360** to 31% was observed (Scheme 74). PMR and *ab initio* calculations were used to confirm the structures of the products and are discussed further in Sections 9.09.2 and 9.09.3.1.



Scheme 74

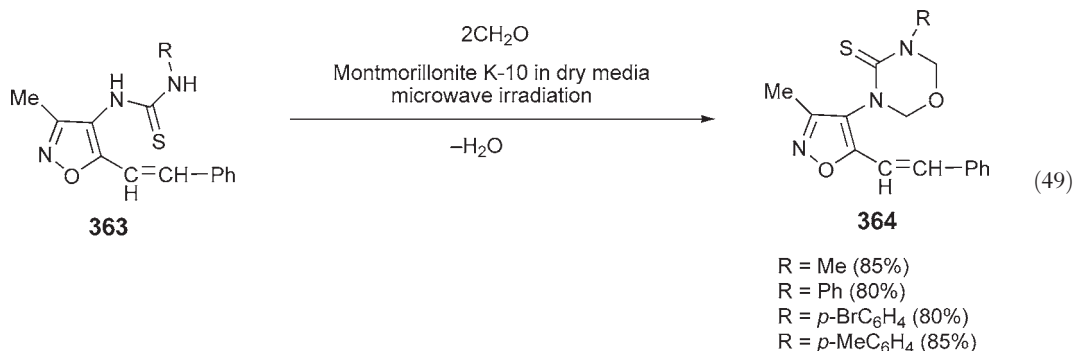
With the aim of inserting both nitrogen and sulfur atoms at the same time, liquid-phase thiomethylation of primary aromatic amines, for example **361**, using formaldehyde and hydrogen sulfide is carried out in a two-phase water–ether

system. The composition of the array of products depends on the nature of the amine, relative stoichiometry of the starting materials, and reaction temperature. More basic anilines, for example *p*-toluidine, produce the corresponding thiadiazine (e.g., **362**) (Equation 48) <2003RCB1817>.

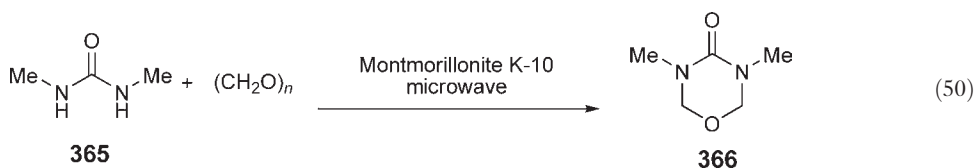


9.09.9.4 Miscellaneous Syntheses

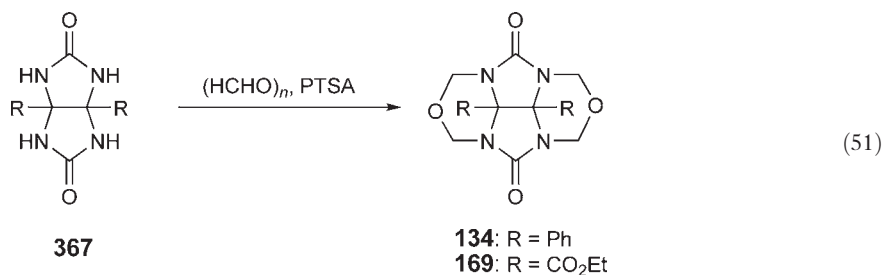
Condensation of *N*-(3-methyl-5-styrylisoxazol-4-yl)-*N'*-arylthioureas **363** and paraformaldehyde, in the presence of Montmorillonite K-10 in dry media under microwave irradiation, is reported to afford isoxazolyl oxadiazinethiones **364** in excellent yields. Formation of the oxadiazinethione results from a nucleophilic attack of the urea nitrogen on formaldehyde followed by cyclodehydration on the surface of the catalyst (Equation 49) <2005JHC711>.



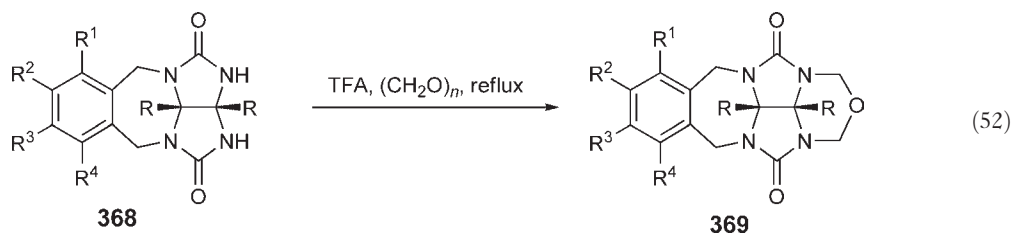
Using the same technology, the synthesis of 4-oxo-oxadiazine **366** has been reported. Montmorillonite K-10 has Lewis acid character leading to the decomposition of paraformaldehyde to formaldehyde, which reacts with the nucleophilic urea nitrogen atoms. Ultimate dehydration on the surface of the clay affords the 4-oxo-oxadiazine **366** in 67% yield (Equation 50) <1999JCM392>.



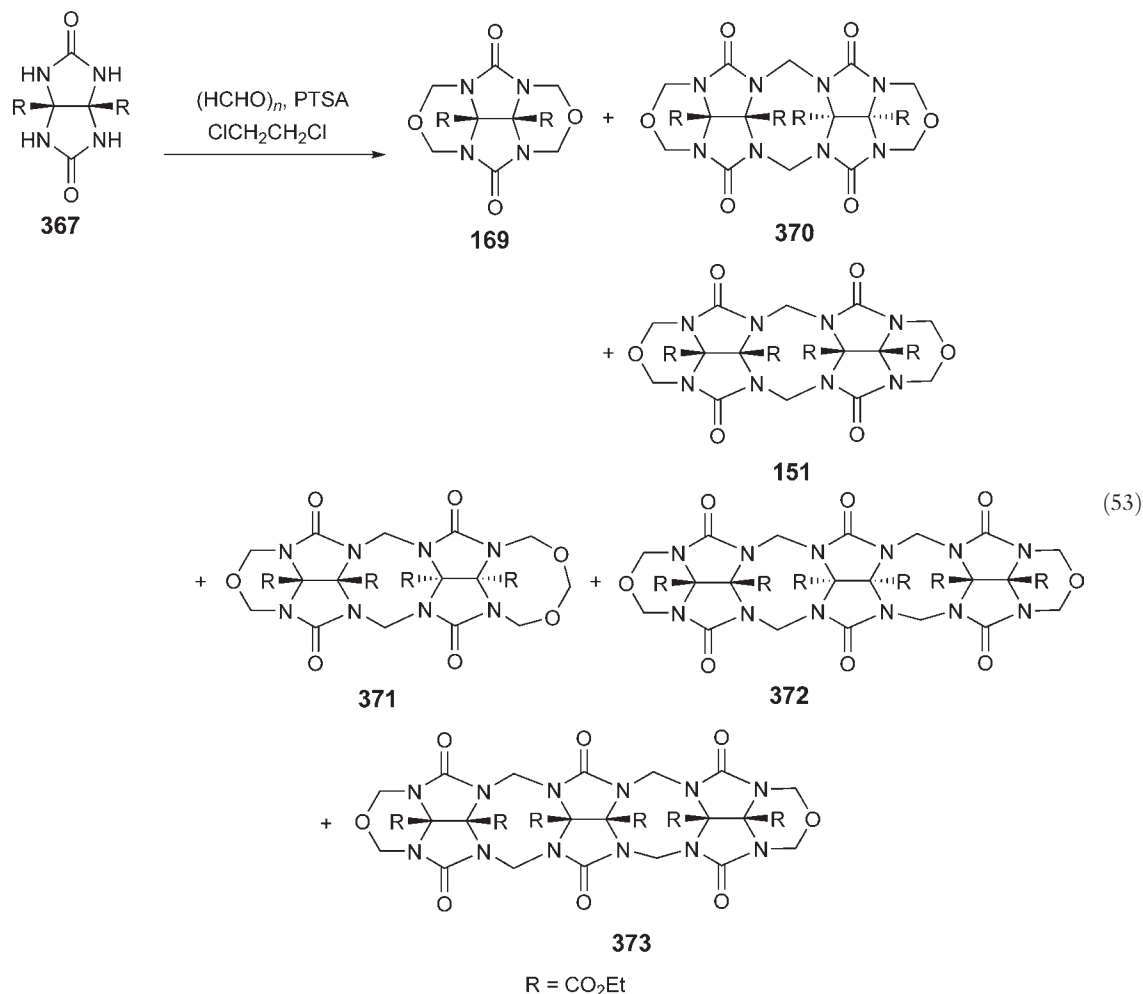
1,3,5-Oxadiazine derivatives of diphenylglycouril **134**, **169**, generally referred to as 'cyclic ethers' in the literature, are obtained by the treatment of diphenylglycouril **367** with paraformaldehyde in the presence of PTSA (Equation 51) <1989JOC3710>. In addition, the same reaction can be carried out under anhydrous conditions <2003T1961>. The anhydrous TFA used in this latter reaction is sufficiently acidic, easy to remove, and an excellent solvent for **367**.



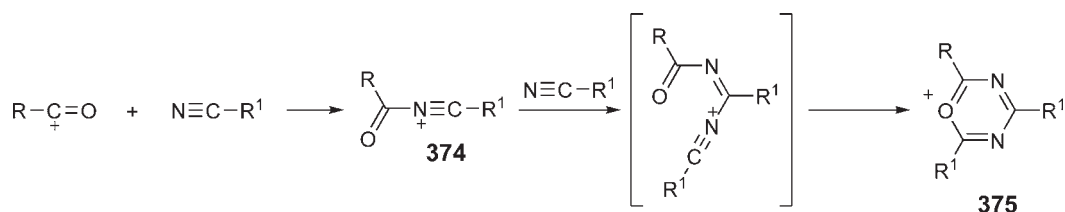
Using the same procedure, glycouril derivatives bearing an aromatic group on one side and the cyclic ether on the other, for example **369**, have been synthesized (Equation 52) <2002JOC5817>.



Controlled oligomerization of glycouril **367** furnishes a mixture of cyclic ethers **151**, **169**, and **370–373** as shown in Equation (53) <2003OL3745>.

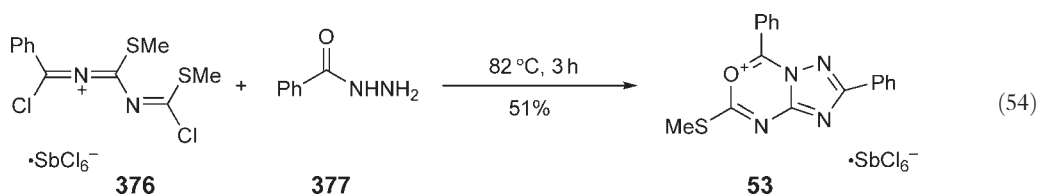


With the help of a combination of selective dissolution and chromatographic separation, several of the cyclic ethers have been separated and isolated <2003OL3745>. Though not of synthetic value, gas-phase cyclization reactions of acylium ions with nitriles, forming 1,3,5-oxadiazinium ions **375** by double nitrile addition followed by cyclization, have been reported (Scheme 75) <2001MI445>. Similarly, the gas-phase reactions of acylium and thioacylium ions with isocyanates (**18**: Y = O) and isothiocyanates (**18**: Y = S) have been reported to result in oxadiazinium (**16**: X = O) and thiadiazinium (**16**: X = S) salts, respectively (see Scheme 2) <2005JAM1602>.

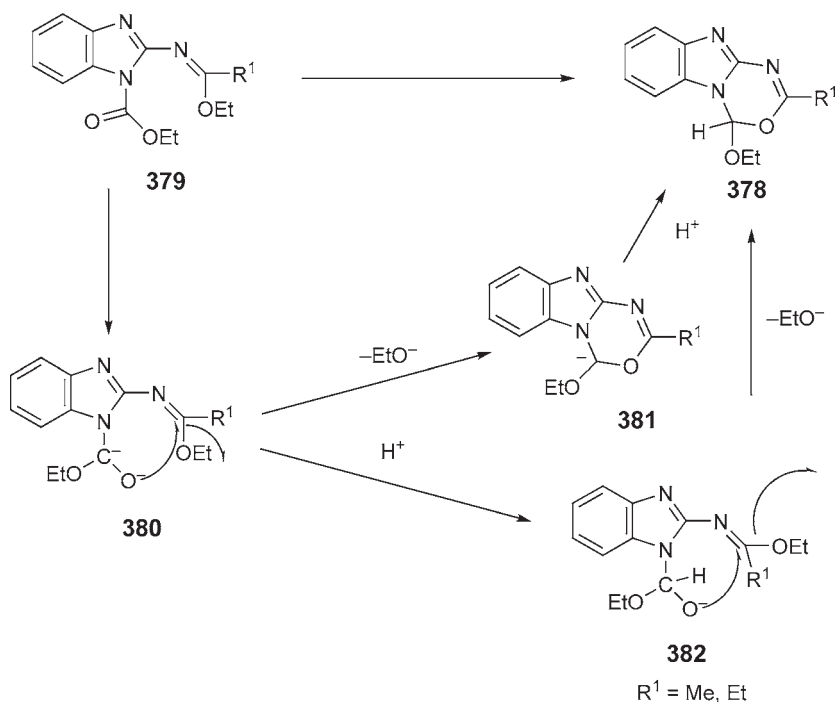


Scheme 75

The 1,5-dichloro-substituted 2-azoniaallene salt **376** reacts as a trivalent electrophile with benzohydrazine **377**, to furnish the bicyclic oxadiazinium salt 5-methylthio-2,7-diphenyl[1,2,4]triazolo[1,5-*c*][1,3,5]oxadiazinium hexachloroantimonate **53**, which represents a new ring system (Equation 54). Very little is known about these compounds; however, the structure of the oxadiazinium salt is confirmed by X-ray analysis (see Section 9.09.3.2 <1995JPR274>).



The 1,3,5-oxadiazines **378** are obtained by the cathodic reduction of iminoesters **379** containing strong electron-donating groups such as alkoxy groups. The reductive cyclization takes place in aprotic solvents such as DMF. The proposed mechanism is initiated by an ECE reaction resulting in the formation of the dianion **380**, which may undergo cyclization via two routes in subsequent steps, as shown in Scheme 76 <2002SC241>.

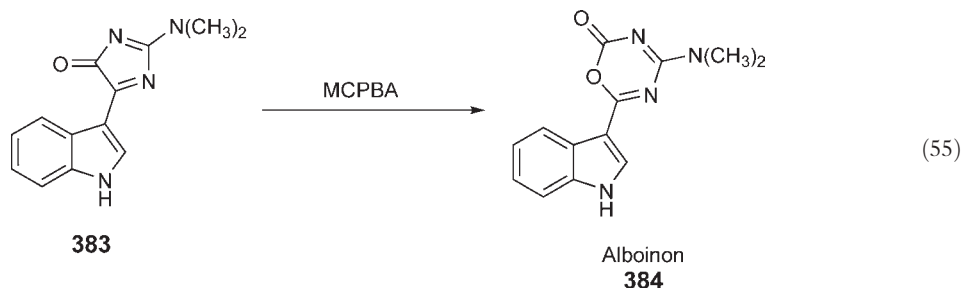


Scheme 76

9.09.10 Ring Syntheses by Transformation of Another Ring

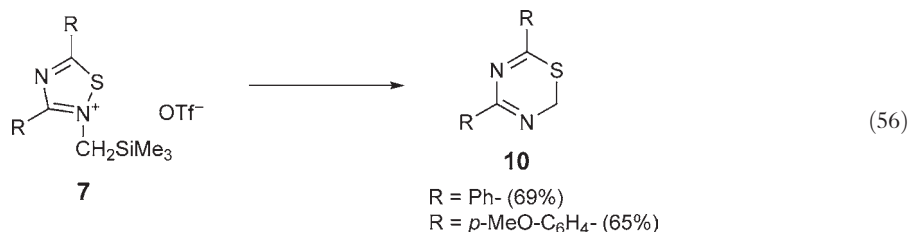
9.09.10.1 To Give 1,3,5-Oxadiazines

Baeyer–Villiger oxidation is utilized to afford the marine natural product alboinon **384** in a single step by treatment of the starting imidazole **383** with *m*-chloroperbenzoic acid (Equation 55) <1997T2055>.

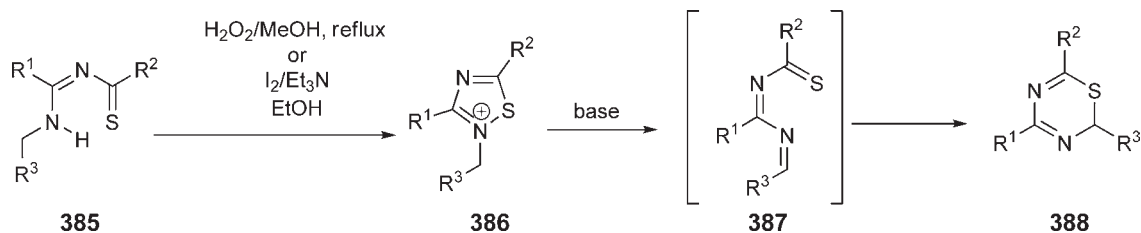


9.09.10.2 To Give 1,3,5-Thiadiazines

The desilylation of 3,5-diaryl-1,2,4-thiadiazole quarternary ammonium salts **7** with CsF results in ring expansion to afford substituted 2*H*-1,3,5-thiadiazines **10** in moderate yield (Equation 56) <1999JP1>1709>. *Ab initio* studies have been carried out for this transformation and the details are presented in Section 9.09.2.

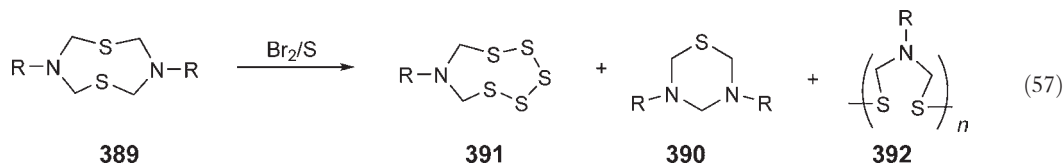


2*H*-1,3,5-Thiadiazines have been identified as intermediates during the synthesis of highly substituted imidazoles. In this approach, oxidation of thiocarbonylamidines **385** causes the initial ring closure to 1,2,4-thiadiazolium salts **386**. Deprotonation of these salts at the NCH₂ position brings about the ring opening to *N*-(thiocarbonyl)-*N*-alkylideneamidines **387**. The latter undergo electrocyclic ring closure to 2*H*-1,3,5-thiadiazines **388** (Scheme 77) <1997JOC3480>.



Scheme 77

Treatment of 1,5,3,7-dithiadiazocanes **389** with bromine–elemental sulfur or disulfur dichloride gives thiadiazine **390** as a by-product, as shown in Equation (57) <2002CL90>.



9.09.11 Synthesis of Particular Classes of Compounds and Critical Comparison of Various Routes

9.09.11.1 1,3,5-Oxadiazines

In the past decade, numerous unique and novel structures containing the 1,3,5-oxadiazine moiety have been reported. Often the focus of the reported research is on the utility and not the synthetic methodology. Therefore, many of the older, more robust approaches remain very much in use. For perhydro-1,3,5-oxadiazines, the approach most utilized continues to be the cyclodehydration of *N,N'*-bis (hydroxymethyl) ureas, thioureas, or guanidines (Section 9.09.9.1.1). In particular, nitroguanidine appears with frequency in this role in the literature (Section 9.09.9.1.1) and PTSA and TFA are common acid catalysts. A solvent-free, microwave-irradiated reaction in the presence of Montmorillonite K-10, as Lewis acid, has also been reported (Section 9.09.9.4). When unsymmetrical *N*-hydroxymethyl-*N'*-ethylimidate urea is cyclized, 2*H*-1,3,5-oxadiazine-4(3*H*)one is formed (Section 9.09.9.1.1), while the *N,N'*-diacyl compound affords 1,3,5-oxadiazin-4-one (Section 9.09.9.1.1). Insertion of an oxygen atom into an imidazole ring system via a Baeyer–Villiger approach yields 6-substituted-4-dialkylamino-1,3,5-oxadiazine-2-ones (Section 9.09.10.2). Many examples of [4+2] cycloaddition reactions of heterodienes to a donor dienophile are also represented (Section 9.09.9.2). Some of these fragment pairs are shown in Table 2.

Table 2 Dienophile–heterodiene fragment pairs

Dienophile	Heterodiene

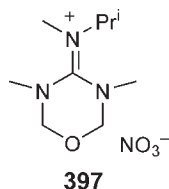
Included also is the reaction of *N*-acyl guanidines with phosgene to afford 6-substituted-4-dialkylamino-1,3,5-oxadiazine-2-ones (Section 9.09.9.2).

9.09.11.2 1,3,5-Thiadiazines

Many of the methods used for the preparation of 1,3,5-oxadiazines also apply to the 1,3,5-thiadiazines. Similar to the oxygen analogs, the starting *N*-nitroguanidine can be treated with formaldehyde, but in the presence of sodium sulfide to afford the Mannich-type cyclization product 4-nitroimino-1,3,5-thiadiazines (Section 9.09.9.1.2). Primary amines react with carbon disulfide under basic conditions to form dithiocarbamate salts which react with 2 equiv of formaldehyde and a second primary amine to furnish tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones (Section 9.09.9.1.3). 3,4-Dihydro-2*H*-1,3,5-thiadiazines containing a ring carbonyl or thiocarbonyl group are synthesized from reaction of thioamides with phenoxycarbonyl isocyanate, dimerization of thiocarbamoylisothiocyanates, or dimerization of carbamoyl isocyanates. The latter two [4+2] cycloaddition reactions complement the tabulated list of dienes and dienophiles presented in Table 2 (Section 9.09.9.2). 3,6-Disubstituted-3,4-dihydro-2*H*-1,3,5-thiadiazines are synthesized by treatment of *N*-substituted *N,N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-amines with thioamides and zinc bromide (Section 9.09.9.1.3).

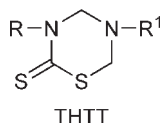
The alkaloid, alboinon **384**, containing the 1,3,5-oxadiazin-2-one system is found in the ascidian *D. grossularia* [<1997T2055>](#). Glycouril derivatives bearing cyclic ethers groups, as in **134**, **151**, **169**, and **368–371**, are the fundamental building blocks for the synthesis of CB[6], its derivatives, and its congeners [<2003T1961>](#). CB[6] is

an intriguing macrocyclic compound possessing a hydrophobic cavity with carbonyl-lined portals that result in remarkable molecular recognition properties. It has also been demonstrated that it is an efficient enzyme mimic for catalyzing various reactions. Additionally, the ether linkages in the above molecules behave as protecting groups and deprotection can be accomplished by treatment with 3,5-dimethylphenol <2005JOC10381>. Different clip-shaped receptor molecules, functionalized at one side wall with a porphyrin unit, have been synthesized starting from oxadiazines (cf. 368). Multiporphyrin systems have been synthesized and studied to obtain insight into energy and electron-transfer processes, which are very important with respect to the efficient solar energy conversion processes observed for photosynthetic bacteria <1999JOC6653>. Ionic liquids have emerged as promising alternative media for the replacement of conventional organic solvents. These salt-based materials often possess advantages over nonionic molecules since they exhibit very low vapor pressure, eliminating the risk of exposure through inhalation. The compound 397 has a high molar enthalpy of formation (704 kJ mol^{-1}) and falls into the ionic liquid class <2005IC1704>.

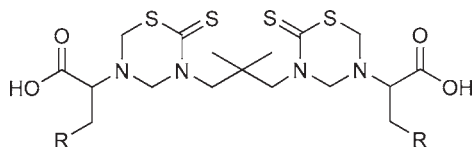


9.09.12.2 1,3,5-Thiadiazines

Over the last decade, more papers have appeared in the literature on the antibacterial <2003BMC4369>, antifungal, <1990AP605, 2000MI281, 2002MI438, 2005MI38>, antiparasitic, <2005AF232, 2003AF526>, anticancer <2000AF854>, antiprotozoan activities <1999AF764, 2005BMC3413> and antimycobacterial <2004MI35> and antitubercular activities <2003BMC4369> of THTT derivatives.

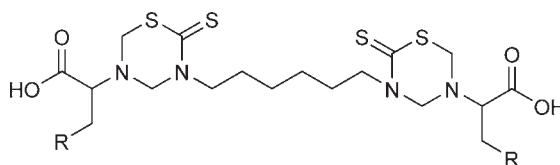


THTT derivatives have also found increased application in the drug research arena as biolabile prodrugs in the design of drug delivery systems (DDSs) due to their high lipid solubility and enzymatic rate of hydrolysis <1997MI327, 1999PHA244>. To enhance the antiprotozoal effect of 1,3,5-thiadiazines, alkyl-linked bis(2-thioxo-[1,3,5]thiadiazinan-3-yl)carboxylic acids were synthesized with the aim of using them as prodrugs to inhibit the cysteine proteinase of some protozoans. Two THTT rings were incorporated into one molecule by connecting the two rings via their N-3 atoms using a linear or branched aliphatic backbone. Additionally, carboxyalkyl residues were attached at N-5 <2005BMC3413>. Compounds 258a and 258b were found to be more active against *Trypanosoma*, while 258c and 258d were most active against trichomonas <2005BMC3413>.



258a: R = Prⁱ

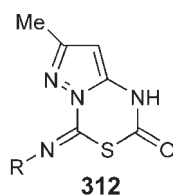
258b: R = Ph



258c: R = CH₂SCH₃

258d: R = CONH₂

Methyl 2-benzyl-6-diethylamino-4-phenyl-2H-1,3,5-thiadiazine **48** was shown to have significant antifungal activity <2004AXE713>. Dazomet **154** is known as a major fumigant for soil fumigation with high application rates (~320 lb ac⁻¹). Pyrazolo[1,5-*c*][1,3,5]thiadiazine-2-ones **312** have been synthesized as potential inhibitors of the photosynthetic electron-transport chain at the photosystem II level. Their biological activity was evaluated *in vivo* upon both the growth of blue-green algae and the oxygen evolution by eukaryotic algae and *in vitro* from their ability to interfere with light-driven reduction of ferricyanide by isolated spinach chloroplasts. Compounds **312c** and **312d** were found to be very active <2004JFA1898>.



c: R = Et

d: R = Buⁿ

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9.10

Dioxazines, Oxathiazines, and Dithiazines

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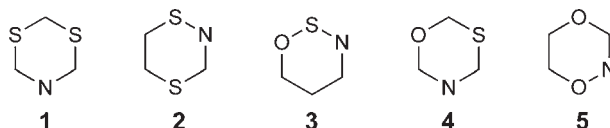
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9.10.1 Introduction

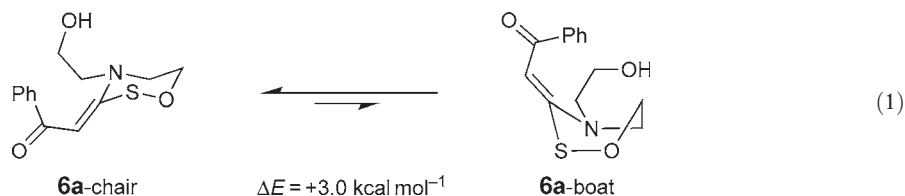
This chapter deals with heterocyclic compounds containing one nitrogen as part of the ring, as well as two oxygens (dioxazines), one oxygen and one sulfur (oxathiazines), or two sulfurs (dithiazines). An excellent overview of these systems was provided in CHEC(1984) <1984CHEC(3)1039>, which was updated in CHEC-II(1996) <1996CHEC-II(6)825>. For the present edition, this chapter covers new developments reported since 1996. In particular, the decade 1996–2005 has witnessed novel reports on 15 different classes of the heterocycles of interest: four isomeric dioxazines, six oxathiazines, and five dithiazines. Most studied are 1,3,5-dithiazines **1**, 1,4,2-dithiazines **2**, 1,2,3-oxathiazines **3** (and their 2,2-dioxide derivatives), 1,3,5-oxathiazines **4**, and 1,4,2-dioxazines **5**.



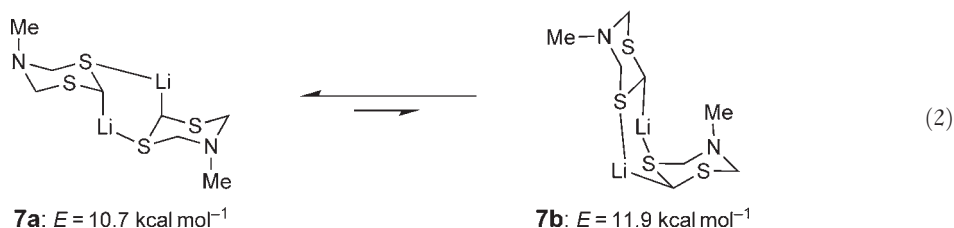
9.10.2 Theoretical Methods

Presently, theoretical studies of the heterocyclic compounds of interest in this chapter are most relevant. Indeed, the use of computational modeling of these systems has increased substantially during the last decade.

Molecular mechanics calculations (MMFF94 program) for oxathiazine **6a** showed the distorted chair conformation of the heterocyclic ring to be more stable than the boat by $3.0 \text{ kcal mol}^{-1}$ (Equation 1) <2005ZNB945>.

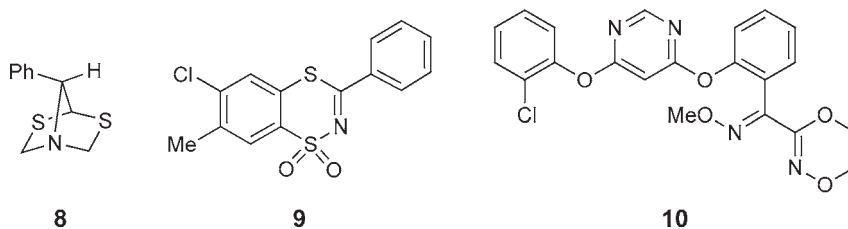


Also, by means of molecular mechanics, the relative energies of dimeric lithio derivatives, axial **7a** and equatorial **7b**, were estimated as 10.7 and $11.9 \text{ kcal mol}^{-1}$, respectively. Thus, it is suggested that the organolithium presenting the axial carbon–lithium bond is more stable than the equatorial isomer (Equation 2) <1997CB813>. This is most surprising in view of the very large preference for equatorial lithium in analogous 2-lithio-1,3-dithianes <1977JA8262, 1997JA7545>.

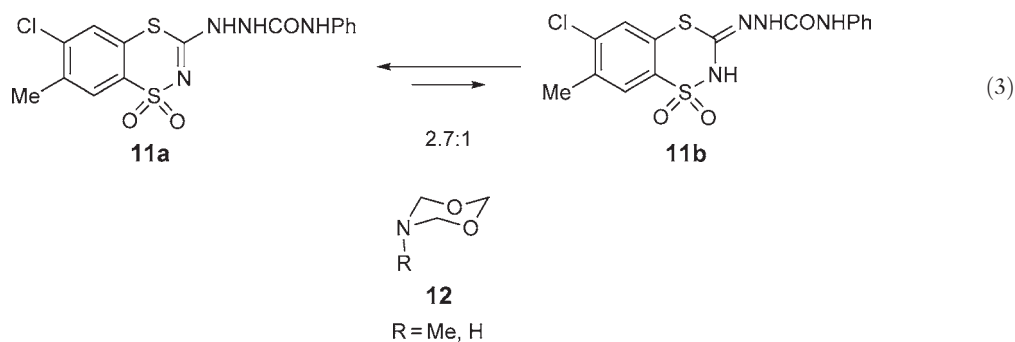


Also of interest is the density functional theory (DFT) (B3LYP/3-21G* level) study of the 1,3,5-dithiazine bicyclic derivative **8**, whose optimized geometry shows interproton distances that are in good agreement with observed nuclear magnetic resonance (NMR) nuclear Overhauser effect (NOE) values <2003SL1731>.

Density functional calculations (B3LYP method, 6-31** basis set) revealed that dithiazine **9** exhibits a preference for a boat conformation, which is $3.4 \text{ kcal mol}^{-1}$ more stable than the sofa conformation <2005JHC1297>. High-level (DFT/TZVP) calculations provided the minimum-energy conformation for dioxazine **10**. Furthermore, ^{13}C and ^1H NMR spectra for these low-energy conformations were calculated by means of GIAO-DFT/BP/TZVP <2004PNB299>.



Ab initio and density functional calculations afforded also the relative energies as well as dipole moments for tautomers **11a** and **11b** (Equation 3). The recorded data indicate that tautomer **11a** is more stable than imino tautomer **11b** by $1.76 \text{ kcal mol}^{-1}$, which is in line with available experimental observations <2003FA423>. *Ab initio* HF/6-31G** studies for 1,3,5-dioxazine **12** suggest a predominance of axial N–R, which was ascribed to $n_{\text{N}} \rightarrow \sigma_{\text{C-O}}^*$ hyperconjugation <1997JOC6144>.



9.10.3 Experimental Structural Methods

9.10.3.1 X-Ray Crystallography

X-Ray diffraction crystallography has been used extensively to establish the precise structural parameters and conformations of dioxa-, oxathia-, and dithiazines. In this section, several representative examples are presented.

The crystallographic structure of 1,3,5-dithiazine **13** revealed a chair conformation for the heterocyclic ring. Furthermore, the C(2) 2-[bis-(4-fluorophenyl)methoxy]ethyl substituent was found to occupy an equatorial position, whereas the *N*-(3-phenylpropyl) group adopts an axial orientation <2003JHC827>. In this regard, the preference for axial substituents at nitrogen in 1,3,5-dithiazines has been explained in terms of $n_N \rightarrow \sigma_{C-S}^*$ hyperconjugative stabilization (Figure 1) <1989JA6745>.

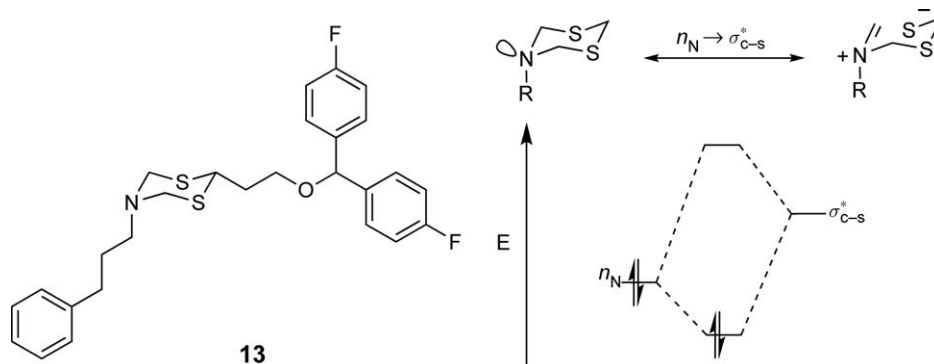
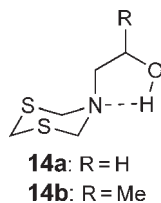


Figure 1 Preferred conformation of 1,3,5-dithiazine **13** and the stereoelectronic interaction stabilizing axial N-R substituents.

Dithiazines **14a** and **14b** present chair conformations in the crystal, with the *N*-substituent adopting again an axial orientation. The hydroxyl proton orients toward N(5), suggesting hydrogen bond formation <2004H(63)2269>.



1,4,2-Dithiazine sulfone **15** exhibits all atoms in the heterocyclic ring as coplanar (to within $\pm 0.04 \text{ \AA}$) <1997JP11157>. In contrast, analog **16** was shown previously to adopt a boat ring conformation <1992JP12295>. Table 1 summarizes the relevant bond lengths in **15** and **16**.

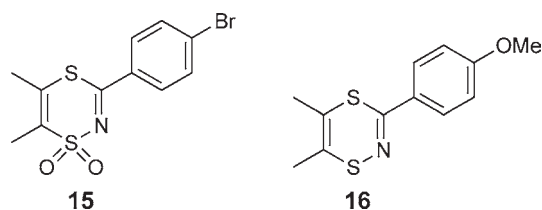
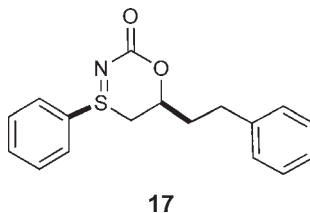


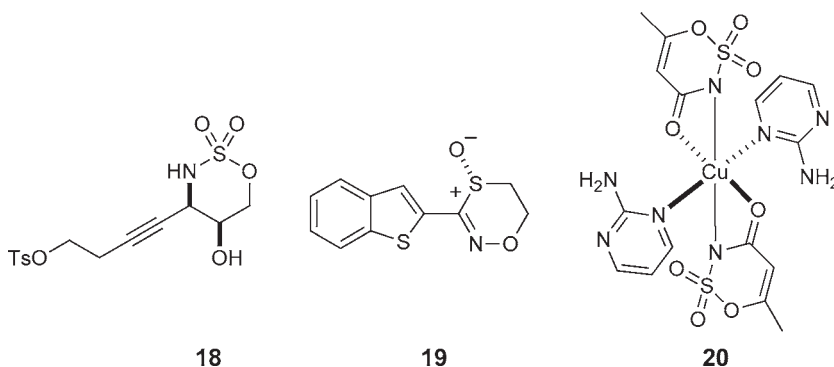
Table 1 Selected bond distances (Å) in 1,4,2-dithiazines **15** and **16** <1997JP11157>

Bond	15	16
S(1)–N(2)	1.622	1.709
S(1)–C(6)	1.754	1.752
N(2)–C(3)	1.287	1.274
C(3)–S(4)	1.739	1.785
S(4)–C(5)	1.751	1.762
C(5)–C(6)	1.336	1.336

In 1,4,3-oxathiazinone **17**, the segment composed by N(3), C(2), C(6), O(1), and O(carbonyl) is nearly planar (maximum deviation from the mean plane 0.047 Å) <2001AXEo252>.



1,2,3-Oxathiazine **18** adopts a chair conformation with the alkynyl group equatorial and the hydroxyl group axial <2003JA2028>. By contrast, 1,4,2-oxathiazine sulfoxide **19** presents a half-chair ring conformation <1997AXC823>. Finally, Cu(II) mixed complex **20** incorporates a 1,2,3-oxathiazin-4-one heterocycle in a distorted octahedral geometry <2005AXCm228>.



9.10.3.2 NMR Spectroscopy

^1H and ^{13}C NMR spectroscopic methods have been used extensively to secure the identification of most compounds reviewed in this chapter. Furthermore, ^{15}N NMR spectroscopy is employed frequently; for example, 1,4,2-dioxazine **10** shows a ^{15}N chemical shift of -66.4 ppm <2004PNB299>, whereas dithiazine **14b** exhibits a ^{15}N chemical shift of -310.6 ppm <2004H(63)2269>. Reports on the use of ^{17}O and ^{33}S nuclei did not appear in the period of time covered in the present review. ^1H NMR data were particularly useful for the stereochemical assignment of sulfamidites

21 by comparison with sulfamidate **22** (Figure 2) <2001OL2965>. Variable-temperature experiments permitted estimation of kinetic and thermodynamic data such as ring inversion barriers <1999H(51)2079, 2004H(63)2269>.

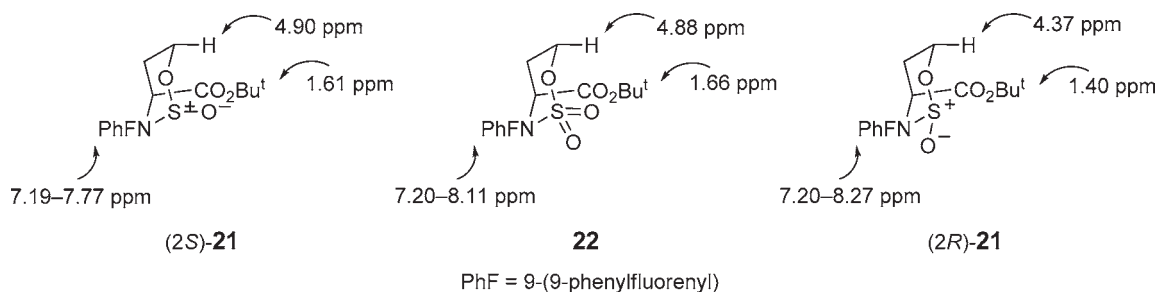
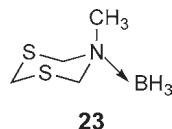


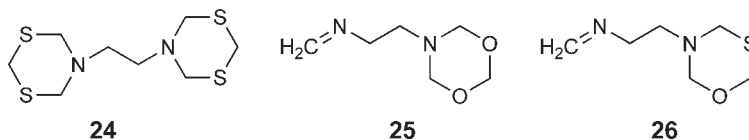
Figure 2 Anisotropic effect of the S–O group on the ^1H NMR chemical shifts of compounds **21** and **22** <2001OL2965>.

NOEs are most useful in this area. For example, dithiazine **8** gives rise to NOE enhancements that are consistent with the orientation of the phenyl ring predicted from DFT calculations (Section 9.10.2) <2003SL1731>. Relaxation time measurements ^1H - T_1 confirmed the existence of $\text{C}-\text{H}^{\delta+}\cdots\delta^-\text{H}-\text{B}$ interactions in dithiazine **23** <2001IC3243>.



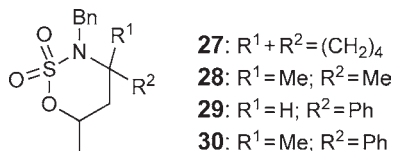
9.10.3.3 Mass Spectrometry

Mass spectrometry (MS) has been used for the identification of most heterocycles included in this chapter. Typical fragments observed from these compounds are: CO, CO₂, CH₂O, S and SO₂ <1996CHEII(6)829>. For example, in addition to the molecular ion, dithiazine **24** afforded fragmentation ions $[\text{M}-\text{HS}]^+$, $[\text{M}-\text{CH}_2\text{S}]^+$, $[\text{M}-\text{SCH}_2\text{S}]^+$, $[\text{M}-\text{SCH}_2\text{SCH}_2\text{S}]^+$, and $[\text{M}-\text{SCH}_2\text{SCH}_2\text{SCH}_2\text{S}]^+$. By the same token, 1,3,5-dioxazine **25** gave peaks $[\text{M}]^+$, $[\text{M}-\text{OCH}_2]^+$, $[\text{M}-\text{CH}_2\text{OCH}_2]^+$, $[\text{M}-\text{CH}_2\text{OCH}_2\text{O}]^+$ and $[\text{M}-\text{CH}_2\text{OCH}_2\text{OCH}_2]^+$. Finally, oxathiazine **26** produced the molecular ion as well as fragments $[\text{M}-\text{S}]^+$, $[\text{M}-\text{SCH}_2]^+$, $[\text{M}-\text{CH}_2\text{SCH}_2]^+$, $[\text{M}-\text{CH}_2\text{SCH}_2\text{O}]^+$, and $[\text{M}-\text{CH}_2\text{SCH}_2\text{OCH}_2]^+$ <2005RCB432>.



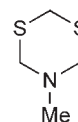
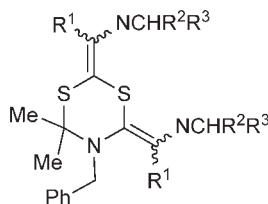
9.10.3.4 IR Spectroscopy

This spectroscopic technique typically complements NMR and MS methods and serves to identify functional groups such as C=O, C=N, C=S, C=C, and SO₂. For example, the SO₂ group in **27–30** gives rise to bands arising from S=O stretching at 1370–1190 cm⁻¹ <2004CHE1097>.



9.10.3.5 UV/Vis Photoelectron Spectroscopy

Apparently, electron spin resonance (ESR) spectroscopy has not been employed during the 1996–2005 time period in the published studies of the systems of interest. By contrast, ultraviolet (UV) spectra of 1,3,5-dithiazines **31a–c** are discussed in their preparation <1998JP13731>. Furthermore, ultraviolet photoelectron spectroscopy of 5-methyl-1,3,5-dithiazine **32** was used to gather relevant conformational data <1996JOC786>.



32

31a: $R^1 = \text{Me}$; $R^2 = R^3 = \text{H}$; λ_{max} (C_6H_{12})/nm 260 (ϵ 10700 mol $^{-1}$ cm $^{-1}$)

31b: $R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{Me}$; λ_{max} (C_6H_{12})/nm 260 (ϵ 9550 mol $^{-1}$ cm $^{-1}$)

31c: $R^1 + R^2 = -(\text{CH}_2)_4-$; $R^3 = \text{H}$; λ_{max} (C_6H_{12})/nm 259 (ϵ 11900 mol $^{-1}$ cm $^{-1}$)

9.10.4 Thermodynamic Aspects

9.10.4.1 Boiling and Melting Points

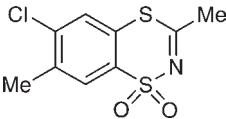
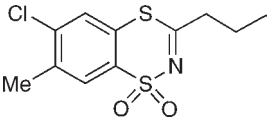
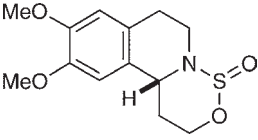
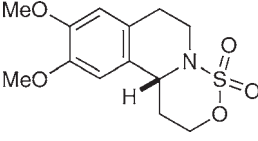
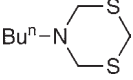
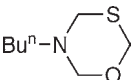
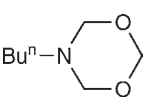
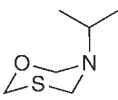
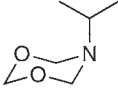
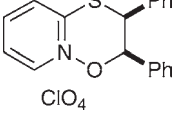
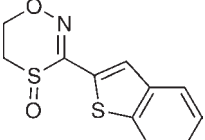
The compounds of interest in this chapter present boiling and melting points that reflect their molecular structure. One of the salient tendencies is that molecules with ring unsaturations become more rigid and show higher melting points relative to the corresponding saturated analogs. The second is that the presence of aromatic group substituents increases the melting point temperature. By contrast, flexible and/or bulky alkyl substituents usually lead to lower melting points. Third, for heterocyclic compounds with sulfur, melting points increase as the oxidation state of sulfur increases. That is, incorporation of the sulfonyl group in the ring usually leads to melting points that are higher than those observed in analogs containing the sulfinyl (S(O)) or sulfide (S) groups <1996CHEC-II(6)825>. Finally, for equally substituted 1,3,5-heterocycles, melting points decrease in the order dithiazines > oxathiazines > dioxazines. **Table 2** collects several illustrative examples.

Table 2 Boiling and melting points for several illustrative dioxazines, oxathiazines, and dithiazines

Compound number	<i>m.p.</i> (°C)	<i>b.p.</i> (°C) (mm Hg)	Solvent of crystallization	Reference
	145–147			2005JHC1297
	194–195		Acetone	2005JHC1297
	200–201			2005JHC1297

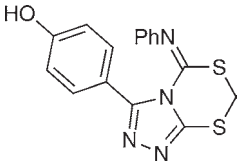
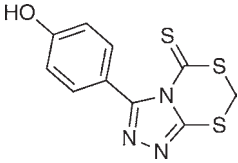
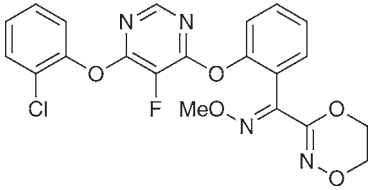
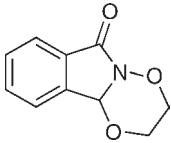
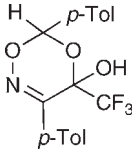
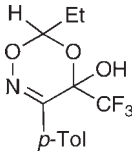
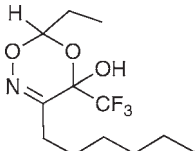
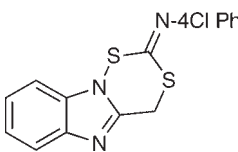
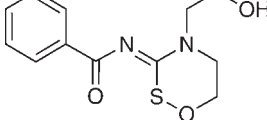
(Continued)

Table 2 (Continued)

<i>Compound number</i>	<i>m.p.</i> (°C)	<i>b.p.</i> (°C) (mm Hg)	<i>Solvent of crystallization</i>	<i>Reference</i>
	176–177			2005JHC1297
	108–109			2005JHC1297
	118–119		Diisopropyl ether	2000JCS(P2)287
	133–134		Diisopropyl ether	2000JCS(P2)287
	95–96			2005RCB432
	88–89			2005RCB432
	45–46			2005RCB432
	40 (1)			1999H(51)2079
	20 (0.7)			1999H(51)2079
	245–247		Chloroform: acetonitrile, 3:1	2003CHE1263
	143–150			2003FLS5

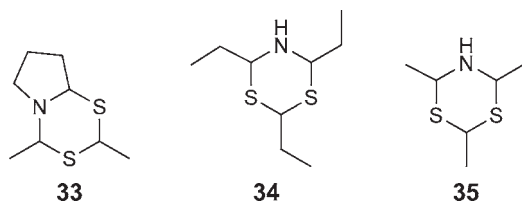
(Continued)

Table 2 (Continued)

<i>Compound number</i>	<i>m.p. (°C)</i>	<i>b.p. (°C) (mm Hg)</i>	<i>Solvent of crystallization</i>	<i>Reference</i>
	109		Dipropylene: ethanol, 1:2	1997IJB442
	99		Ethanol	1997IJB442
	103–108			2004PNB299
	142–144		Methanol	1999TL2117
	177–179		CCl ₄	1999JHC917
	118–119		CCl ₄	1999JHC917
		Syrupy oil		1999JHC917
	167–168		Ethanol	1996IJB748
	142–144		Ethanol:hexane	2005ZNB945

9.10.4.2 Chromatographic Behavior

Gas chromatography–orthogonal acceleration time-of-flight mass spectrometry (GC–oaTOFMS) facilitated the identification of 1,3,5-dithiazine **33** from extracts of marine natural products <2003JAF2708>. Similarly, GC coupled to MS allowed identification of dihydro-2,4,6-triethyl-(4*H*)-1,3,5-dithiazine **34** as one main component of seed oil in *Azadirachta indica* <2005JWS185>. By the same token, GC–MS techniques made possible the identification of each isomer of 1,3,5-dithiazine **35** (thialdine) <1997FST411>.



9.10.4.3 Aromaticity

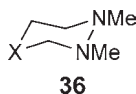
Six-membered heterocycles containing one nitrogen and two oxygens and/or sulfurs cannot be aromatic unless they are completely delocalized π -systems <1996CHEC-II(6)825>. For instance, dithiazine **16** corresponds actually to an antiaromatic system with 8π electrons.

As a consequence, the X-ray crystallographic structure of **16** shows a boat rather than planar conformation. By contrast, analog **15** exhibits a nearly planar ring with short endocyclic bonds, suggesting enhanced delocalization <1997JP11157>.

9.10.4.4 Conformational Analysis

In the last decades, the conformational behavior of six-membered heterocycles has been studied thoroughly <B-1991MI>. From these studies, several tendencies have been established:

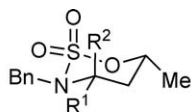
1. Inclusion of endocyclic sulfur atoms lowers the barrier to ring inversion on account of the longer C–S bond and smaller C–S–C angle.
2. Oxygen-containing rings also present lower ring inversion barriers relative to their nitrogen analogs. For analogs **36**, the inversion barrier decreases along the series $X = \text{CH}_2 > \text{NMe} > \text{O} > \text{S}$ <1980JP2279>.



3. A sulfoxide group preferentially occupies an axial orientation.
4. Systems containing nitrogen can undergo conformational change through ring inversion or umbrella inversion at the nitrogen center. The latter process usually requires lower energy.
5. α -Heteroatom substitution on nitrogen raises the barrier to nitrogen inversion while β -heteroatom substitution lowers it <1996CHEC-II(6)825>.

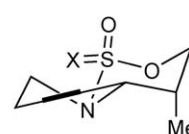
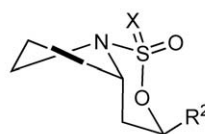
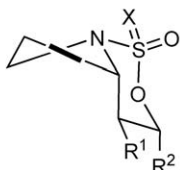
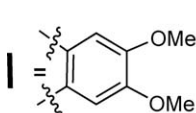
9.10.4.4.1 Oxathiazines

According to ^1H NMR data, oxathiazines **37** and **38** adopt a chair conformation with an equatorial C(6)–Me group <2004CHE1097>. The relative configurations and the predominant conformations in 1,2,3-oxathiazino[4,3-*a*]-isoquinolines **39–47** were determined by ^1H and ^{13}C NMR <2000JP2287>.



37: $R^1 + R^2 = (CH_2)_4$

38: $R^1 = R^2 = Me$



39: $X = \text{O}; R^1 = R^2 = H$

40: $X = O; R^1 = R^2 = H$

41: $X = \text{O}; R^1 = Me; R^2 = H$

42: $X = \text{O}; R^1 = H; R^2 = Me$

43: $X = O; R^1 = H; R^2 = Me$

44: $X = \text{O}; R^2 = Me$

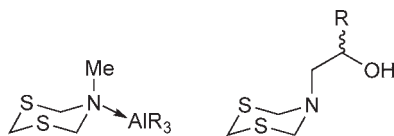
45: $X = O; R^2 = Me$

46: $X = \text{O}$

47: $X = O$

9.10.4.4.2 Dithiazines

^1H NMR analysis of complexes **48a–c** was interpreted in terms of chair conformations with aluminium adopting an equatorial orientation. Variable-temperature NMR experiments afforded the ring inversion barriers, $\Delta G^\ddagger$: 62.6 ± 0.5 , **48a**; 68.5 ± 0.5 , **48b**; and 51.7 ± 0.5 kJ mol^{-1} , **48c** <2004EJI601>. Similarly, variable-temperature ^1H NMR spectra of dithiazine carbinols **14a–c** provided $\Delta G^\ddagger$ values: 45.4 , **14a**; 49.5 , **14b**; and 49.3 kJ mol^{-1} , **14c**. These values are quite similar to the one determined for N-methylated analog N-methyl-1,3,5-dithiazine ($\Delta G^\ddagger = 46.0$ kJ mol^{-1}) <2004H(63)2269>.



48a: $R = Me$

48b: $R = Cl$

48c: $R = Br$

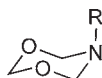
14a: $R = H$

14b: $R = Me$

14c: $R = Ph$

9.10.4.4.3 Dioxazines

Variable-temperature ^1H NMR spectroscopy was also the tool employed for the determination of the activation energy for ring inversion in 1,3,5-dioxazines **49a–c**: $\Delta G^\ddagger = 45.0$, **49a**; 46.0 , **49b**; and 49.0 kJ mol^{-1} , **49c** <1999H(51)2079>.



49a: $R = \text{Pr}^i$

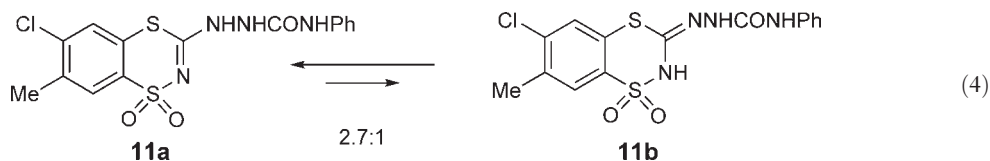
49b: $R = \text{Bu}^t$

49c: $R = (R)\text{-}\alpha\text{-methylbenzyl}$

9.10.4.5 Tautomerism

9.10.4.5.1 Prototropic tautomerism

This type of tautomerism may take place in systems containing an amide functionality <1996CHEC-II(6)825>. One example is 1,4,2-benzodithiazine 1,1-dioxide **11**, where ^1H NMR spectra indicated the existence of a tautomeric equilibrium between **11a** and **11b** in a 2.7:1 ratio (Equation 4) <2003FA423>.

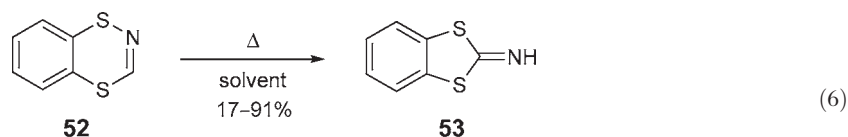
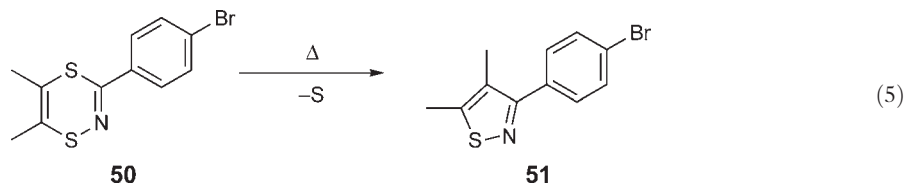


9.10.5 Reactivity of Fully Conjugated Rings

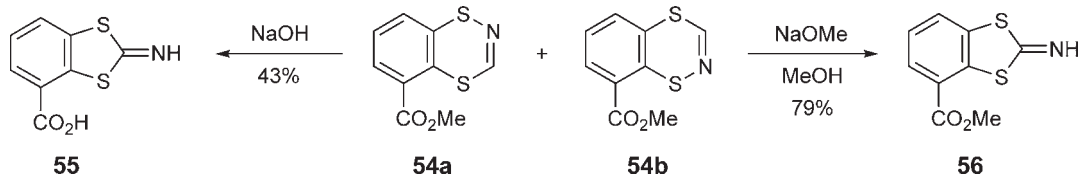
This section deals with the reactivity of fully conjugated dioxazines, dithiazines, and oxathiazines; that is, heterocycles that do not contain sp^3 -hybridized carbon or nitrogen.

9.10.5.1 Unimolecular Thermal and Photochemical Reactions

The thermal process of sulfur S(4) extrusion in 1,4,2-benzodithiazines to give isothiazoles is well known <1996CHEC-II(6)825>. This reaction is illustrated with the conversion of compound **50** to afford **51** (Equation 5) <1997JP11157>. Unsubstituted 1,4,2-benzodithiazines **52** undergo rearrangements that produce 2-imino-1,3-benzodithiols **53** (Equation 6) <1984H(22)27, 1996CHEC-II(6)825>. This rearrangement can be promoted also with strong base (EtONa, Bu^tOK and BuLi, NaOH, NaOMe). Examples are the transformations of substrates **54a** and **54b** into **55** and **56**, respectively (Scheme 1) <2000JHC955>.



Solvent = pyridine, EtOH, none

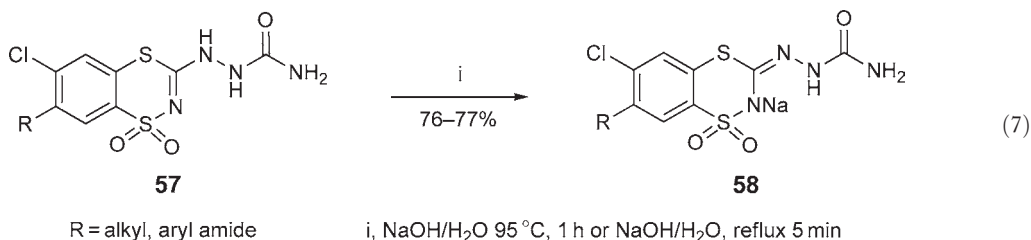


Scheme 1

9.10.5.2 Electrophilic Attack at Nitrogen

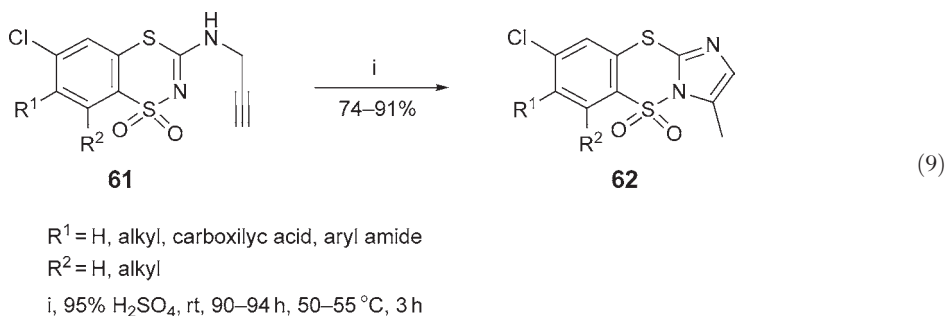
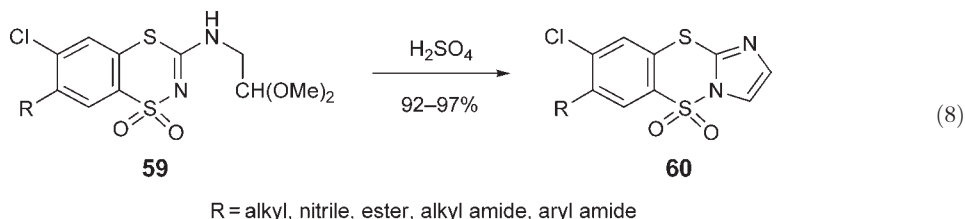
9.10.5.2.1 Salt formation

Treatment of semicarbazides **57** with NaOH generated the corresponding sodium salts **58** (Equation 7) <2003FA423>.



9.10.5.2.2 Intramolecular cyclization

Electrophilic addition at N(2) in 3-substituted-1,4,2-benzodithiazines leads to intramolecular cyclization. For example, cyclocondensation of ketals **59** affords imidazo-1,4,2-benzodithiazines **60** (Equation 8) <1997APP293>. Similarly, treatment of **61** with excess H₂SO₄ generated 3-methylimidazo-1,4,2-benzodithiazine **62** (Equation 9) <2006BMC2985>.



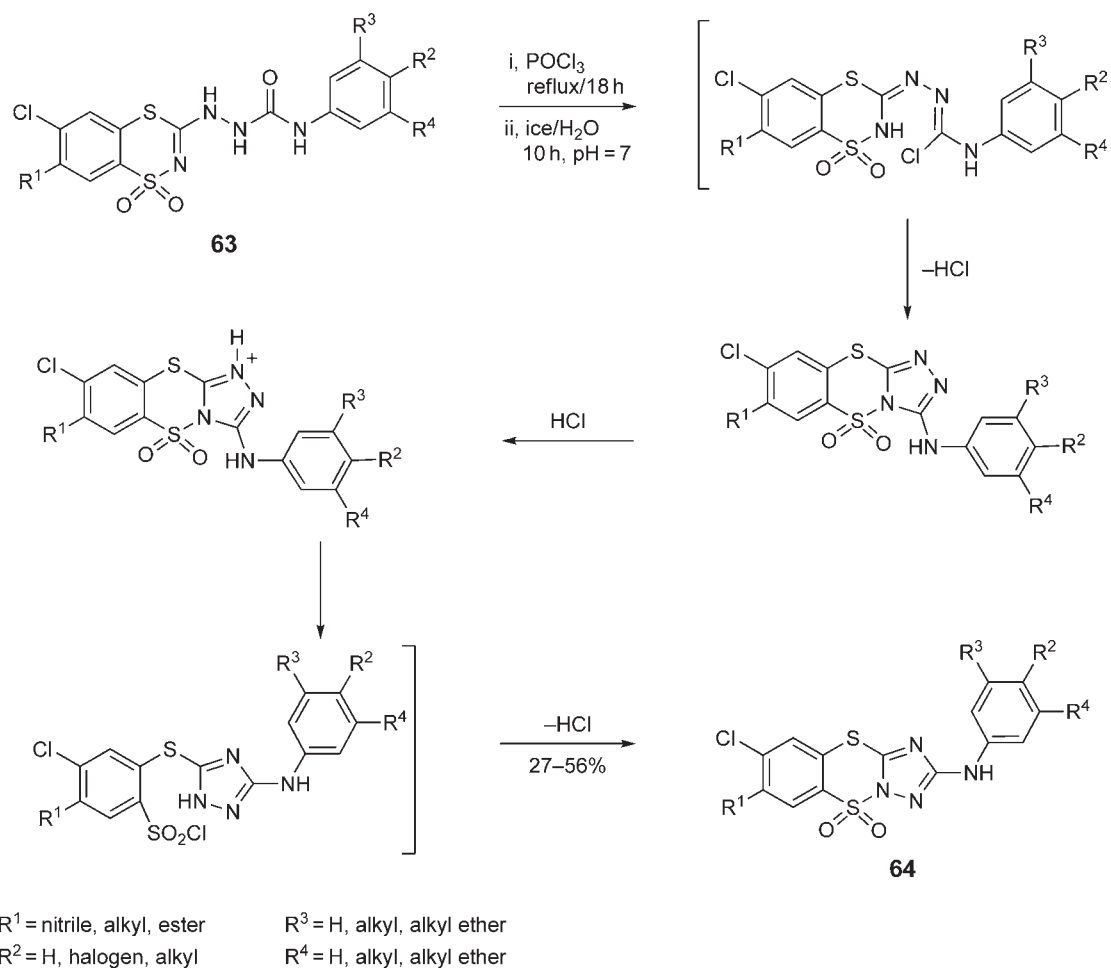
9.10.5.2.3 Miscellaneous electrophilic reactions

Semicarbazides **63** react with POCl₃ to give triazolo-1,4,2-benzothiazines **64**, possibly according to the mechanism depicted in Scheme 2 <2003BMC1259>.

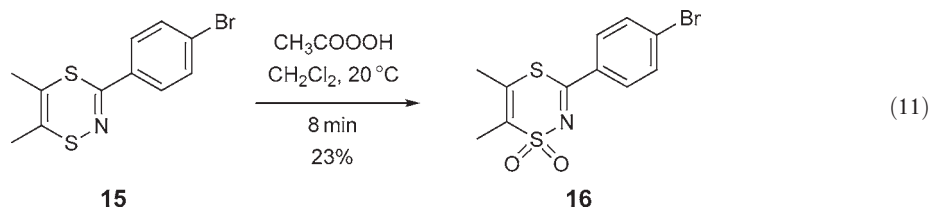
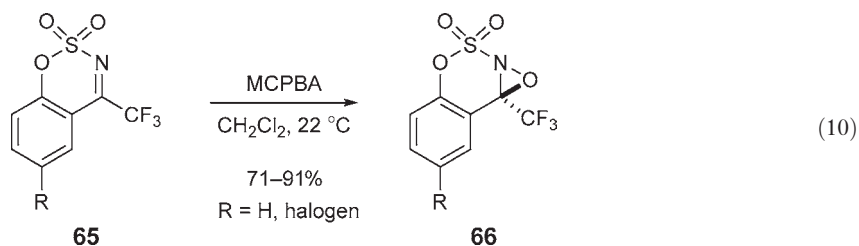
9.10.5.2.4 Oxidation reactions with peracids

Benzothiazines **65** were subjected to oxidation with *meta*-chloroperbenzoic acid (MCPBA) to afford oxaziridines **66** (Equation 10) <2005JA15391>.

In heterocycles containing endocyclic sulfur, peracids are efficient electrophilic oxidizing reagents <B-2000MI194>. One illustrative example is the preparation of 1,4,2-dithiazine 1,1,-dioxide **16**, via oxidation of dithiazine **15** (Equation 11) <1997JP11157>.



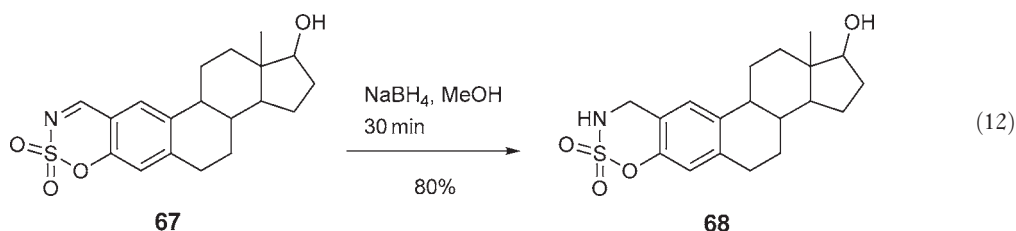
Scheme 2



9.10.5.3 Nucleophilic Attack at Carbon

9.10.5.3.1 With hydride as nucleophile

Reduction of the C=N bond in steroidal 1,2,3-oxathiazine **67** was accomplished with sodium borohydride to give derivative **68** (Equation 12) <2003ST97>. Lithium aluminium hydride has been employed also for this kind of reduction <1996CHEC-II(6)825>.

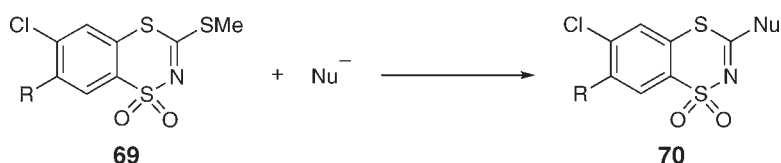


9.10.5.3.2 With nitrogen as nucleophile

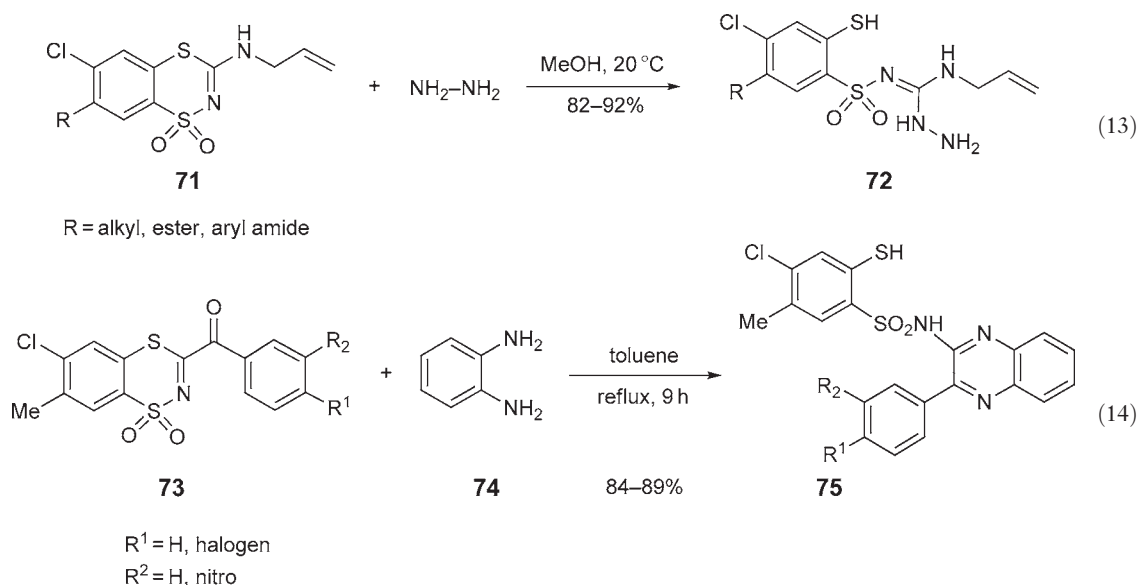
In the presence of nucleophiles, 3-methylthio-1,4,2-benzodithiazines **69** suffer displacement of the leaving group at C(3) to afford derivatives **70**. Nucleophilic reagents include amines <2002EJM285, 1997APP293, 2006BMC2985>, hydrazines <1997APP49, 1998APP473>, semicarbazides <2003BMC1259>, 2003FA423> and arylsulfamides <2003BMC3673>.

Table 3 collects several representative examples of this reaction. When the substrate does not incorporate a good leaving group at C(3), nucleophilic attack takes place with concomitant ring opening. Examples are the reaction of **71** with excess hydrazine to give guanidines **72** (Equation 13) <2002EJM285>, and the nucleophilic addition of diamine **74** to substrate **73**, followed by cyclization to afford products **75** (Equation 14) <2004JMC385>.

Table 3 Representative examples of nucleophilic displacements in substrates **69**

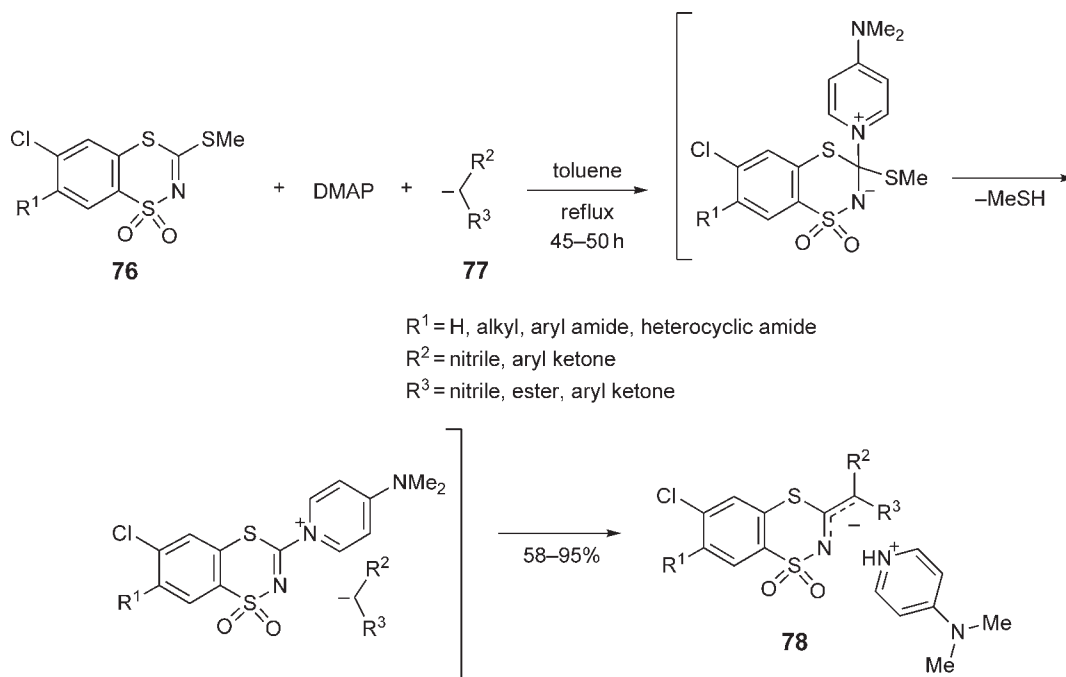


Entry	R	Conditions	Nu ⁻	Yield (%)	Reference
1	Me	NH ₄ OH/EtOH, rt, 120–144 h	NH ₃	73	2001PJC1309
2	Me	Benzene, rt, 3 h		95	2002EJM285
3	Me	Toluene, 8–14 h		97	1997APP293
4	Me	Benzene, 20 °C for 3h, reflux for 40–50 h		96	2006BMC2985
5	Me	DMAP, toluene H ₂ SO ₄ , MeCO ₂ H		84	2003BMC3673
6	MeOCO	MeOH, reflux, 9–15 h		91	1997APP49
7	2-ClPhNHCO	MeOH, reflux, 30 h		93	2003FA423



9.10.5.3.3 With carbon as nucleophile

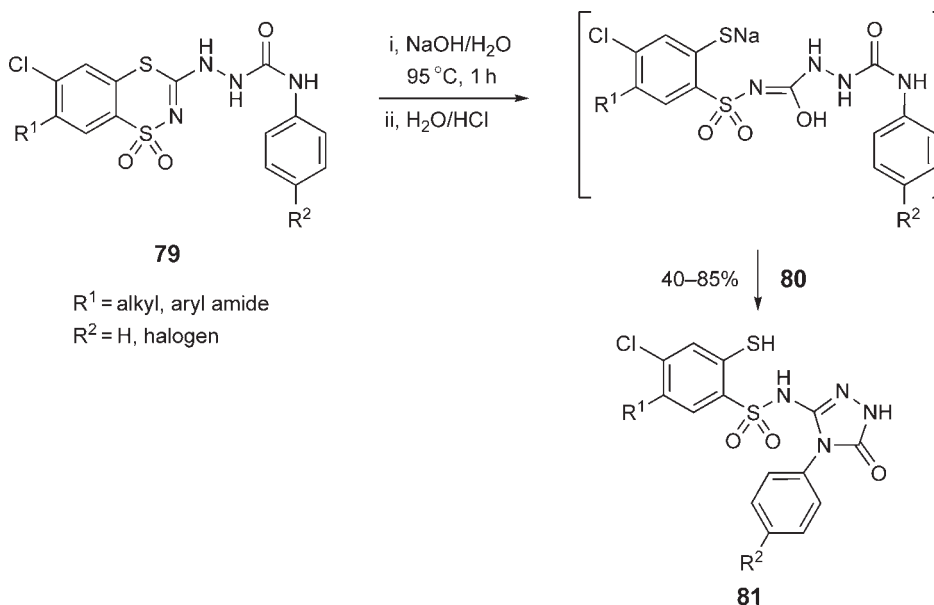
3-Methylthio-1,4,2-benzodithiazine 1,1-dioxides **76** are prone also to nucleophilic displacement reactions by carb-anionic reagents of the general type **77** in the presence of 4-dimethylaminopyridine (DMAP) to give pyridinium salts **78** (Scheme 3) <2003EJM991>.



Scheme 3

9.10.5.3.4 With oxygen as nucleophile

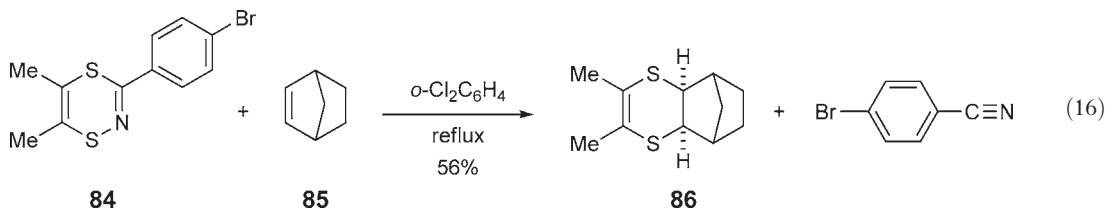
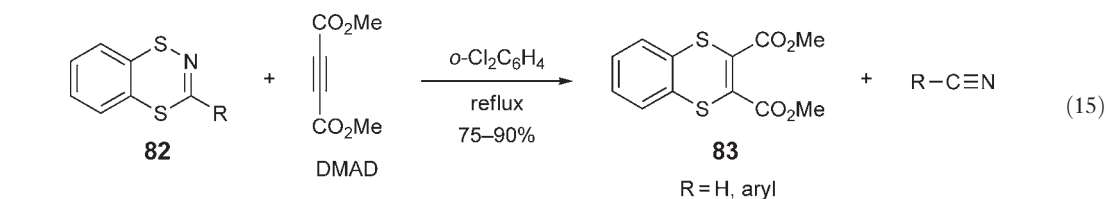
Upon treatment with NaOH, 1,1-dioxo-1,4,2-benzodithiazin-3-yls **79** suffer ring opening to give intermediates **80**, which cyclize to provide triazole derivatives **81** (Scheme 4) <2003FA423>.



Scheme 4

9.10.5.4 Intermolecular Cyclic Transition State Reactions

Under refluxing conditions, 1,4-benzothiazines **82** undergo a cycloaddition reaction with dimethyl acetylenedicarboxylate (DMAD) to afford 1,4-benzodithiin **83** (Equation 15) <1982CC612>. Similarly, heating 1,4,2-dithiazine **84** in the presence of norbornene **85** produced 1,4-dithiine **86** (Equation 16) <1997JP11157, 2000JHC955>. 1,3-Dipolar cycloadditions of 1,2,3-oxathiazines with 1,3-diphenylnitrilimine were described in CHEC-II(1996) <1996CHEC-II(6)825>.

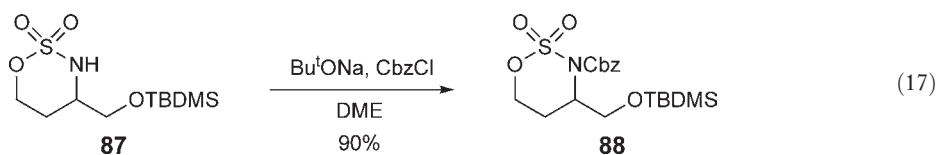


9.10.6 Reactivity of Nonconjugated Rings

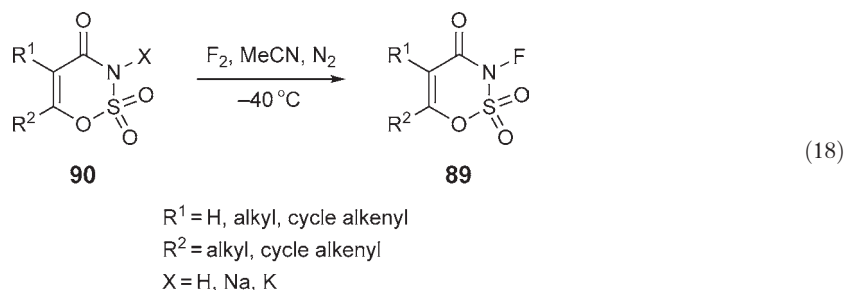
9.10.6.1 Reactivity at Nitrogen

9.10.6.1.1 Reaction with electrophiles

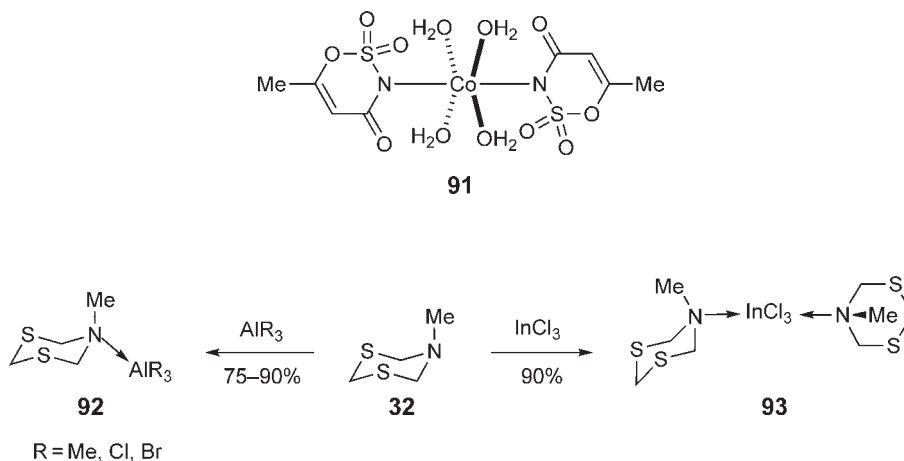
Under this heading, the most common types of reaction are those carried out to protect the nitrogen atom in the heterocycle. For example, tetrahydro-1,2,3-oxathiazine **87** has been protected with CbzCl to give derivative **88** (Equation 17) <2005OBC603>.



In the same vein, fluorinated dihydrooxathiazines **89** are obtained by the reaction of 1,2,3-oxathiazines **90** with F_2 at low temperature under a nitrogen atmosphere (Equation 18) <1995T10205, 1997USP5614626>.



Recently, the formation of complexes from acesulfame with cobalt (to give **91**) <2005AXCm1> and copper (to give **20**) <2005AXCm228> has been reported. Furthermore, N-adducts of 5-methyl-1,3,5-dithiazine **32** with aluminium-containing Lewis acids (to give **92**) and with InCl_3 to afford bis-adduct **93** were described recently (Scheme 5) <2004EJI601>.



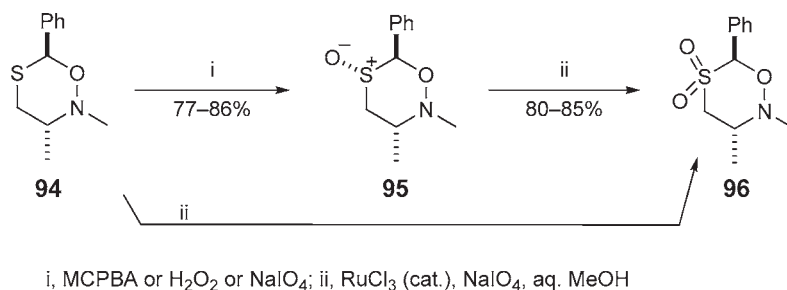
Scheme 5

9.10.6.2 Reactivity at Sulfur

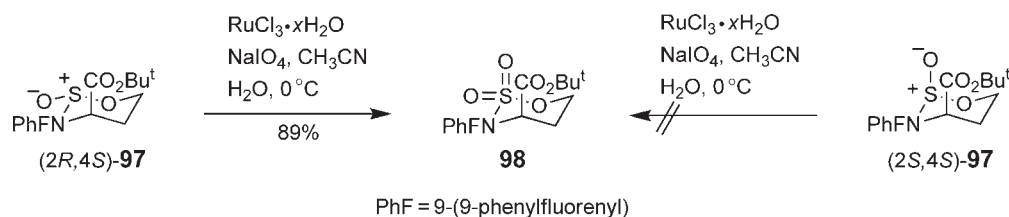
9.10.6.2.1 Reaction with electrophiles

In a nonconjugated system, the sulfur atom is particularly susceptible toward oxidation to give the corresponding sulfoxide or sulfone, depending on the reaction conditions. For example, dihydro-oxathiazine **94** has been oxidized with a variety of agents (MCPBA, H_2O_2 , NaIO_4) to provide sulfoxide **95**. By contrast, sulfone **96** was prepared by oxidation of either **94** or **95** with NaIO_4 in the presence of ruthenium trichloride (Scheme 6) <1997TL8549>.

By the same token, sulfamidite (2*R*,4*S*)-**97** was oxidized under catalytic conditions with RuCl_3 and NaIO_4 to provide sulfamate **98**. Interestingly, similar treatment of diastereomeric (2*S*,4*S*)-**97** did not afford the expected product **98**, owing to steric hindrance by the PhF group that hinders access by the oxidant (Scheme 7) <2001OL2965>.

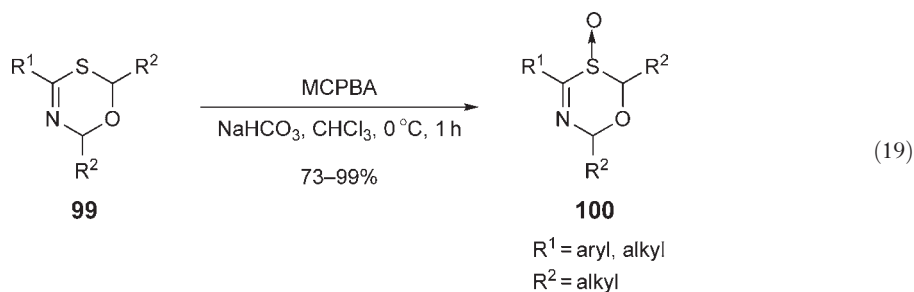


Scheme 6



Scheme 7

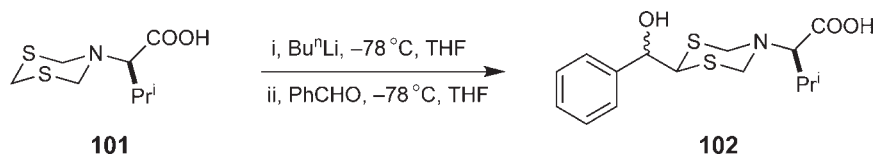
When 1,3,5-oxathiazines **99** were treated with MCPBA in chloroform, the corresponding *S*-oxides **100** were obtained (Equation 19) <2004HAC175>.



9.10.6.3 Reactivity at Carbon

9.10.6.3.1 Reaction with Brønsted bases

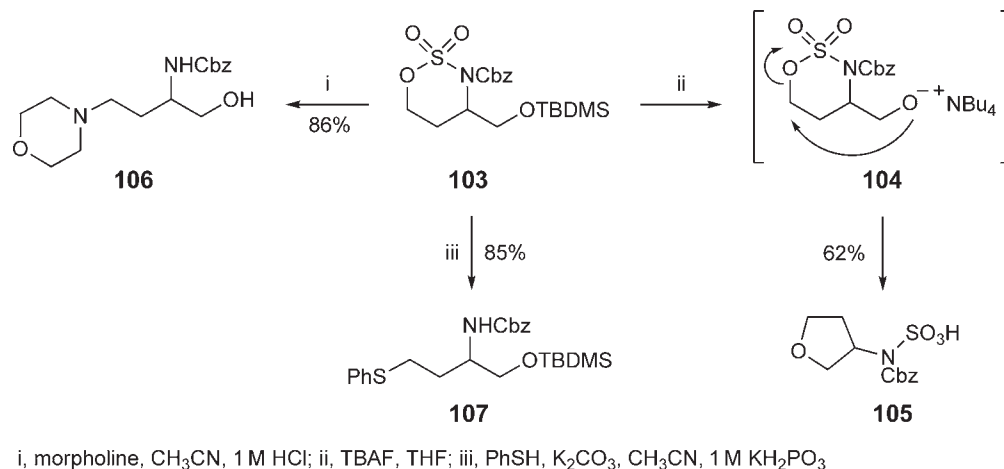
Dihydro-1,3,5-dithiazines **101** contain acidic hydrogens at C(2) that can be abstracted by strong bases such as *n*-butyllithium, affording a carbanionic species that is particularly reactive toward electrophiles such as benzaldehyde (Scheme 8) <2002OL4129, 2003JHC827, 2003SL1731>.



Scheme 8

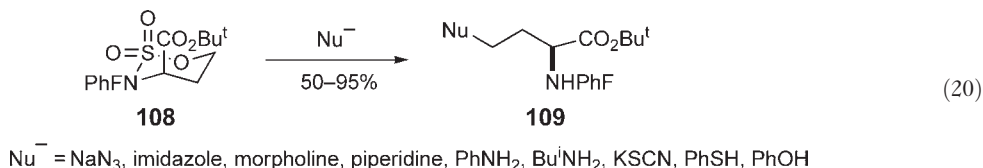
9.10.6.3.2 Reaction with nucleophiles

Nucleophilic attack at carbon atoms is quite common and usually results in opening of the heterocycle. Among the most typical types of substrate, one finds 1,2,3-oxathiazines. For example, in the nucleophilic addition of tetrabutylammonium fluoride (TBAF) to 1,2,3-oxathiazine **103**, the tetrabutylammonium alkoxide intermediate **104** reacts intramolecularly to give 3-aminotetrahydrofuran **105** <2005OBC603>. Substrate **103** undergoes similar nucleophilic additions with morpholine and phenylthiolate to afford derivatives **106** and **107** (Scheme 9).

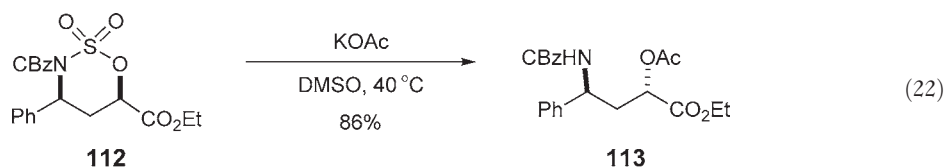
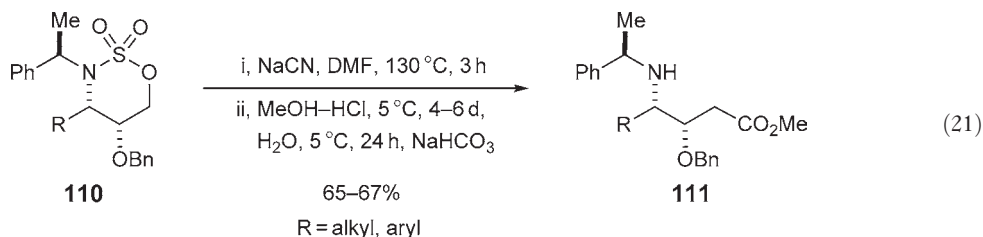


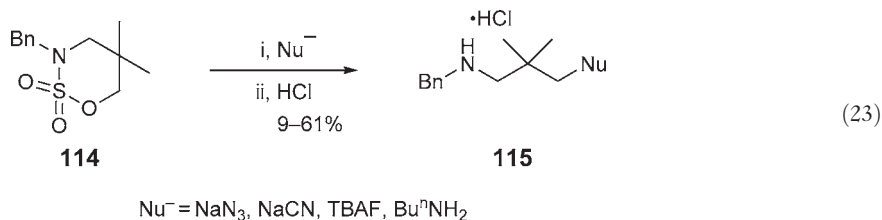
Scheme 9

1,2,3-Oxathiazine 2,2-dioxide **108** reacted at C(6) upon treatment with several nucleophiles to afford enantiopure α -amino acids **109** (Equation 20) <2001OL2965>.

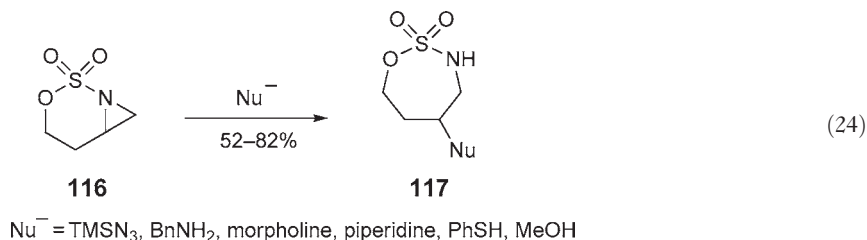


More drastic conditions may be required for the ring opening of other 1,2,3-oxathiazine 2,2-dioxides. For example, heterocycle **110** requires a high reaction temperature to produce **111** (Equation 21) <1996CC331>, whereas the ring opening of *N*-Cbz-oxathiazine **112** takes place at moderate temperature (40 °C) (Equation 22) <2001JA6935>. Oxathiazine **114** reacts with some nucleophiles, but presents a more limited reactivity owing to its neopentyl nature (Equation 23) <2002S859>.

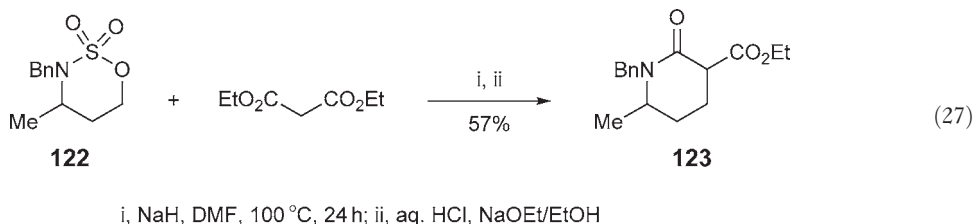
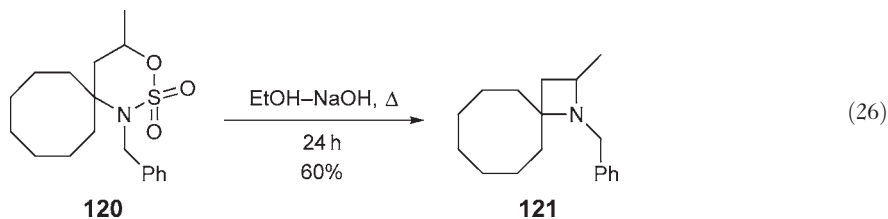
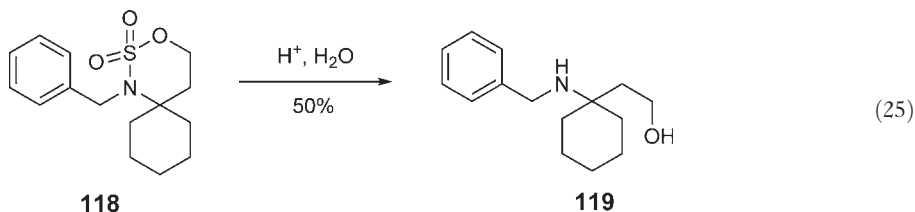




The presence of the aziridine ring in bicyclic system **116** leads to nucleophilic attack at C(4), affording seven-membered heterocycles **117** (Equation 24) <2002OL2481>.



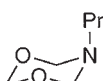
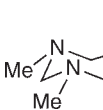
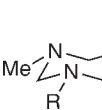
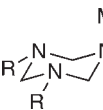
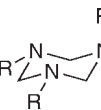
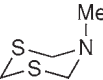
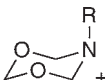
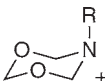
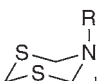
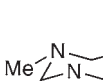
The amino alcohol **119** is obtained via hydrolysis of spiro-1,2,3-oxathiazine **118** (Equation 25) <1999CHE199>. When 1,2,3-oxathiazine **120** was treated with NaOH in EtOH, spiroazetidine **121** was produced (Equation 26) <2000H(53)785>. Finally, nucleophilic addition of methyl malonate to substrate **122** provided lactam (Equation 27) <2004OL4727>.

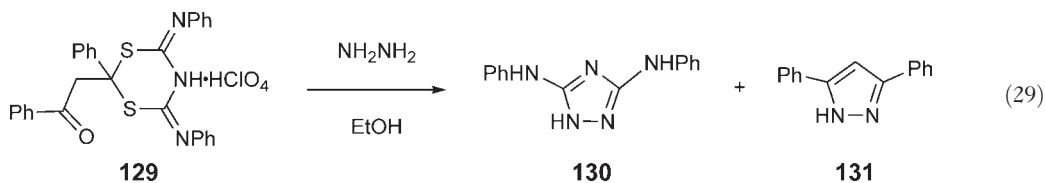
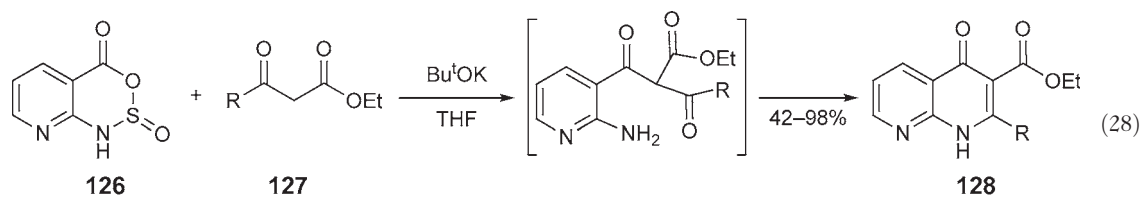


1,3,5-Dioxazine **124** and 1,3,5-dithiazine **125** undergo amination and/or transamination reactions with methylamine or *N*-methyl 1,3,5-triazine to give products arising from substitution of one, two, or three heteroatoms (Table 4). <1999H(51)2079>.

Nucleophilic additions are possible also at sp^2 carbons, either iminic or carbonylic <1996CHEC-II(6)825>. For example, 1,2,3-oxathiazine-2-oxides **126** react with β -keto esters **127** to afford open-chain intermediates that then cyclize to give products **128** (Equation 28) <2001JOC4413>. Reaction of dithiazine **129** with hydrazine generates 1,2,4-triazole **130**, the product of nucleophilic substitution at both C(4) and C(6). Pyrazole **131** is a by-product in the reaction, and originates via nucleophilic substitution at C(2) (Equation 29) <2004RJO1222>.

Table 4 Amination and transamination reaction products of 1,3,5-dioxazine **124** and dithiazine **125**

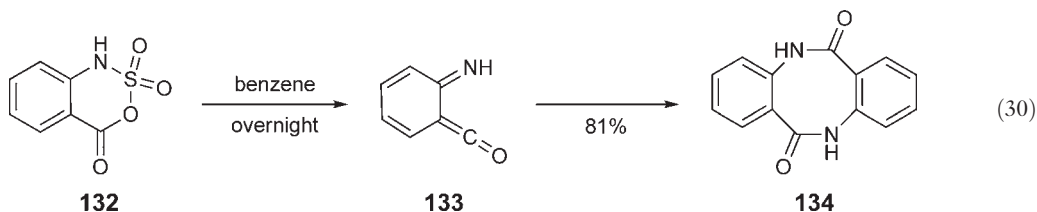
						
	124	125				
	<i>Products, (% yield)</i>					
<i>R</i>						
 + MeNH ₂ (1:2) MeCN/H ₂ O	Pr ⁱ	Minor product ^a	52	Minor product ^a	Minor product ^a	
 + MeNH ₂ (1:1) C ₆ H ₆ /H ₂ O	Pr ⁱ		44	40	Minor product ^a	
 +  (1:2) without solvent	Bu ^t					90

^aLess than 35% yield.

9.10.6.4 Miscellaneous Reactions

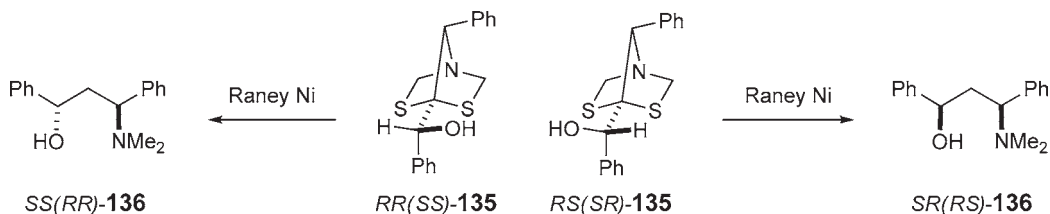
9.10.6.4.1 Cycloaddition reactions

Sulfinamide **132** decomposes to iminoketone **133**, which undergoes a $[8\pi+8\pi]$ cycloaddition reaction to give heterocycle **134** (Equation 30) <2004MI1396>.



9.10.6.4.2 Desulfurization and reductive ring cleavage

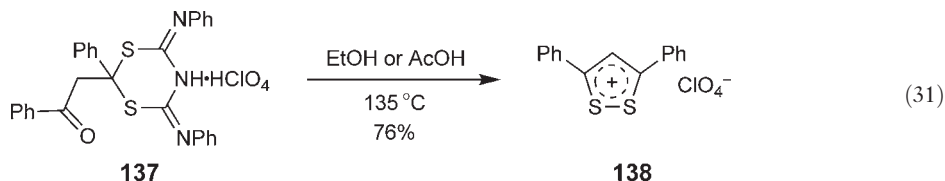
Upon treatment with Raney nickel, the bicyclic dithiazines **135** suffer reductive desulfurization to give 1,3-aminoalcohols **136** (Scheme 10) <2003SL1731>.



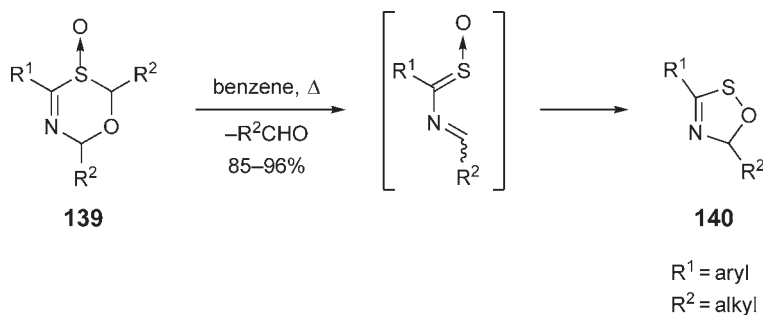
Scheme 10

9.10.6.4.3 Ring contraction reactions

Upon heating, dithiazine **137** suffers thermal rearrangement to give heterocyclic salt **138** (Equation 31) <2004RJO1222>.

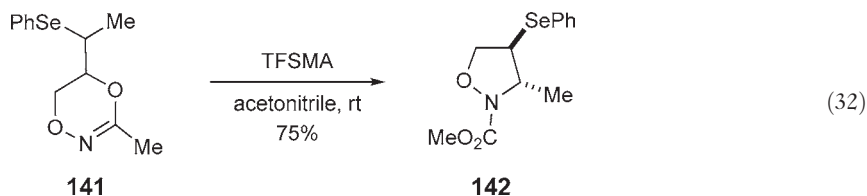


5*H*-1,2,4-Oxathiazoles **140** were obtained via thermal cycloreversion of *S*-oxides **139** (Scheme 11) <2004HAC175, 2003TL2517>.



Scheme 11

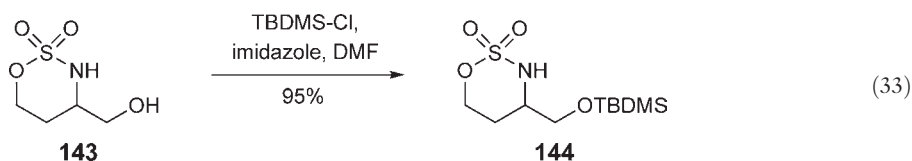
On the other hand, when 1,4,2-dioxazine **141** was treated with trifluoromethanesulfonic acid, *N*-acyl isoxazolidine **142** was produced (Equation 32) <1995CC237>.



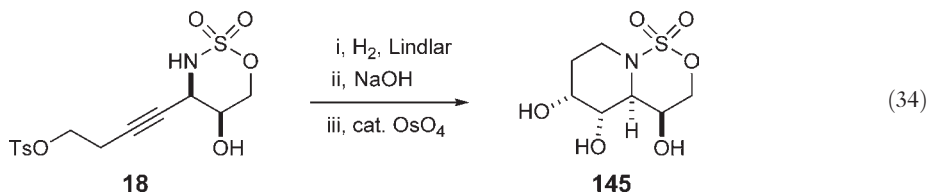
9.10.7 Reactivity of Substituents Attached to Ring Carbon Atoms

9.10.7.1 C-Linked Substituents

C-Linked substituents undergo the transformations characteristic of any alkyl chain, as dictated by the functionality present. For example, the hydroxyl group in 1,2,3-oxathiazine **143** was protected with TBSCl to give derivative **144** (Equation 33) <2005OBC603>.

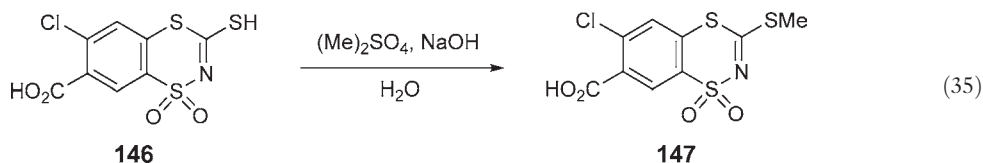


In an additional example, the acetylenic side chain at C(4) in the 1,2,3-oxathiazine **18** was reduced, dihydroxylated, and cyclized to give bicyclic derivative **145** (Equation 34) <2003JA2028>.



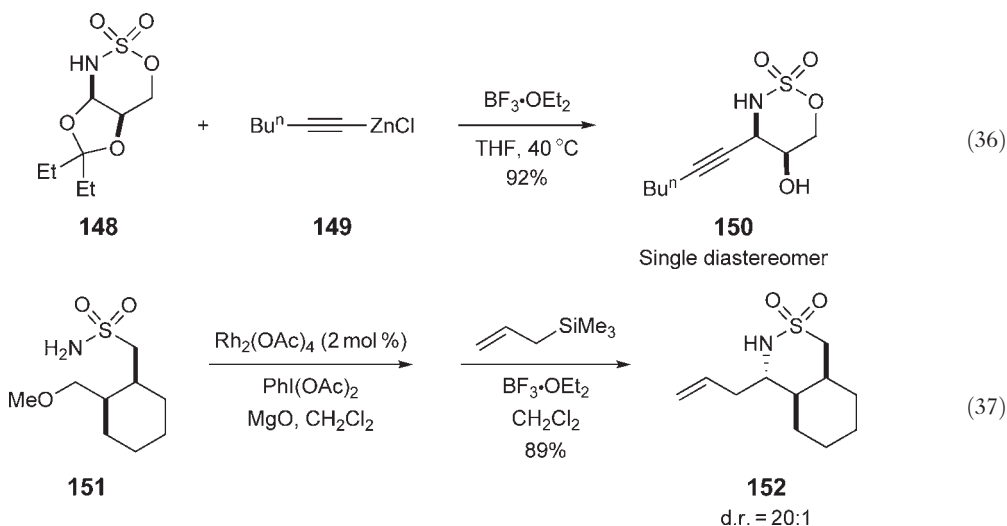
9.10.7.2 S-Linked Substituents

3-Thio-1,4,2-benzodithiazine **146** can be methylated according to the traditional procedure to afford derivative **147** (Equation 35) <2001FA571>.



9.10.7.3 O-Linked Substituents

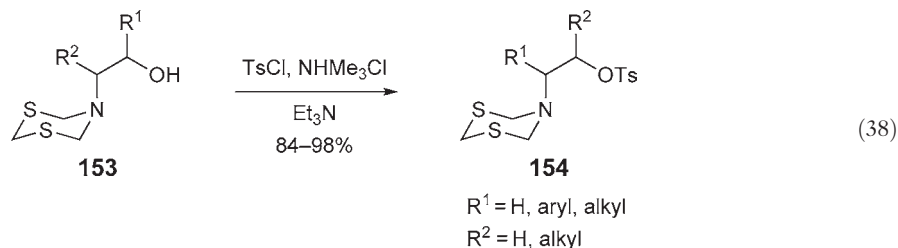
The 1,2,3-oxathiazinane *N,O*-ketal **148** undergoes a coupling reaction with organozinc reagent **149** to provide the acetylenic product **150** (Equation 36) <2003JA2028>. A different type of coupling was observed with *N,O*-ketals **151** and allylsilanes to produce derivatives **152** via the reaction sequence detailed in Equation (37) <2004AGE4349>.



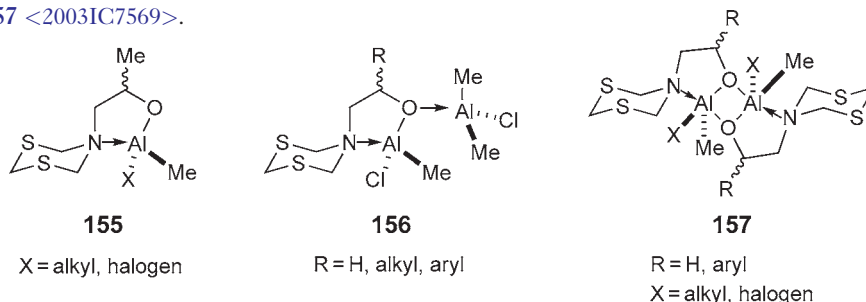
9.10.8 Reactivity of Substituents Attached to Ring Heteroatoms

9.10.8.1 Substituents Attached to Ring Nitrogen Atoms

This section deals with the reactivity of substituents bound to nitrogen. Positively charged sulfur or oxygen analogs are short-lived and prone to rearrangements <1996CHEC-II(6)825>. Dithiazines **153** contain a hydroxyl group that, when exposed to tosyl chloride, affords the tosylated derivatives **154** (Equation 38) <2004H(63)2269>.



1,3,5-Dithiazines **14** react with AlMe₂Y (Y = Me or Cl) to provide monomeric complexes **155** and **156**, or dimeric complexes **157** <2003IC7569>.

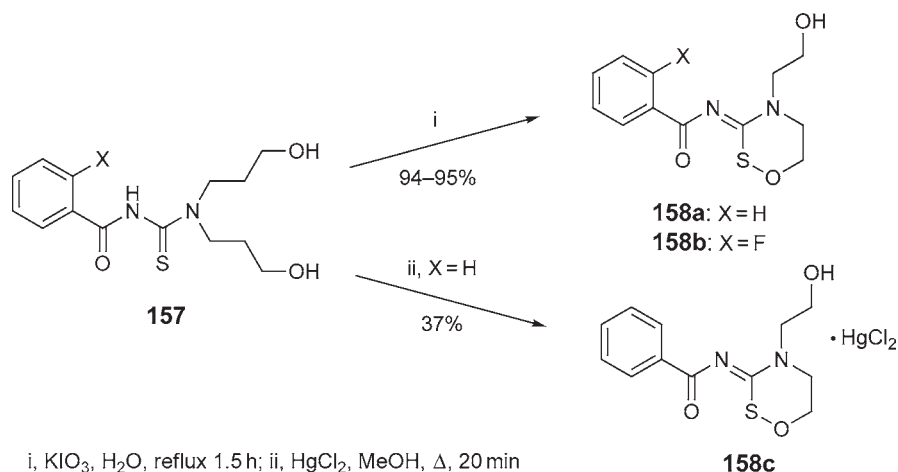


9.10.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

During the last decade, a great variety of novel methodologies have been developed for the preparation of oxathiazines, dithiazines, and dioxazines. This section classifies those procedures according to the kind and number of bonds that are made. For previous versions of this topic, the interested reader can consult Chapters 6.19 of CHEC-II(1996) and 2.28 of CHEC(1984). An additional review covering 1,2,3 oxathiazines has appeared recently <2003T2581>.

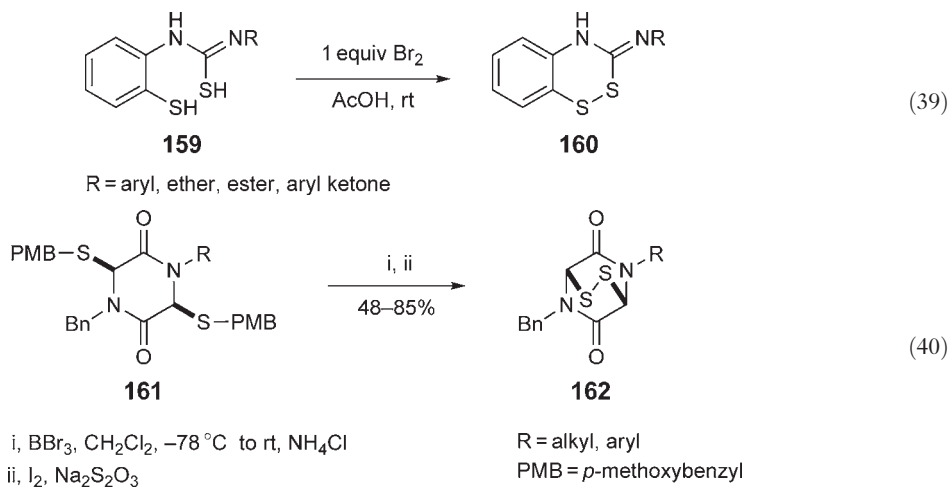
9.10.9.1 Formation of One Bond

One way to prepare the heterocycles of concern in this chapter is through the formation of a bond between two heteroatoms. For example, 1,2,4-oxathiazinanes **158a** and **158b** were prepared by oxidation of 1,1-bis(2-hydroxyethyl)-3-arylthiureas **157**, whereas complex **158c** was obtained when the reaction was carried out in the presence of HgCl_2 (Scheme 12) <2005ZNB945>.

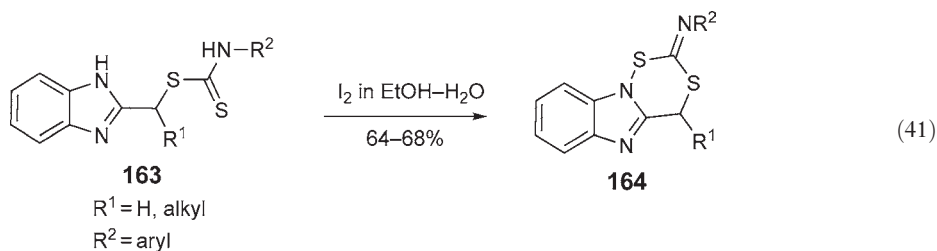


Scheme 12

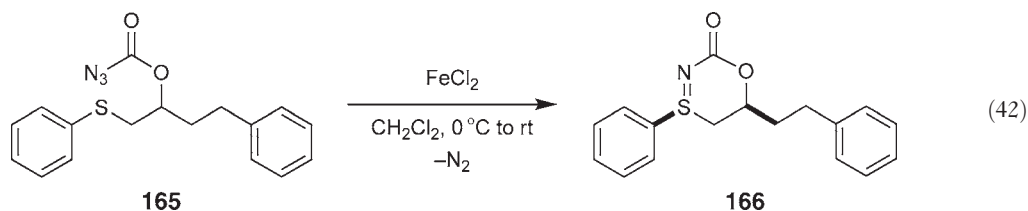
Benzo[1,2,4]dithiazines **160** were synthesized via oxidative coupling of the sulfanyl group and the thiol group on substrate **159** (Equation 39) <2003MI>. Epidithiodiketopiperazine **162** was obtained via deprotection and subsequent oxidation of substrate **161** (Equation 40) <2006TL2387>.



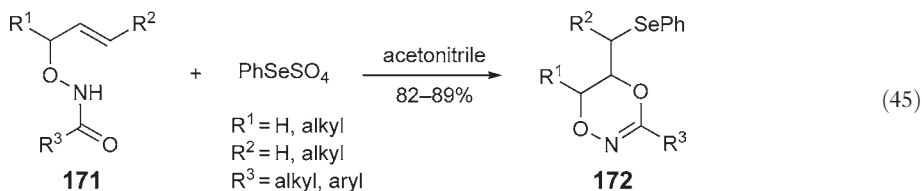
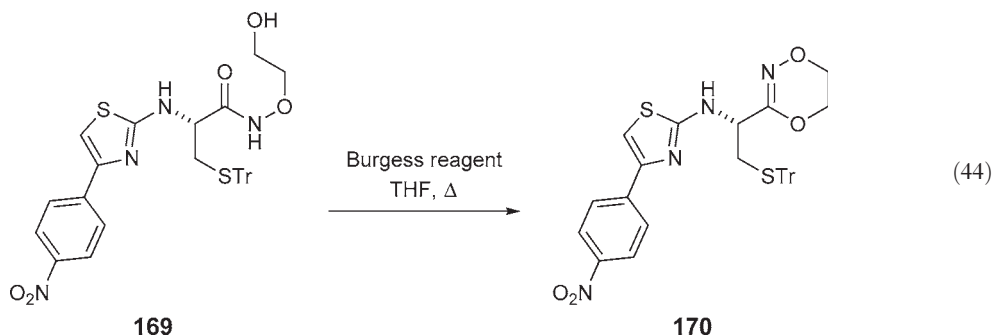
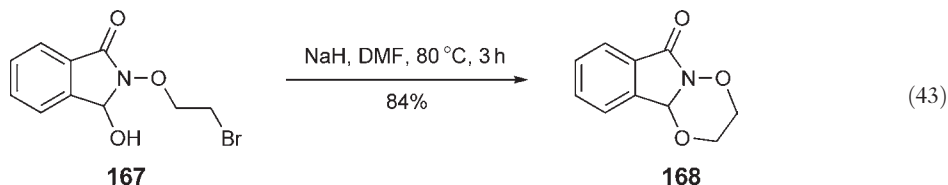
Oxidative cyclization of dithiocarbamates **163** afforded 1,3,4-dithiazines **164** (Equation 41) <1996IJB748>.



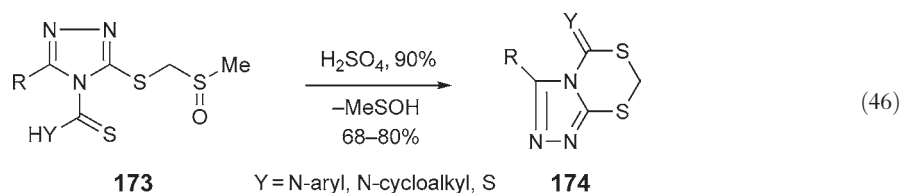
Unusual 1,4,3-oxathiazine **166** was prepared from substrate **165** by means of iron(II) catalysis (Equation 42) <2001AX(E)o252>.



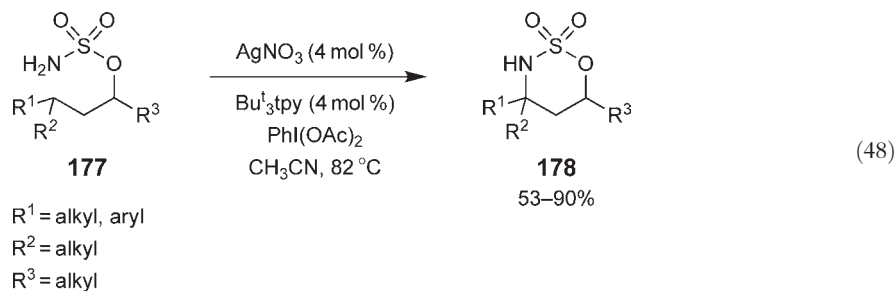
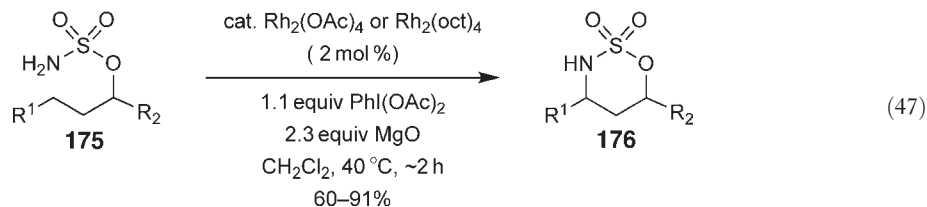
Regarding bond formation between carbon and one heteroatom, 1,4,2-dioxazine **168** was obtained via intramolecular nucleophilic substitution on 3-hydroxyisoindolone **167** (Equation 43) <1999TL2117>. A milder cyclization procedure was employed in the preparation of 1,4,2-dioxazine **170** from substrate **169**, by means of the Burgess reagent ((methoxycarbonylsulfamoyl)triethylammonium *N*-betaine) (Equation 44) <2001JMC619>. *O*-Allyl hydroxamic acids **171** cyclize with phenylselenenyl sulfate to give 1,4,2-dioxazines **172** (Equation 45) <1995CC237>.



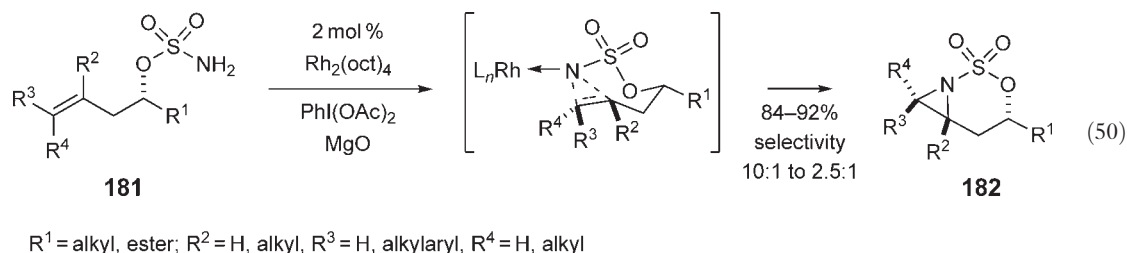
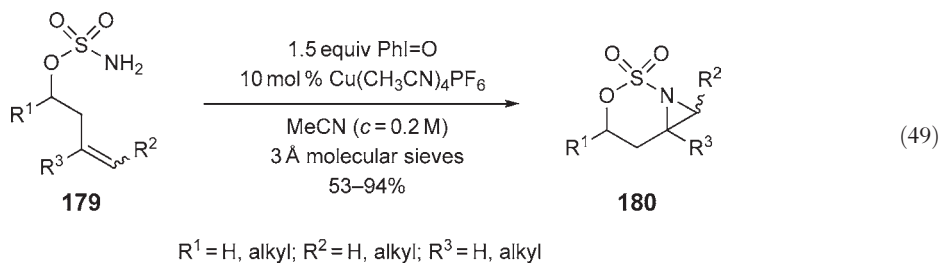
A related nucleophilic intramolecular displacement was reported for the preparation of 1,3,5-dithiazines **174** from 5-aryl-3-methanesulphonylmethylthio-1,2,4-triazoles **173** (Equation 46) <1997IJB442>.



Sulfamates **175** were found to react with $\text{PhI}(\text{OAc})_2$, MgO , in the presence of rhodium catalysis, to provide oxathiazines **176** via C–H insertion (Equation 47) <2001JA6935>. This type of reaction can be catalyzed also by silver(i) complexes to give products **178** from substrates **177** (Equation 48) <2004AG(E)4210>.

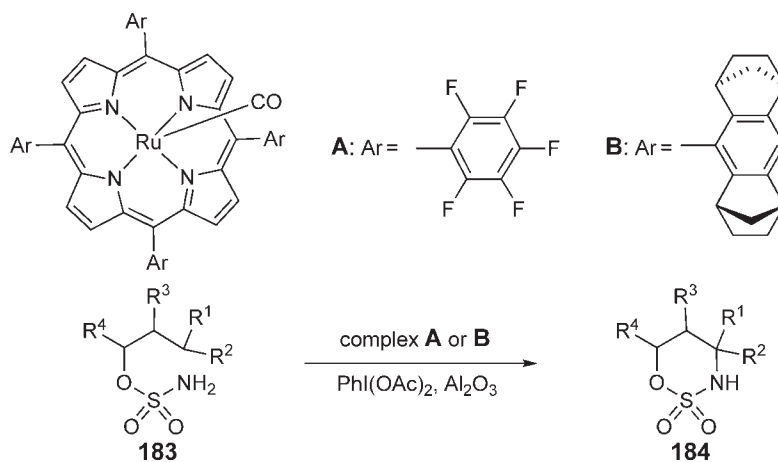


In this context, unsaturated sulfamates **179** underwent intramolecular aziridation mediated by iodosylbenzene under copper catalysis to afford bicyclic 1,2,3-oxathiazines **180** (Equation 49) <2002OL2481>. A related intramolecular aziridation reaction was performed on substrate **181** to give derivative **182** (Equation 50) <2003OL4823>.



Electron-deficient ruthenium–porphyrin complexes **A** and **B** have been used to catalyze intramolecular amidation reactions in sulfamates **183**, to give cyclic products **184**. When the chiral porphyrin **B** is employed, optically active products **184** are generated (Scheme 13; Table 5) <2002AGE3465>.

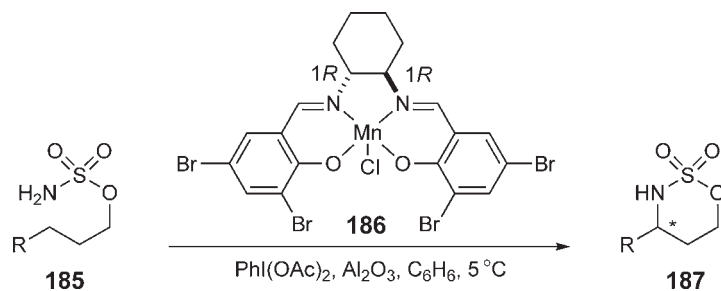
The enantioselective intramolecular amination of sulfamates **185**, catalyzed by manganosalen **186**, constitutes an efficient method for the preparation of 1,2,3-oxathiazines **187** (Equation 51). Illustrative examples are collected in Table 6 <2005TL5403>.



Scheme 13

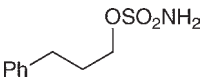
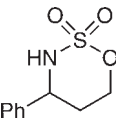
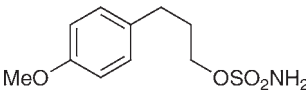
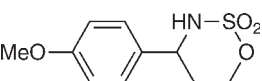
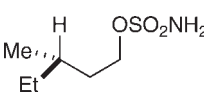
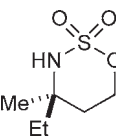
Table 5 Representative examples of the intramolecular amidation reaction of sulfamates **183** (Scheme 13) <2002AGE3465>

Entry	Substrate	Product	Catalyst	Solvent (°C)	Yield (%)	ee (%)
1			A	CH ₂ Cl ₂ , 40 °C	76	
2			A	CH ₂ Cl ₂ , 40 °C	88	
3			A	CH ₂ Cl ₂ , 40 °C	88	
4			B	C ₆ H ₆ , 5 °C	48	84

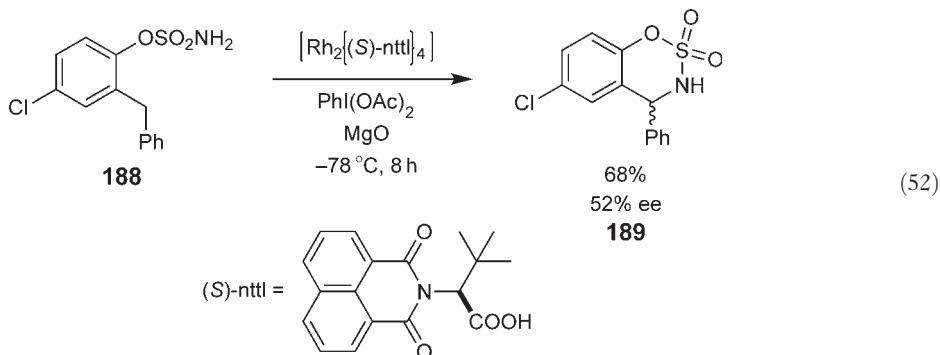


(51)

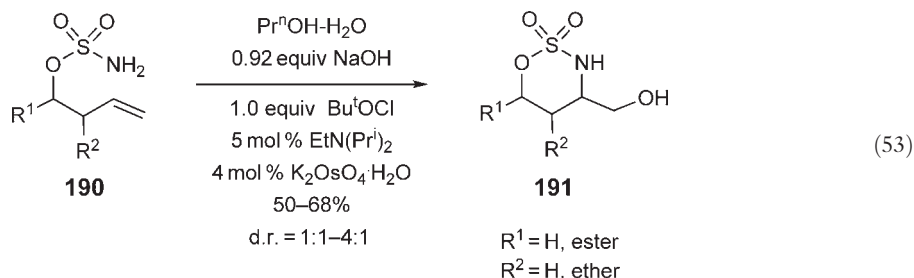
Table 6 Representative examples of the enantioselective intramolecular amidation of sulfamates **185** under manganese(III) catalysis (Equation 51) <2005TL5403>

Entry	Substrate	Product	Yield (%)	ee (%)
1			68	55
2			69	36
3			60	>99

1,2,3-Benzoxathiazine-2,2-dioxide **189** was prepared from aromatic sulfamate **188** by means of an enantioselective intramolecular insertion catalyzed by chiral rhodium(II) complexes (Equation 52) <2004TA1019>.



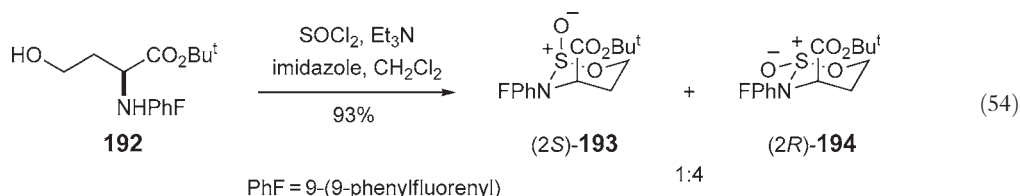
Along similar lines, 1,2,3-oxathiazines **191** were obtained from homoallylic sulfamates **190**, via tethered aminohydroxylation. The yields and diastereoselectivities depend on the nature of the substrate (Equation 53) <2005OBC603>.



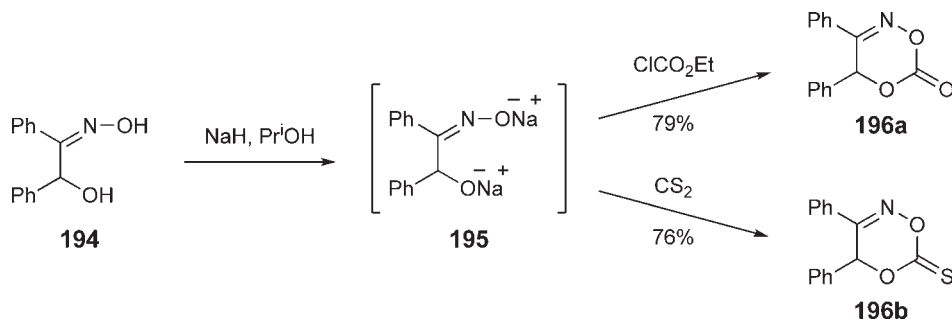
9.10.9.2 Formation of Two Bonds

9.10.9.2.1 From [5+1] atom fragments

Most typically, electrophilic carbon or sulfur fragments react with two functionalities in the substrate to afford the heterocycles of interest. For example, the hydroxyl and amino groups in **192** react with thionyl chloride to give diastereomeric 1,2,3-oxathiazines (2*R*)-**193** and (2*S*)-**194** in a 4:1 ratio (Equation 54) <2001OL2965>. For additional examples, see references <1996CC331> and <2002S859>.

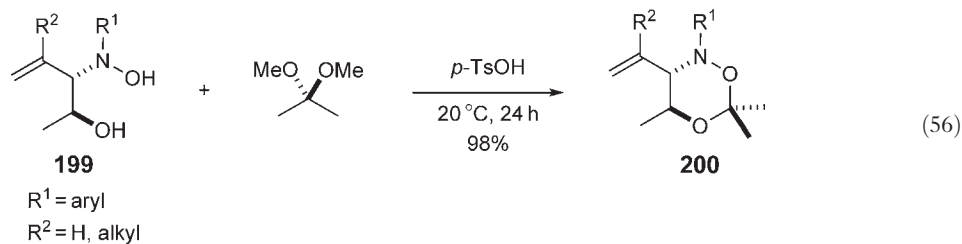
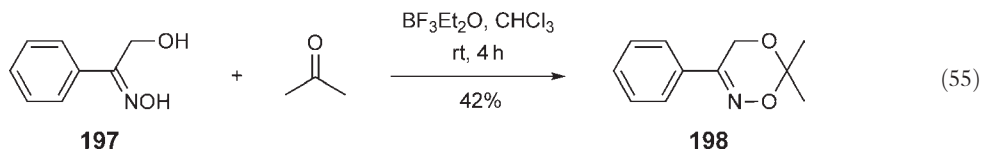


The synthesis of **196a** and **196b** involves the formation of dianion **195** from **194** (Scheme 14) <2004S837>.

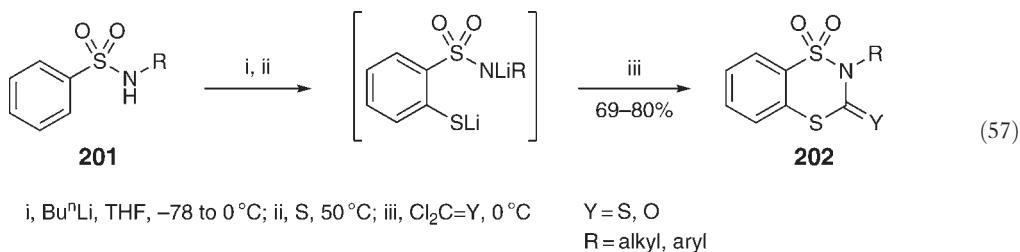


Scheme 14

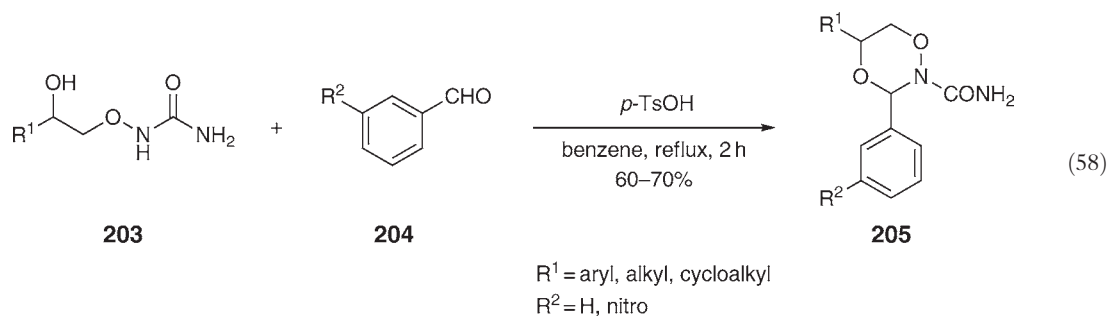
In a related example, oxime **197** was condensed with acetone in the presence of a Lewis acid to give 1,5,2-dioxazine **198** (Equation 55) <1996IJB475>. Chiral analogs **200** were prepared similarly from hydroxylamine **199** (Equation 56) <2000JA9846>.



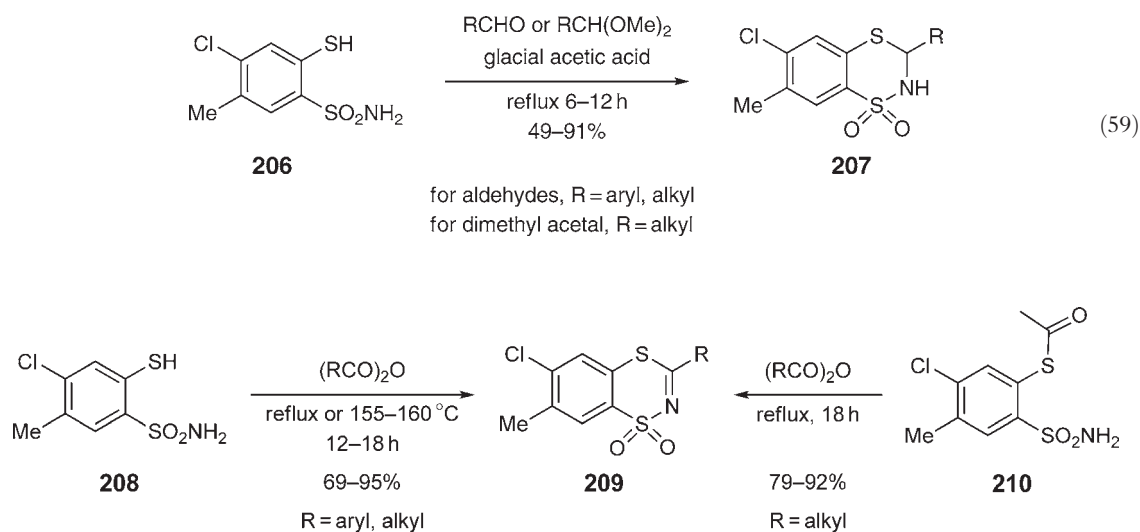
ortho-Lithiation of benzenesulfonamides **201** with *n*-butyllithium, followed by addition of sulfur and then a bifunctional electrophile, afforded 1,4,2-benzodithiazines **202** (Equation 57) <2001JHC723>.



Tetrahydro-1,4,2-dioxazines **205** were prepared from aromatic aldehydes **204** and β -ureidoxyalcohols **203** in dry benzene and *p*-toluenesulfonic acid at reflux (Equation 58) <2000APF180>.



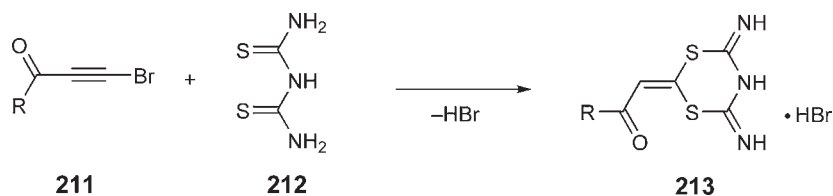
2,3-Dihydro-1,4,2-benzodithiazine-1,1-dioxides **207** were obtained by condensation of various aldehydes and dimethyl ketals with 4-chloro-2-mercapto-5-methyl benzenesulfonamide **206** (Equation 59). Unsaturated dithiazines **209** resulted from heating alkyl or aryl anhydrides with 4-chloro-2-mercapto-5-methyl benzenesulfonamide **208** or 2-acetylthio-benzenesulfonamide **210** (Scheme 15) <2005JHC1297>.



Scheme 15

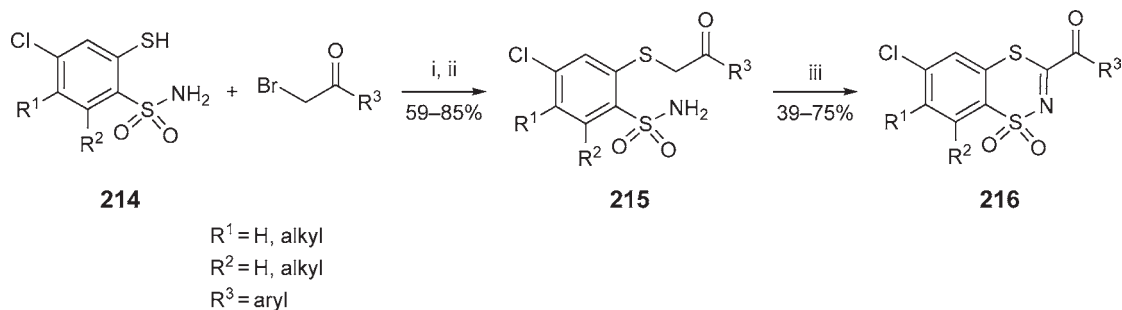
Intramolecular cyclization of dithiobiurea **212** with alkynes **211** provided the dithiazine hydrobromides **213** (Table 7) <1998CHE384>.

Table 7 Preparation of dithiazines **213** <1998CHE384>



R	Condition A	Yield (%)	Condition B	Yield (%)
Ph	Glacial AcOH, 20 °C, 5 h	86	Benzene, 20 °C, 5 h	64
2-thienyl		88		61

An alternative avenue to 3-substituted 1,1-dioxo-1,4,2-benzothiazines **216** consists of initial nucleophilic substitution of bromomethyl ketones with benzosulfonamides **214** to afford the S-substituted derivatives **215**, which are then cyclized with thionyl chloride (Scheme 16) <2004BMC3663>.

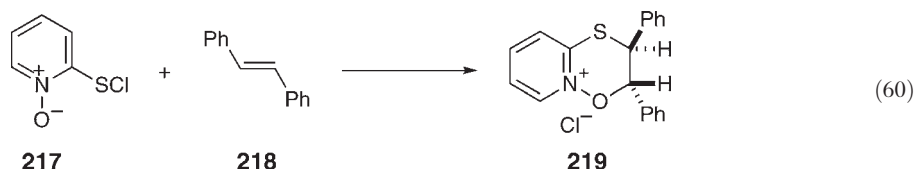


i, Et₃N (1.1 M equiv), CH₂Cl₂, 18–24 °C; ii, bromomethyl ketones (1.1 M equiv), 18–24 °C, 1 h, reflux, 6 h;
 iii, SOCl₂ (excess), reflux, 46 h

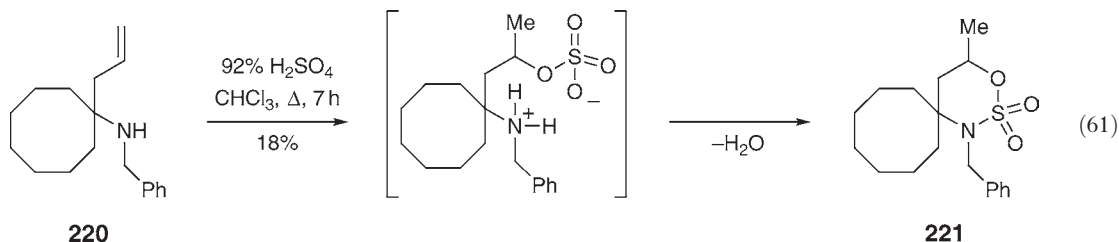
Scheme 16

9.10.9.2.2 From [4+2] atom fragments

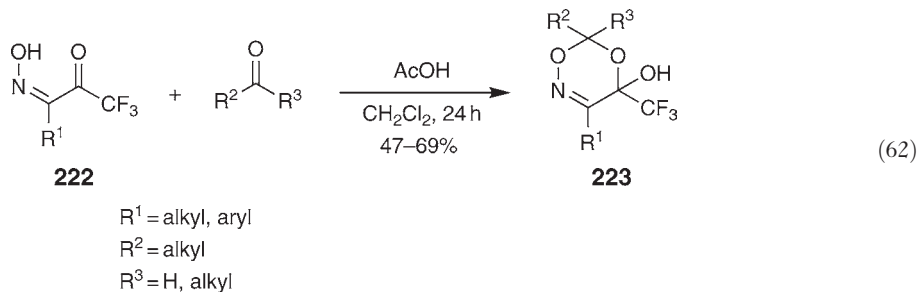
One example of this type of process is the preparation of 1,4,2-oxathiazines **219** from the reaction of sulfonyl chloride **217** with *trans*-stilbene **218** (Equation 60) <2003CHE1263>.



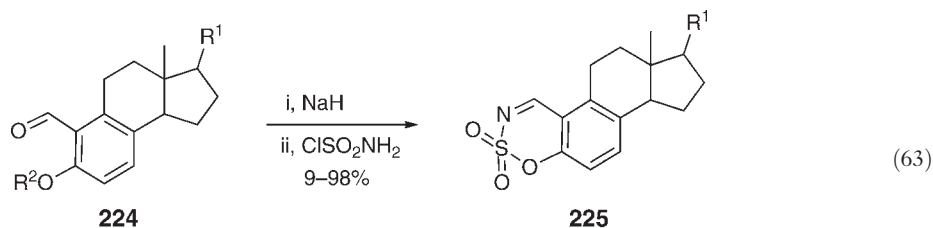
Treatment of homoallylamine **220** with sulfuric acid provided spiro-1,2,3-oxathiazine **221** (Equation 61) <2000H(53)785, 2004CHE1097>.



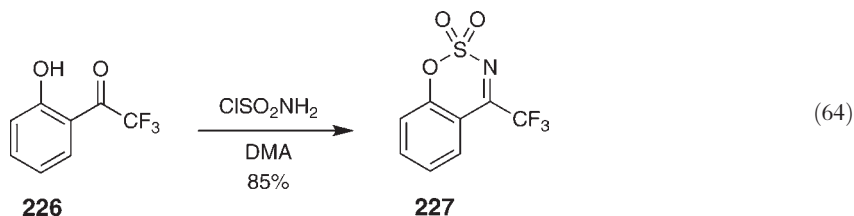
Oximes **222** reacted with various aldehydes and ketones to give 4-trifluoromethyl-4*H*-[1,5,2]dioxazines **223** (Equation 62) <1999JHC917>.



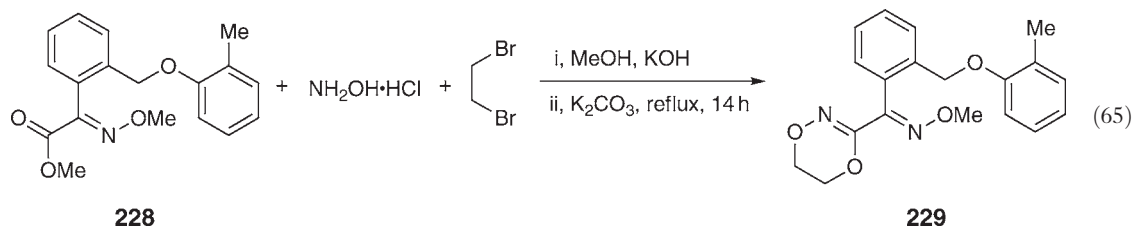
Steroidal 1,2,3-oxathiazines **225** were prepared from substrate **224**, and 1,2,3-benzoxathiazines **227** from **226** (Equations 63 and 64) <2003ST97, 2005JA15391>.



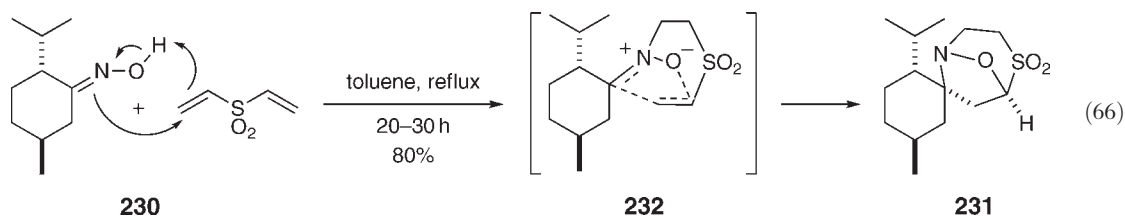
$R^1 = \text{O, ether, hydroxy, alkenyl, alkyl, halogen}$
 $R^2 = \text{H, ketone}$



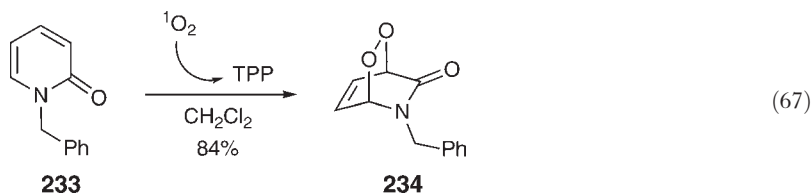
3-Substituted-1,4,2-dioxazine **229** was synthesized by reaction of substrate **228** with hydroxylammonium chloride and subsequent reaction of the resulting oxime with 1,2-bromoethane (Equation 65) <2002USP6451790>.



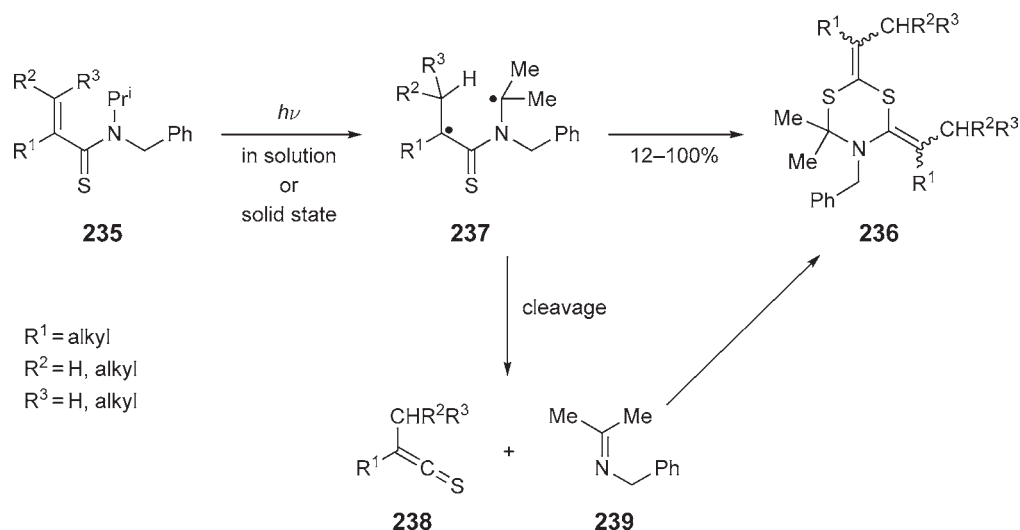
The formation of bicyclic oxathiazine dioxide **231** from oxime **230** was explained in terms of conjugate addition to the divinyl sulfone via transition state **232** (Equation 66) <2000HCO113, 1996TL4597>.



N-Substituted pyridone **233** reacts with singlet oxygen to form the endoperoxide **234** (Equation 67) <2005CC483>.



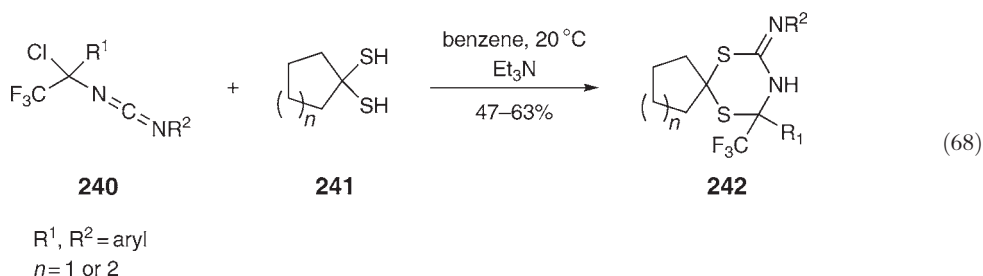
The photochemical reaction of thioamides **235** to produce 1,3,5-dithiazinanes **236** was explained in terms of diradical intermediates **237**, which cleave to provide thioketenes **238** and benzylimine **239** (Scheme 17) <1998JP13731>.



Scheme 17

9.10.9.2.3 From [3+3] atom fragments

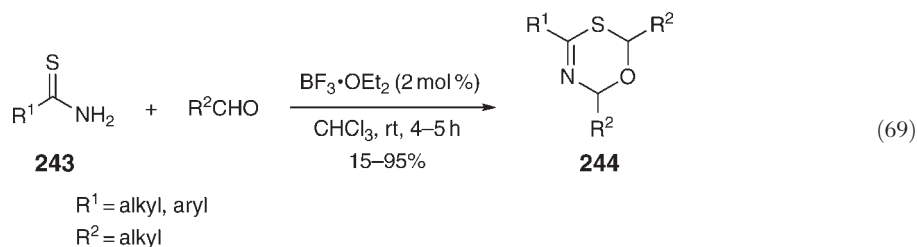
Many of the heterocycles of interest in this review may be formed via condensation of two fragments in a [3+3] fashion. For example, carbodiimides **240** reacted with 1,1-dithiols **241** to afford 4-imino-1,3,5-dithiazinanes **242** (Equation 68) <1997RJ096>.



9.10.9.3 Formation of Three or More Bonds

During the last decade, several successful procedures for the preparation of dithiazines, dioxazines, and oxathiazines have been developed, where the formation of three or more bonds is involved.

Oxathiazines **244** have been prepared by condensation of thioamides **243** with aliphatic aldehydes in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (Equation 69) <2004HAC175>.



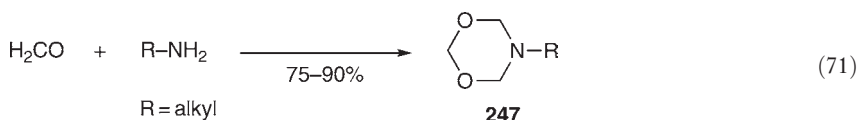
A common method for the preparation of 1,3,5-dithiazines consists of the reaction of aldehydes and primary amines in the presence of H_2S (or SH^-) <2003IC7569, 2003JHC827, 2004H(63)2269>. Depending on the substrate and the reaction conditions, oxathiazines, dioxazines <2005RCB432>, or oxathiazines <2003RCB1817> may be obtained as

$$\text{H}_2\text{N}-\text{CH}(\text{R})-\text{CO}_2\text{H} + \text{H}_2\text{CO} \xrightarrow[0^\circ\text{C}]{\text{NaSH}} \text{S}_2\text{N}(\text{R})\text{CH}_2\text{CO}_2\text{H}$$

245 246

R = H, alkyl, aryl

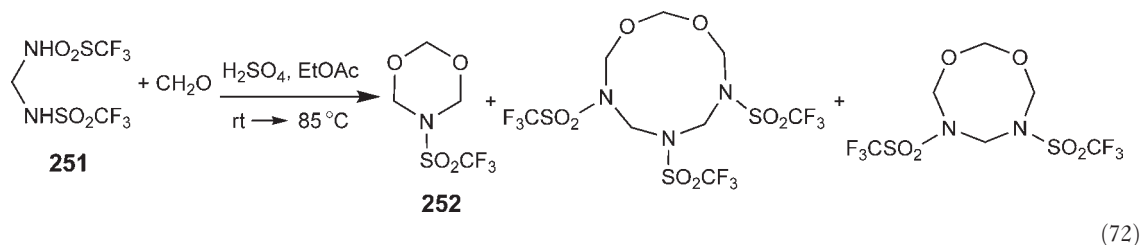
(70)



$2 \text{ 248} + 2\text{HCHO} \xrightarrow[\text{50-75\%}]{\text{EtOH, R}^1\text{NH}_2} \text{249} \xrightarrow[\text{HCHO}]{\text{H}_2\text{S or Na}_2\text{S}} \text{250}$

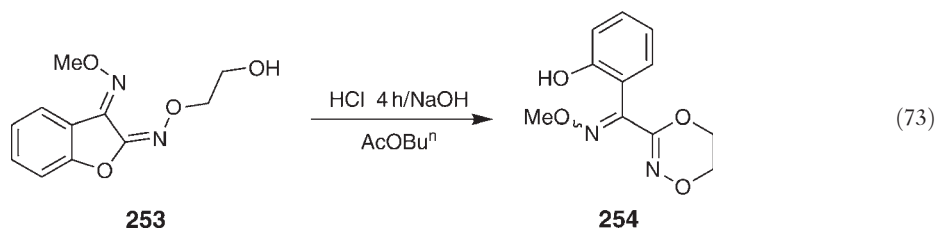
$\text{R}^1 = \text{alkyl, aryl}$

The reaction of bis(trifluoromethylsulfonylamino)methane **251** with paraformaldehyde afforded 1,3,5-dioxazine **252**, together with other condensation products (Equation 72) <2005RJO1381>.

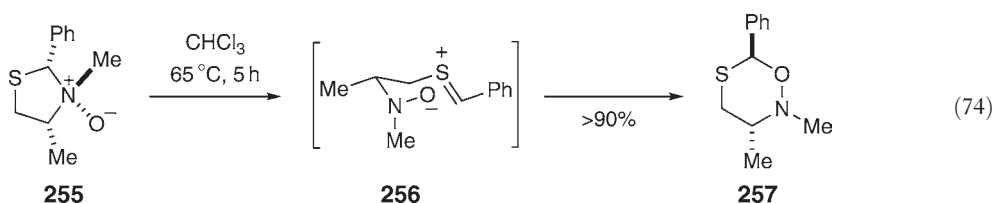


9.10.10 Ring Syntheses by Transformation of Another Ring

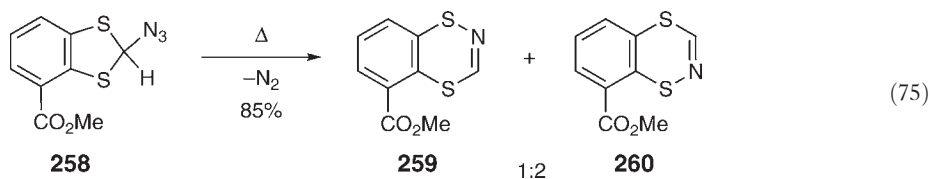
An interesting method for the preparation of six-membered heterocycles involves ring expansion of smaller rings. One example is 1,4,2-dioxazine **254**, which was prepared via acid-catalyzed rearrangement of benzofurandione dioxime **253** (Equation 73) <2006GEP2006021368>.



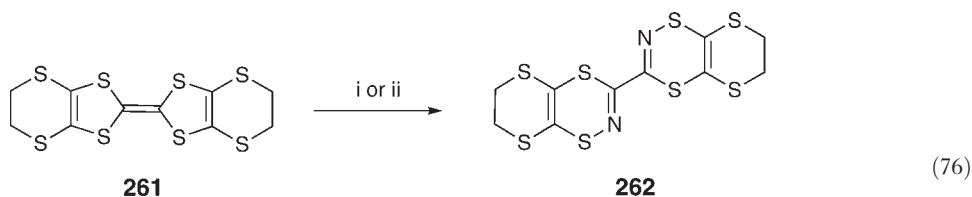
Under refluxing conditions in chloroform, thiazolidine-*N*-oxide **255** underwent rearrangement to provide *trans*-1,5,2-oxathiazine **257** in excellent yield (Equation 74). The stereochemical course of the reaction is explained in terms of chair intermediate **256** <1997TL8549>.



1,4,2-Benzodithiazines **259** and **260** were prepared by thermally induced rearrangement of azide **258** (Equation 75) <2000JHC955>.

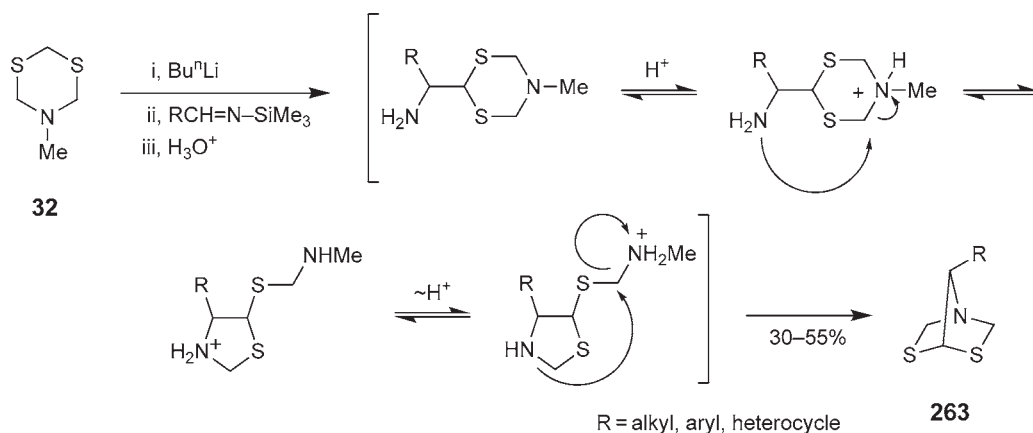


Chemically or electrochemically induced nitrogen insertion on 3,4,3',4'-bis(ethylenedithio)-2,2',5,5'-tetrathiafulvalene **261** gave rise to ring expansion and formation of derivative **262** (Equation 76) <1998JSC88>.



- i, chemical synthesis: benzonitrile, H₂O₂, HCl, rt, 6 h, Ph₄P[Au(N₃)₄]
 ii, electrochemical synthesis: chlorobenzene or THF or benzonitrile, Ph₄P[Au(N₃)₂],
 Ph₄P[Au(N₃)₄] and KN₃ as background electrolytes, 1 μA.

An unusual transformation of 1,3,5-dithiazine **32** results in the formation of bicyclic dithiazines **263** via 2-aminoalkyl-1,3,5-dithiazines (Scheme 19) <2003SL1731>.



Scheme 19

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

This section presents an evaluation of the synthetic methods described above, in terms of the following factors: (1) availability of precursors, (2) structural diversity of substrates, and (3) overall yields.

9.10.11.1 Dioxazines

9.10.11.1.1 1,5,2-Dioxazines

This class of compounds has been prepared by (1) condensation of α -hydroxy β -oximes with electrophilic carbonyl derivatives (Scheme 13 and Equation 55); (2) condensation of 1,1,1-trifluoroalkane-2,3-dione 3-oximes with aldehydes and ketones (Equation 62); and (3) Reaction of hydroxylamines with ketals (Equation 56). From these methods, the most convenient seems to be (2), because the yields of the reactions are generally high, and the starting materials are easily available.

9.10.11.1.2 1,4,2-Dioxazines

These heterocycles have been synthesized via (1) cyclization of 3-hydroxyisoindolone (Equation 43); (2) cyclization with Burgess reagent (Equation 44); (3) reaction between oximes and 1,2-dibromoethane (Equation 65); (4) ring expansion of benzofurandione dioxime (Equation 73); (5) cyclization of *O*-allylhydroxamic acid with phenylselenenyl sulfate (Equation 45); and (6) condensation of β -ureidoxyalcohols and aromatic aldehydes (Equation 58). The last of these methods seems to be the most convenient in terms of observed reaction yields and substrate diversity.

9.10.11.1.3 1,3,5-Dioxazines

This system has been prepared by (1) the traditional method with formaldehyde and primary amines (Equation 71), and (2) condensation of bis(trifluoromethylsulfonylamino)methane and paraformaldehyde (Equation 72). The ready availability of the starting materials and the high yields that are usually achieved in the first method recommend it for the preparation of dihydro-1,3,5-dioxazines.

9.10.11.2 Oxathiazines

9.10.11.2.1 1,2,3-Oxathiazines

From the various methods reported for the preparation of 1,2,3-oxathiazine 2,2-dioxides, the intramolecular amidation of sulfamates catalyzed by rhodium and silver (Equations 47 and 48) reveals itself as the best approach, in view of the high yields.

9.10.11.2.2 1,5,2-Oxathiazines

These heterocycles are conveniently prepared via intramolecular dipolar cycloaddition (Equation 66) or by thermal rearrangement of thiazolidine-*N*-oxides (Equation 74). The first method is generally more successful and general.

9.10.11.3 Dithiazines

9.10.11.3.1 1,3,5-Dithiazines

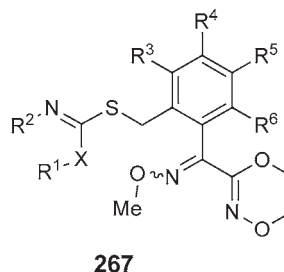
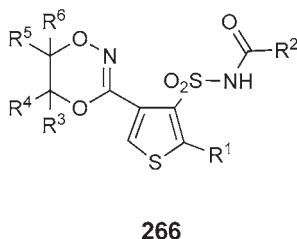
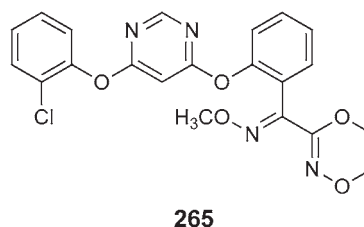
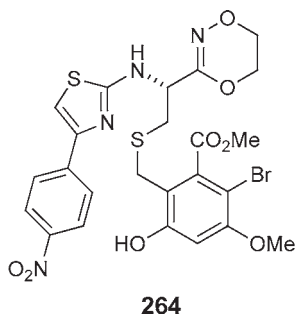
The most accessible and simple method for the preparation of these compounds involves the reaction of aldehydes, primary amines and H₂S (Equation 70). The starting materials are readily available and the observed yields are usually good.

9.10.12 Important Compounds and Applications

9.10.12.1 Biological Activity and Industrial Applications

A significant number of dioxathiazines, oxathiazines, and dithiazines have shown biological activity. For example, *seco*-cyclothialidine BAY50-7952 **264** is a powerful antibiotic, which exhibits high and selective activity against bacterial DNA gyrase and against Gram-positive bacteria <2001JMC619>. The authors suggest that the 1,4,2-dioxazine ring is determinant for adequate membrane penetration. Methoxyimino dihydrodioxazine fluoxastrobin **265** is the first strobilurin with fungicidal activity <2004PNB299>. Heterocycles of type **266** have shown herbicidal activity <2006GEP2006012982>, whereas 1,4,2-dioxazines **267** present microbial activity <1999GEP9919312>.

The 1,4,2-oxathiazine 4-oxide **268** known as bethoxazin is a wide-spectrum fungicide and algacide <2003FLS5>. Steroidal 1,2,3-oxathiazine-2,2,-dioxide **269** has shown antitumor activity against breast cancer in experiments *in vivo* (MCF-7 breast cancer xenografts in Blab/c athymic nude mice) <2003ST97>. 1,2,3-Oxathiazines are artificial sweetening agents and the most relevant is acesulfame K **270**, which is employed in low-calorie and diabetic foods.



R¹ = H, halo, CN, etc.

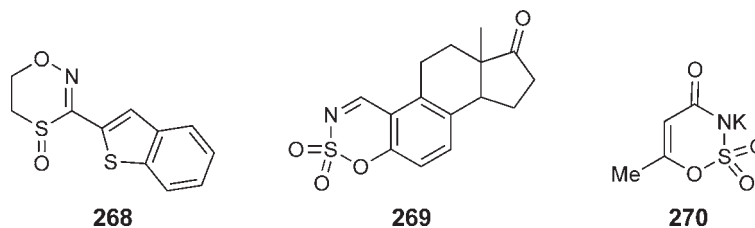
R² = heterocycle, (un)substituted triazine, diazine, etc.

R³, R⁴, R⁵, R⁶ = H, halo, CN, etc.

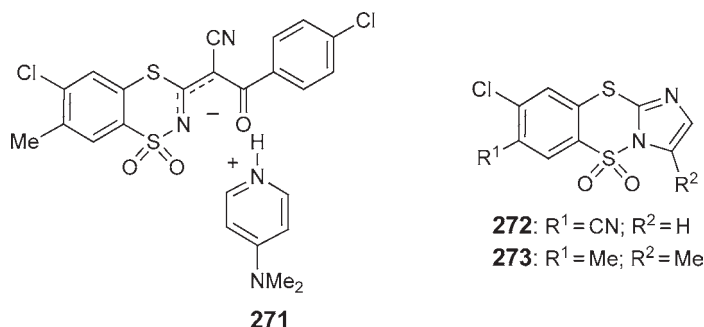
R¹ = alkyl, cycloalkyl

R² = substituted cycloalkyl, aryl, alkylaryl, heterocyclyl or heterocyclylalkyl

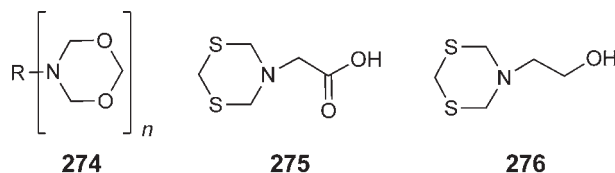
R³, R⁴, R⁵, R⁶ = H, halogen, cyano, nitro, alkyl



1,4,2-Benzodithiazines exhibit biological activity as antitumoral agents <2003BMC1259, 2005JHC1297, 1997APP49, 2003BMC3673> as well as antiviral agents <2004BMC3663>. For instance, compound **271** has shown antitumoral activity *in vitro* <2003EJM991>. Also, in some *in vitro* studies, benzodithiazine **272** has shown anti-carcinogenic activity, whereas compound **273** presents anti-HIV-1 biological activity <2006BMC2985>.

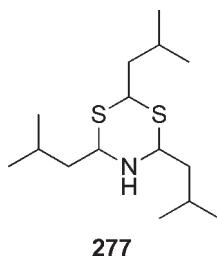


Dioxazines **274** have been employed to remove mercaptans and hydrogen sulfide from crude oil <2003MIP2242499>. 2-(1,3,5-Dithiazin-5-yl)acetic acid **275** and 2-hydroxy-1-perhydro-[1,3,5-dithiazin-5-yl] ethane **276** have been used in the petroleum industry as growth-suppressor agents of sulfate-reducing bacteria <2003MIP2206726, 1999MIP2160233>. Furthermore, 1,3,5-dithiazines have showed activity as organic absorbents for the extraction of metals such as Ag, Au, and Pt in solution <2003MIP2201983>.



R = alkyl, dialkyl, hydroxyalkyl, alkylaryl
n = 1 or 2

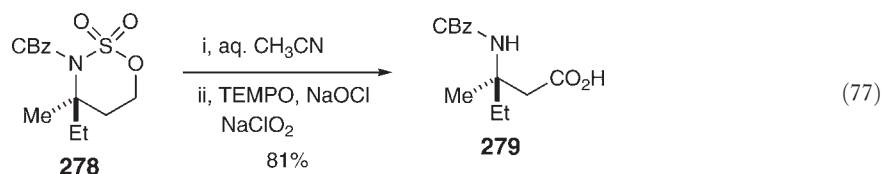
1,3,5-Dithiazines are important also in scent chemistry; for example, 2,4,6-triisobutyldihydro-1,3,5-dithiazine **277** presents a smoked bacon aroma <B-2005MI>.



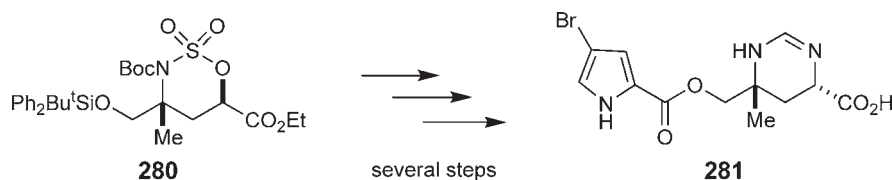
2,4,6-Trimethyl-1,3,5-dithiazine (thialdine) is an aromatic compound isolated from different meats <1997ZLUF73>.

9.10.12.2 Synthetic Applications

Recently, 1,3,5-oxathiazines have been applied in asymmetric synthesis. For instance, the nucleophilic opening of oxathiazine **278** provided (*R*)-*N*-CBz- β -isoleucine **279** (Equation 77) <2001JA6935>.

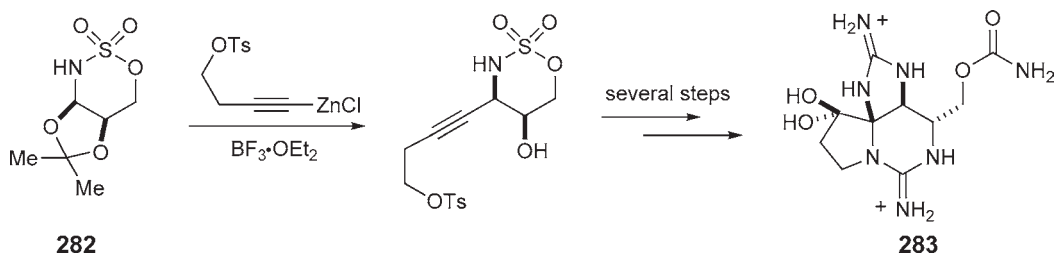


In a similar fashion, manzacidin **281** was obtained from oxathiazine **280** (Scheme 20) <2002JA12950>.



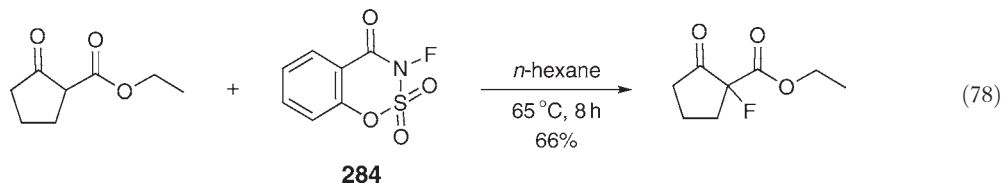
Scheme 20

The paralytic agent (+)-saxitoxin **283** was obtained from 1,2,3-oxathiazine **282** (Scheme 21) <2006JA3926>.



Scheme 21

Finally, 3-fluoro-1,2,3-oxathiazin-4-one 2,2-dioxide **284** has been employed as an electrophilic fluorinating agent (Equation 78) <1995T10205>.



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9.11

Six-membered Rings with 1,2,4-Oxygen or Sulfur Atoms

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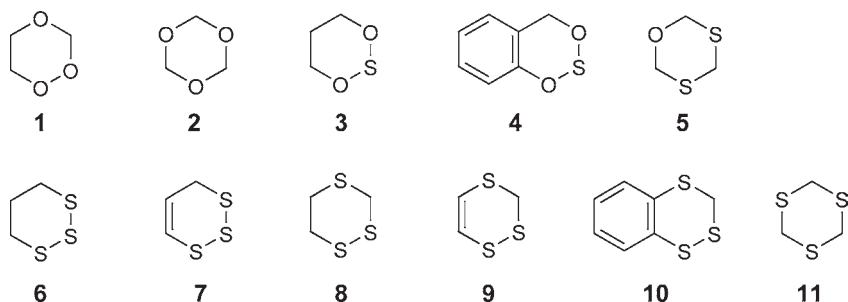
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9.11.1 Introduction

In CHEC(1984), Chapter 2.26 covered the literature through to 1982 for six-membered rings containing more than one oxygen or sulfur atom. From the compounds appearing there, only those with 1,2,4-oxygen or -sulfur atoms were reviewed in CHEC-II(1996). Thus, this chapter concentrates on relevant material from 1996 onward only in the case of 1,2,4-substitution; in the other cases, the relevant literature published from 1983 onward has been reviewed.

From all possible ways of substituting three oxygen and/or sulfur atoms into the 1,2,3-, 1,2,4-, and 1,3,5-positions of cyclohexene and cyclohexane rings, only the ring systems **1–11** were reported. In a few references, two benzo derivatives **4** and **10** and two unsaturated derivatives **7** and **9** were described. However, the attention of the chemical community is concentrated on only a relatively few structures: 1,2,3-trisubstitution in 1,3,2-dioxathiane oxides and dioxides; 1,2,4-trisubstitution in 1,2,4-trioxane derivatives (due to the continuous interest in artemisinin derivatives as antimalarial drugs); and on 1,3,5-trioxanes and 1,3,5-trithianes in the case of 1,3,5-trisubstitution. Other substitution patterns have been noted but with very little accompanying information, for example, *4H*-1,2,3-trithiin **7** was mentioned only in the context that it is a component of the volatiles of garlic, that it was found in analytical amounts among the thermal degradation products of allyl isothiocyanate and that it is present as an environmental organic pollutant in sediments from the eastern Gulf of Finland.



The material found is presented according to the usual format. After beginning with the theoretical, structural, spectroscopic, and thermodynamic studies, the main body of the chapter deals with the reactivities and syntheses of the different heterocyclic systems categorized by the heteroatoms present. These heterocyclic ring systems have

been particularly well investigated theoretically, and because the theoretical techniques are now so well developed, they replicate experimental results extremely closely. Thus, at the state-of-the-art level, both the electron distributions and geometries of the structures are well understood.

The 1,2,4-trioxane pharmacophore is an important structural element in medicinal chemistry and as such remains of continuous interest (cf. CHEC-II(1996)). It is found in the artemisinins which react with heme generating cytotoxic radicals; the latter are the entities that finally kill the malaria parasites. More recently, 1,2,4-trioxane monomers and dimers were shown also to be potent inhibitors of cancer cell proliferation.

Besides the artemisinin derivatives, which dominate the 1,2,4-trisubstitution sections, both 1,3,5-trioxane and 1,3,5-trithiane derivatives continue to be of interest. The corresponding parts of the chapter are in a certain sense related to the equilibrium of 1,3,5-trithiane/trioxane with 3 mole of the corresponding thioaldehyde/aldehyde. Both the synthesis of the ring systems by this route as well as their decomposition (as *in situ* sources of thioaldehyde/aldehyde for certain reactions, especially polymerization or copolymerization), have been studied in detail.

9.11.2 Theoretical Methods

9.11.2.1 1,2,3-Trioxanes

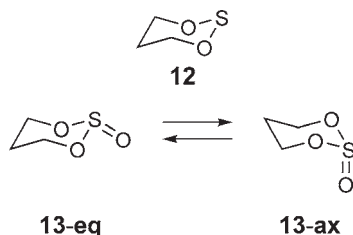
Ab initio MP2 as well as density functional theory (DFT) calculations at the highest level have been performed for 1,2,3-trithiane and its 5,5-dimethyl analog <2003IJQ443, 2004JPO32>; the chair, 1,4-twist, and 2,5-twist conformers were confirmed as stable structures, whereas the distorted 1,4-boat and 2,5-boat structures represented the transition states for the six-membered ring conformational interconversion process (Figure 1). The chair conformer proved to be the ground-state structure while the twist conformers were found to be less stable by at least 5 kcal mol⁻¹ or more in energy, though the magnitude was dependent on the method applied. Differences in bond lengths in the various conformers were discussed with respect to stereoelectronic hyperconjugative interactions within the conformers. The barrier to ring inversion of 1,2,3-trioxane was evaluated to be 13.7–13.8 kcal mol⁻¹, in excellent agreement with the reported experimental value of 13.2 kcal mol⁻¹ <1980ISJ173>.



Figure 1 Conformers of 1,2,3-trioxane.

9.11.2.2 1,3,2-Dioxathianes

The structure, stereochemistry, and potential conformational equilibria (Scheme 1) of 1,3,2-dioxathian **12** have not yet been studied theoretically but *ab initio* molecular orbital (MO) calculations at the MP2 level of its 2-oxide **13**, both in the gas phase and in various solvents, have been reported <2000JPO187>. In the gas phase and in low-polarity solvents, **13-ax** proved to be the only conformer present. In medium-polarity solvents such as acetonitrile or dimethyl sulfoxide, the *equatorial* counterpart **13-eq** is of importance and participates up to 12% in the conformational equilibrium. In addition, both the dipole moments ($\mu_{13-ax} = 3.87$ D; $\mu_{13-eq} = 6.57$ D) and the S=O stretching vibrations (**13-ax**: 1177–1180 cm⁻¹; **13-eq**: 1230–1231 cm⁻¹) of the two conformers were calculated and compared to the experimental values ($\mu_{gas} = 3.6$ D; $\mu_{DMSO \text{ or } CH_3CN} \text{ ca. } 4.5$ D (DMSO = dimethyl sulfoxide); $\nu_{S=O} = 1190$ cm⁻¹ (**13-ax**); $\nu_{S=O} = 1230$ cm⁻¹ (**13-eq**),

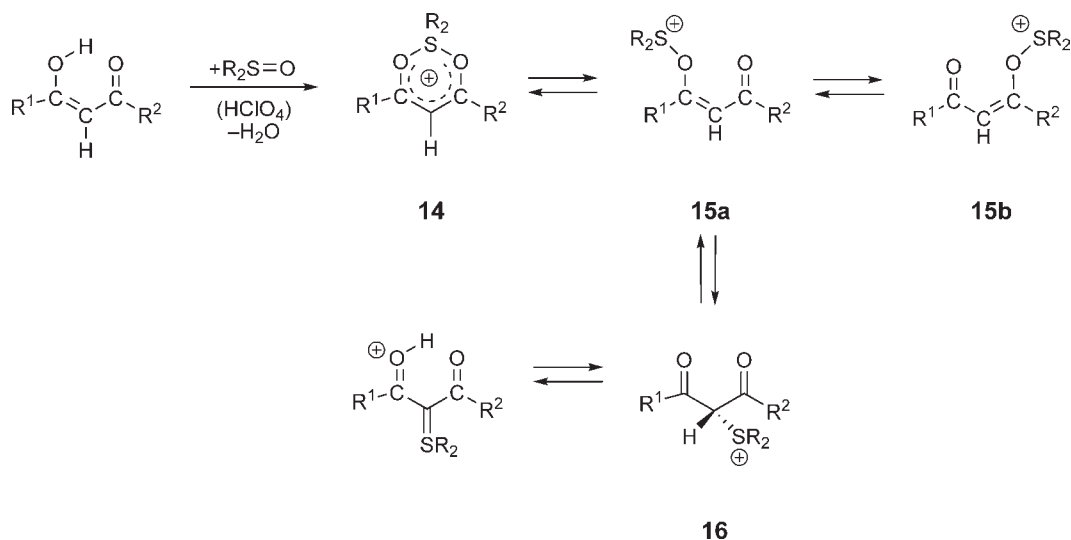


Scheme 1

increasing in intensity compared with the gas phase) to prove the position of the conformational equilibrium <2000JPO187>. The calculated free energy difference between the conformers ($\Delta G^\circ = 4.6 \text{ kcal mol}^{-1}$) is in good agreement with experimental estimates ($\Delta G^\circ > 4.4 \text{ kcal mol}^{-1}$) with **13-ax** being the preferred conformer.

In comparison with *ab initio* MO calculations, the results of an accompanying complete neglect of differential overlap (CNDO/2) study were examined <1984IZV2279>, wherein the latter method proved to be useful for estimating the structure of cyclic sulfites but failed completely in determining the energy differences of the axial and equatorial conformers.

The structural and configurational isomerism of the cation of protonated 1,3,2-dioxathiins **14** was studied by semi-empirical calculations using the PM3 method <1996ZOR293>. The cyclic form **14**, synthesized from enolizable 1,3-diketones and $\text{R}_2\text{S}=\text{O}$ (cf. Scheme 2), proved to be thermodynamically unstable (ca. $6.4 \text{ kcal mol}^{-1}$) with respect to the cation of the *O*-sulfonium structure **15**, while the latter was found to be kinetically stable with respect to isomerization via the sigmatropic shift of hydrogen or the SR_2 group. However, the acyclic cation of this *C*-sulfonium derivative **16** is thermodynamically preferred both in the gas phase and in solution – in full agreement with the nuclear magnetic resonance (NMR) data. The *C*-sulfonium derivative **16** rearranges via 1,5-prototropic shift.



Scheme 2

9.11.2.3 1,2,4-Trioxanes

Artemisinin **17**, 1,2,4-trioxane **18** itself, and some ring-fused, artemisinin-analogous 1,2,4-trioxanes have been studied theoretically and reported previously in CHEC-II(1996). While the unsubstituted 1,2,4-trioxane ring prefers an envelope conformation, structurally related analogs favor a twist boat conformation. 1,2,4-Trioxane-5-one **19** and a number of derivatives, also investigated theoretically, prefer half-chair conformations (cf. Figure 2). Molecular electrostatic potentials (MEPs) obtained by theoretical studies (CHEC-II(1996)) of certain derivatives of **17** and **18** were included in structure/antimalarial activity correlations; however, distinct conclusions between MEPs and antimalarial activities were not drawn.

1,2,4-Trithianes and all remaining arrangements of O and S (namely dioxathianes and oxadithianes) have not been studied theoretically, and, moreover, the latter compounds are partly still unknown (*vide infra*).

1,2,4-Trioxane and its halogenated derivatives also were theoretically calculated semi-empirically using AM1 and PM3 methods <2000JST(530)137> and by DFT at the B3LYP/6-31G* level of theory <1999JST(459)103>. In contrast to results published previously in CHEC-II(1996) (*vide infra*), the chair conformer **20** proved to be the most stable for 1,2,4-trioxane followed by the twist conformer **21**, which is only less stable by just $2.5 \text{ kcal mol}^{-1}$. The 3,6-difluoro and 3,6-dichloro derivatives of **20** also prefer the stable chair conformation (Figure 2); however, the difference in energy to the twist conformers was found to be even smaller. For both 3,3,6,6-tetrafluoro- and 3,3,6,6-tetrachloro-1,2,4-trioxane, the twist conformers were concluded to be of lowest energy <2000JST(530)137>. Besides the 'anomeric effect' of the substituents, the electronic effects between the 1,2-lone pairs and the O–O torsional

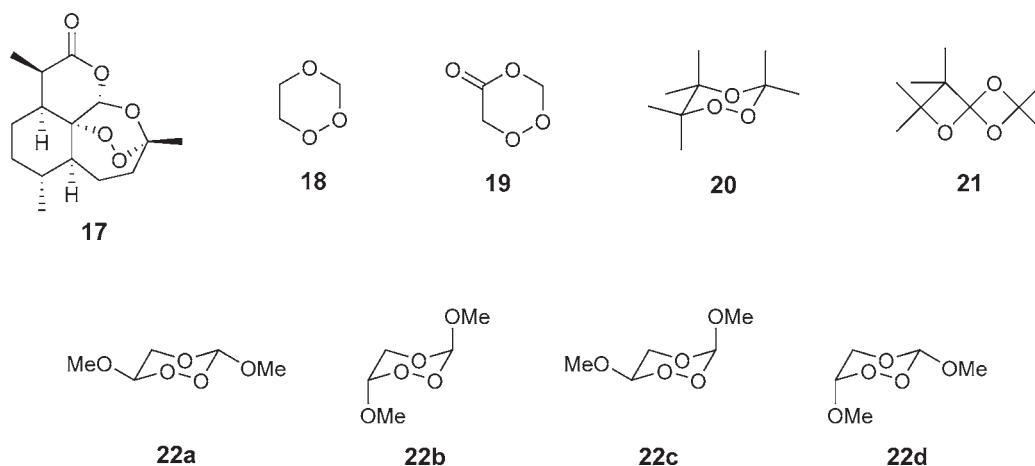


Figure 2 Preferred conformers of 1,2,4-trioxane derivatives.

angle play a central role in determining the conformational stability of the halogenated 1,2,4-trioxanes. Crucial for the calculations employing various methods is the O–O bond length; the best-modeled value of 1.460 Å was derived for artemisinin **17** from the DFT calculations (only 0.018 Å shorter than the experimentally measured value) <1997CPL(277)234>.

trans-3,6-Dimethoxy-1,2,4-trioxane **22** was also studied theoretically in detail by semiempirical AM1 and MP3 methods <2002MI111, 2001RJC1314> and by *ab initio* MO calculations at the 3-21G, 6-31G, and 6-311G levels of theory <2002AFF223> despite the compound having not yet been synthesized. As a major result of these studies, it was found that the *trans*-isomers **22a** and **22b** proved to be more stable than the *cis*-analogs **22c** and **22d** by more than 2.5 kcal mol^{−1}. With respect to conformation, the *ax,ax* conformer **22b** was identified as the preferred structure (cf. Figure 2) due to the anomeric effect, which is actually ring oxygen lone pair–antibonding σ^* -orbital of the exocyclic C–O bond hyperconjugation (i.e., $n_O \rightarrow \sigma_{C-O}^*$). The barrier to rotation of the methoxy substituents was also calculated and is ca. 2 kcal mol^{−1}; here, the synclinal conformations of the methoxy substituents are of lowest energy.

The geometry of artemisinin **17**, optimized at the B3LYP/6-31G* level of theory, has been reported and is in excellent agreement with the X-ray structure <1997CPL(277)234>; the overall structure of the 1,2,4-trioxane subsystem in **17**, predicted in this study, is close to the twist conformation of 1,2,4-trioxane **21** (cf. Figure 2).

9.11.2.3.1 QSAR study of the antimalarial activity of 1,2,4-trioxanes

The molecular structures of five categories of synthetic 1,2,4-trioxane derivatives **A–E** (cf. Figure 3) have been calculated by force fields, implemented in the quantitative structure–activity relationship (QSAR) program CATALYST <1997JCI124>, and compared with those determined by X-ray crystallography and calculated by *ab initio* methods. Generally it was ascertained that force field structures are as good as *ab initio* structures in accurately reproducing the geometry of the 1,2,4-trioxane ring moiety. A search was then concentrated on the particular features of the structures that are most likely to be responsible for their biological activity: it was conjectured that two hydrophobic sites and a hydrogen-acceptor site located on the potential drug are essential for antimalarial activity <1997JCI124>.

Because heme is expected to interact with the biologically active 1,2,4-trioxane derivatives, a search was next directed to the counterparts of the features on heme and therefore corresponding conformations of heme were also studied. A study of the heme–drug complex revealed that one of the peroxy oxygen atoms of the 1,2,4-trioxane ring system was close to the central Fe(II) atom in heme, the critical criterion for parasitocidal action, and the phenyl groups present lie face to face over the pyrrole rings of heme. Obviously therefore, π – π stacking may also be important for stabilizing the heme–drug complex.

Modeling the decomposition mechanism of artemisinin at Hartree–Fock (HF) and DFT theoretical levels supported the current hypothesis that some of the stable neutral intermediates and radical anions could be responsible for the antimalarial activity of artemisinin derivatives <2006BMC1546, 2006PCA7144, 2006JME6065>.

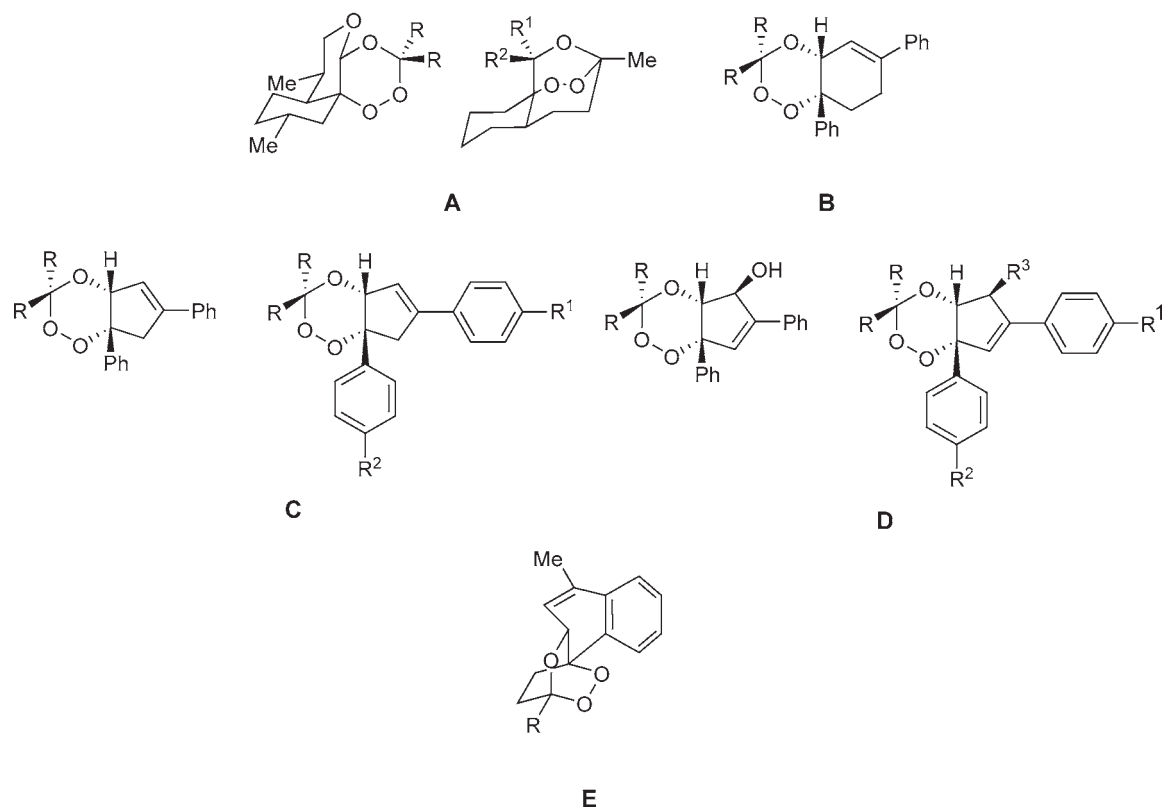
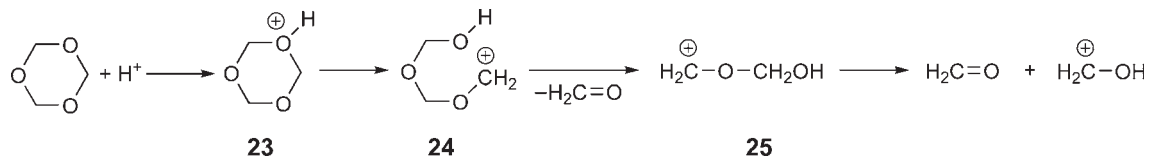


Figure 3 Categories **A–E** of synthetic 1,2,4-trioxane derivatives.

9.11.2.4 1,3,5-Trioxanes

1,3,5-Trioxane preferentially adopts the chair conformation and the relatively large steric hindrance experienced in the boat conformer is borne out by calculations at the MP2/6-31G(d) level of theory which provide an energy difference between the two conformers of $6.28 \text{ kcal mol}^{-1}$ [\[2005JMT\(713\)179\]](#). The interconversion of the six-membered ring was studied by both static and dynamic DFT calculations [\[2005PCA8096\]](#), wherein 1,3,5-trioxane was shown to interconvert through two envelope transition states with a calculated free energy barrier to chair inversion of $11.6 \text{ kcal mol}^{-1}$, in good agreement with the experimental value of $11.0 \pm 0.2 \text{ kcal mol}^{-1}$ [\[B-1995MI201\]](#). Furthermore, the enthalpy of formation of 1,3,5-trioxane ($-111.3 \pm 0.1 \text{ kcal mol}^{-1}$) was calculated at both the G3(MP2)//B3LYP level of theory [\[2001PCP3717\]](#) and by employing force field MM2(82) calculations [\[1984JCC326\]](#). The results were again in excellent agreement with the experimental value.

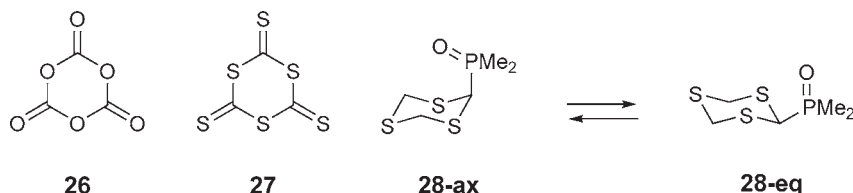
A DFT-based molecular dynamics study of the protonation reaction of 1,3,5-trioxane has been published [\[1994JA11251\]](#), the first step of the economically important polymerization process of this molecule. The decomposition can be divided into four steps (cf. [Scheme 3](#)). A proton approaches the neighboring oxygen atom, forming an OH bond (structure **23**) of average length (ca. $1.1 \text{ \AA}$), accompanied by an asynchronous modulation of the corresponding C–O bond lengths. This is followed by ring opening generating the carbocation **24** which is unstable and expels one formaldehyde molecule to form another carbocation **25** which finally dissociates into one neutral and one



Scheme 3

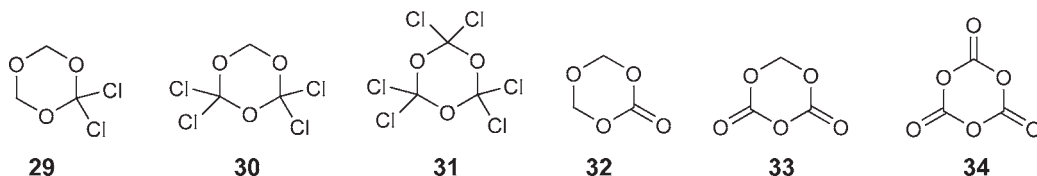
protonated formaldehyde molecule. In a later study, the same authors observed during the complete protolysis of several 1,3,5-trioxane molecules the reformation of small formaldehyde oligomers <1997JA7218>.

The stability of the cyclic trimers of CO₂ (**26**) and CS₂ (**27**) have been calculated at the semi-empirical <1992CPL(192)386>, MP2(FC)/6-31G* <1996JST(363)1>, and B3LYP/6-31G** <2000JA5367> levels of theory (cf. **Scheme 4**). Compound **27** was calculated to be less stable than free CS₂ by under 15 kcal mol⁻¹ (per CS₂ unit) while the oxygen analog **26** is less than 24 kcal mol⁻¹ (per CO₂ unit) higher in energy than free CO₂ <2000JA5367>. The calculated models were found to be planar and, although less stable than their free monomers, the formation of trimers **26** and **27** should be feasible nevertheless. In another detailed DFT study, the hypothetical (SCO)₃ and (OCS)₃ structures were studied and their energies were found also to be higher, by 46.2 and 73.5 kcal mol⁻¹, respectively, than their free noninteracting SCO monomers <2000MI55>. Hence, the fragmentation reactions of all these studied trimers are exothermic processes.



Scheme 4

The thermodynamic and kinetic stabilities of several novel 1,3,5-trioxanes **29–34** have been explored at the DFT level of theory <1999JA8544>: **29** proved to be very stable while **31** and **33** were found to be thermodynamically stable at low temperatures. By contrast, **30** and **32** were predicted to be slightly unstable thermodynamically but kinetically stable and, therefore, their preparation should be realizable. Finally, **34** was predicted to be highly unstable and consequently the realization of its preparation can be considered to be improbable.



9.11.2.5 1,3,5-Trithianes

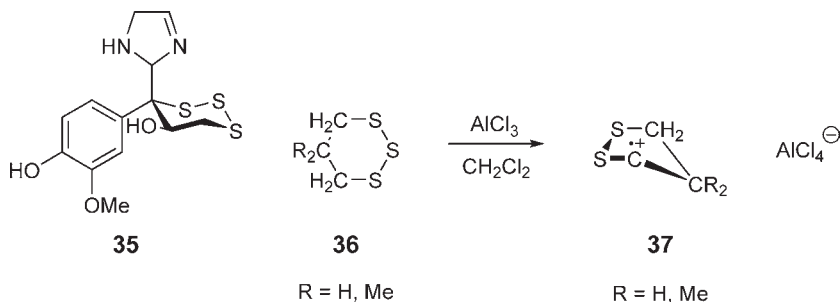
An early semi-empirical study of 1,3,5-trithiane, which was not included in CHEC(1984) <1983JCC84>, validates the modified neglect of diatomic overlap (MNDO) method for calculating well both the dipole moment and ionization energies of this molecule. The geometry of 1,3,5-trithiane has been more fully optimized at the MP2/6-31G(d) and MP2/6-31G(3df,2p) levels of theory <2001JOC5343> and the most stable form is the chair conformation with *C*_{3v} symmetry. It is, however, more puckered than cyclohexane to accommodate better the bond angles and bond lengths of the S–C bonds. The twist conformer proved to be another minimum but is less stable than the chair conformer by more than 3 kcal mol⁻¹; the calculated structural parameters are in good agreement with experimental bond lengths and bond angles (*vide infra*).

The experimental <1986JA2000> and theoretical conformational analysis of one 2-substituted 1,3,5-trithiane derivative **28** at the B3LYP/6-31G(d,p) level of theory has also been published (cf. **Scheme 4**) <2001JOC2925>. In this case, the axial rotamer is estimated to be 5.0 kcal mol⁻¹ more stable than its equatorial analog **28-eq**. Even if the agreement with the experimental values is poor ($\Delta G^\circ = -1.49$ kcal mol⁻¹ in chloroform), the axial preference of the P(=O)Me₂ substituent is reproduced nevertheless. Electrostatic attractive interactions between the negatively charged phosphoryl oxygen and the slightly positively charged *syn*-axial hydrogens, obviously not correctly considered in the *ab initio* calculation, are one reason for the experimentally observed increased predominance of **28-ax**. Support for the contribution of C–H···O=P hydrogen-bonding stabilizing interactions comes from a careful analysis employing the atoms-in-molecules (AIM) theory <2001JOC2925>.

9.11.3 Experimental Structural Methods

9.11.3.1 1,2,3-Trithianes

One unusual 1,2,3-trithiane derivative (+)-**35** has been isolated from a New Zealand marine organism (cf. [Scheme 5](#) <1989TL3703>); the solution-state conformation of the six-membered ring together with the complete structure of **35** was accomplished by ^1H NMR spectroscopy (nuclear Overhauser effect (NOE) experiments and application of vicinal coupling constants) and high-resolution electron ionization (EIMS) (by the observation of three sequential losses of ^{32}S ($342 (\text{M}^+)$, $310 (\text{M}^+ - \text{S})$, $278 (\text{M}^+ - 2\text{S})$, and $246 (\text{M}^+ - 3\text{S})$). Sharp lines in the ^1H NMR spectrum that persisted down to 213 K indicated that only one conformation was predominant. Subsequent bioassay-directed fractionation of sponge extracts afforded the (–)-enantiomer of **35** (cf. [Scheme 5](#) <2001JOC8257>).

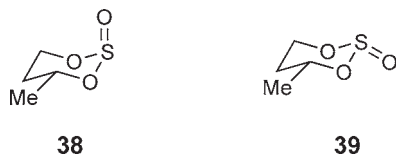


Scheme 5

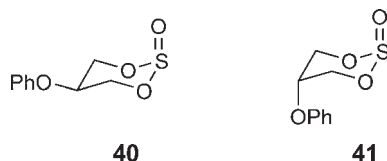
The photoelectron spectra of 1,2,3-trithiane and of its 5,5-dimethyl derivative **36** have been reported and exhibit first ionization energies of 8.36 and 8.15 eV, respectively, to provide radical cation ground states with predominant sulfur lone pair contributions <1988ZNB117>. Upon treatment of the two compounds with $\text{AlCl}_3/\text{CH}_2\text{Cl}_2$ (or $\text{SbCl}_5/\text{CH}_2\text{Cl}_2$) solution, they are converted into the 1,2-dithiolane radical cations **37** which were rationalized from electron spin resonance (ESR) spectra; both the rather high g -value (2.0183) and the ^{33}S coupling constant (1.33 mT) indicate considerable spin density at the sulfur centers.

9.11.3.2 1,3,2-Dioxathianes

X-Ray studies of 1,3,2-dioxathianes and their 2-oxides extend into the time period under coverage. The major difference between the structures of the 4-methyl isomers **38** and **39** in the crystalline state is the orientation of the sulfoxide oxygen, being axial in **38** but equatorial in **39**; the six-membered rings adopt almost ideal chair conformations and the 3-methyls are in equatorial positions in both cases <1996AXB505>. Differences between the structures of **38** and **39** regarding bond lengths and bond angles are insignificant and, furthermore, there is no evidence (*vide infra*) for the existence of conformers other than single chair forms.



The X-ray diffraction analysis of the isomeric pair of 5-phenoxy-1,3,2-dioxathiane 2-oxide **40** and **41** has been reported <2003RJC1282>. In contrast to **39**, the sulfoxide oxygen in **40** was found to be in an axial position and, accordingly, the phenoxy substituent therefore in equatorial (*cis*) and axial positions (*trans*), respectively. The conformations of the isomers are preserved in solution (*vide infra*).

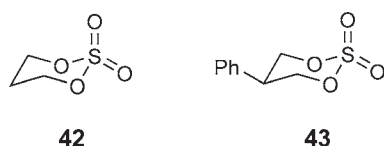


Other 1,3,2-dioxathiane 2-oxide solid-state structures have been published also. Besides chairs with axial <1980AXC187, 1984JA6899, 1987MI39, 1994DOK218, 1996AXB505, 1989J(P2)919, 1990AXC1913, 1992BSB753, 1998CAR297, 2001CH533, 2003OBC2314, 2003ZOB1357, 2006AXE425> or equatorial S=O groups <1996AXB505, 1998CAR297, 1998JCS(P2)919, 2003OBC2314>, distorted boat conformers with axial S=O groups <1984JA6899> have also been reported. A comparison of the experimental bond lengths for the 1,2,3-trithiane and 1,3,2-dioxathiane ring systems is given in **Table 1**; they are unexceptional and deserve no particular comment.

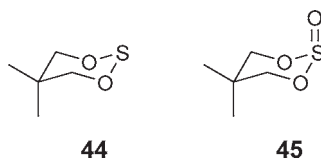
Table 1 Experimental bond lengths in selected 1,2,3-trithiane and 1,3,2-dioxathiane derivatives

<i>Conformation</i> (1,2,3-trithiane)	<i>S(1)–S(2)</i> (Å)	<i>S(2)–S(3)</i> (Å)	<i>S(3)–C(4)</i> (Å)	<i>C(4)–C(5)</i> (Å)	<i>C(5)–C(6)</i> (Å)	<i>C(6)–S(1)</i> (Å)	<i>Reference</i>
Chair	2.041	2.038	1.819	1.521	1.524	1.823	1978CL1219
<i>Conformation</i> (1,3,2-dioxathiane 2-oxide)	<i>O(1)–S(2)</i> (Å)	<i>S(2)–O(3)</i> (Å)	<i>O(3)–C(4)</i> (Å)	<i>C(4)–C(5)</i> (Å)	<i>C(5)–C(6)</i> (Å)	<i>C(6)–O(1)</i> (Å)	<i>Reference</i>
Chair, S=O(ax)	1.603	1.623	1.444	1.502	1.531	1.442	2003ZOB1357
Chair, S=O(eq)	1.612	1.612	1.480	1.510	1.492	1.471	1996AXB505
Twist boat, S=O(ax)	1.592	1.613	1.480	1.533	1.535	1.487	1984JA6899

In addition, some structures of 1,3,2-dioxathiane 2,2-dioxides have been published which completely prefer chair conformations <1988JA8512, 1988DOKC119, 1995CSC1701, 2001OL2563>, for example, the sulfone **42**, 5-phenyl-1,3,2-dioxathiane 2,2-dioxide **43** <1988JA8512>, and 5-*tert*-butyl-5-methyl-1,3,2-dioxathiane 2,2-dioxide <1995AXC1701>. The 5-phenyl substituent in **43** was found, as expected, in an equatorial position. The authors were attempting to find conformationally determining stereoelectronic effects to account for the difference in the infrared (IR) S=O vibrations (1180 cm⁻¹ for the axial S=O bond and 1230 cm⁻¹ for the equatorial analog, *vide supra*). However, the differences between axial and equatorial S=O bond lengths were so small that they could not be discerned by the X-ray experiment.



Ambient temperature ¹H NMR spectra of **12** and **13-ax** (cf. **Scheme 1**) as well as their IR spectra have been reported prior to 1983. The ring interconversion of 5,5-dimethyl-1,3,2-dioxathiane **44** and of its 2-oxide **45** have been studied by dynamic ¹H NMR spectroscopy. Barriers to the ring interconversion of 12.5 and 8.25 kcal mol⁻¹, respectively, fall in the range expected for saturated heterocyclic six-membered ring systems <B-1995MI201>. The downfield shift of the axial H-4 and H-6 protons in **13-ax** and the large diaxial ³J_{Hax,Hax} coupling constants indicated the preference of the sulfite oxygen for the axial position also in solution <2001CH533>.



The ^1H NMR structural analysis of a series of 4-spiro-1,3,2-dioxathiane 2-oxides **46** has been published (Figure 4) <1987SAA1355>. The cyclohexane part of these spiro sulfites always maintains a chair conformation; however, various behaviors for the conformation of the heterocyclic ring system were observed:

1. Unsubstituted compounds prefer the chair-ax conformation (95% in CCl_4 ; in acetonitrile solution this is shifted to 30% chair-eq).
2. The 4-*tert*-butyl derivatives (R^3 or $\text{R}^4 = \text{tert-butyl}$) display either chair-ax anancomers or twist-ax $\rightleftharpoons$ twist-eq $\rightleftharpoons$ chair-eq equilibria (the latter because of strong 1,3-*syn*-axial interactions).
3. Methyl-substituted derivatives (R^1 or $\text{R}^2 = \text{Me}$) exhibit chair $\rightleftharpoons$ twist conformer equilibria due to severe $\text{Me} \cdots \text{Me}$ 1,3-*syn*-axial interactions.

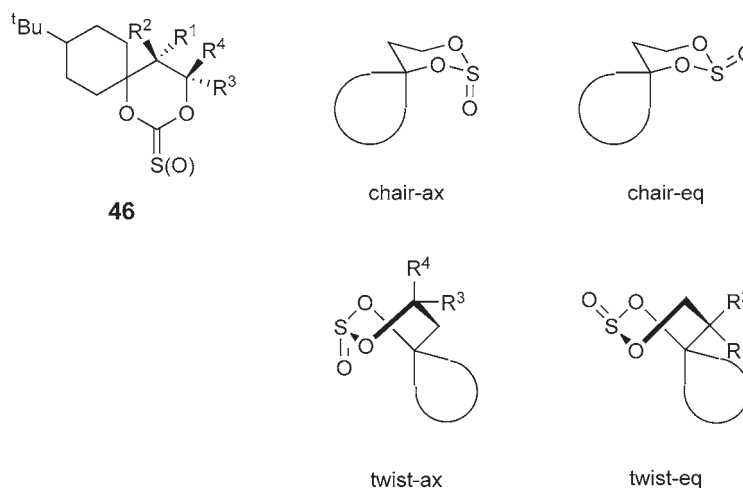


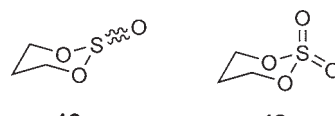
Figure 4 Structural analysis of 4-spiro-1,3,2-dioxathiane 2-oxides **46**.

Thus, it was determined that in the spiro-1,3,2-dioxathiane 2-oxides studied, several twist forms were also present and that only small energy differences exist between them and chair conformations (cf. Figure 4).

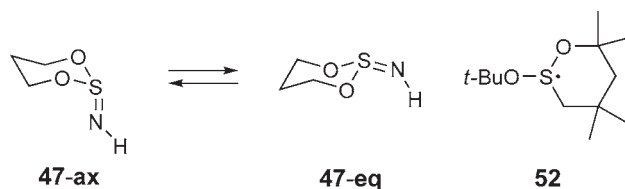
^{13}C and ^{17}O NMR chemical shift data for a variety of methyl- and phenyl-substituted 1,3,2-dioxathiane 2-oxides **13** and 2,2-dioxides **42** have been reported <1988MRC671, 1987MRC569, 1986MRC163, 1985JOC644> (cf. Table 2 also) and employed for the conformational analysis of these compounds in solution. The substituent effects on ^{13}C chemical shifts show that the 1,3,2-dioxathiane 2-oxides **13** attain exclusively chair conformations in solution, preferably with an axial, but often also with an equatorial $\text{S}=\text{O}$ group. On the basis of ^{13}C chemical shift effects, most existing chair–chair conformational equilibria could be defined precisely in close agreement with other spectroscopic data (^1H NMR, IR, and MS) and dipole moment measurements. The corresponding ^{17}O NMR chemical shifts depend strongly on both the measuring temperature and sample concentration <1987MRC569> but, similarly to the ^{13}C chemical shifts, they can be used to render conclusions regarding the preferred conformations as an axial $\text{S}=\text{O}$ resonates at around 180 ppm <1986MRC163>. Also, the ^{13}C NMR chemical shifts of eight cyclic sulfites **13**, chlorinated at C-5, have been published <1983OMR426>. However, studies of conformational equilibria showed that there can be difficulties in using ^{13}C NMR for conformational analysis of these compounds because of the frequent participation of twist forms. By measuring the spin–lattice relaxation time T_1 of the methyl carbon atoms of 5,5-dimethyl-1,3,2-dioxathiane 2-oxide, the methyl rotational barriers were determined <1986MI603>.

A number of IR studies of the conformational analysis of 1,3,2-dioxathiane 2-oxide and its derivatives have been published: the $\text{S}=\text{O}$ stretching alone could not resolve the conformational problem <1983JST(98)221>; however, strong evidence that the molecule has an axial chair conformation **13-ax** was obtained. Accordingly, substituted 1,3,2-dioxathiane 2-oxides were also studied <1984SAA519, 1984JA6899>. IR spectra, interpreted according to accepted criteria, indicated the sulfite ring to be either in a chair or a twist form, with an axial or pseudoaxial $\text{S}=\text{O}$ group. Similarly, the $\nu_{\text{S}=\text{N}}$ vibration in a series of substituted imidosulfites ($\text{S}=\text{NH}$ instead of $\text{S}=\text{O}$) was analyzed <1983SAA943> and found to be applicable for determination of the spatial arrangement of the $\text{S}=\text{NH}$ moiety as well as the rotational isomerism about the $\text{S}=\text{N}$ bond. The iminosulfite **47** of **13** exists as an equilibrium between two inverted chair conformers **47-ax** $\rightleftharpoons$ **47-eq** ($\Delta G^\circ = 0.92 \text{ kcal mol}^{-1}$; Scheme 6).

Table 2 ^{13}C and ^{17}O chemical shift data for substituted 1,3,2-dioxathiane 2-oxides **13** and those of the corresponding 2,2-dioxides **42** <1988MRC671>



Entry	Compound	Substituents	$\delta^{13}\text{C}$ (ppm)			$\delta^{17}\text{O}^a$ (ppm)			
			C-4	C-5	C-6	O-1	O-3	S-O	S-O
1	13a		57.3	26.0	57.3	126.1	126.1	179.8	
2	13b	4-Methyl	64.2	33.0	57.5	123.5	150.5	180.2	
			74.2	31.3	63.5	138.6	166.7	180.0	
3	13c	5,5-Dimethyl	66.5	31.7	66.5	120.2	120.2	174.1	
4	13d	5,5-Diethyl	63.6	36.0	63.6	119.8	119.8	181.8	
5	13e	5-Methyl-5-phenyl							
6	13f	4,6-Dimethyl (<i>cis,cis</i>)	64.7	40.7	64.7	153.8	153.8	201.5	
7	13g	4,6-Dimethyl (<i>cis,trans</i>)	71.6	38.0	62.3	148.9	148.9	179.4	
			73.8	38.7	73.8				
8	13h	4,4,6-Trimethyl	80.7	44.0	60.6	149.1	159.3	195.7	
			81.8	41.9	70.4	162.6	176.6	180.0	
1	42a		73.4	23.5	73.4	125.5	125.5	146.5	146.5
2	42b	4-Methyl	82.4	30.6	72.1	123.0	123.0	147.4	147.4
3	42c	5,5-Dimethyl	81.7	30.8	81.7	124.8	124.8	147.0	147.0
4	42d	5,5-Diethyl	79.3	35.5	79.3	121.5	121.5	147.0	147.0
5	42e	5-Methyl-5-phenyl	80.4	37.2	80.4	124.5	124.5	146.1	146.1
6	42f	4,6-Dimethyl (<i>cis,cis</i>)	81.3	37.9	81.3	151.4	151.4	159.8	159.8
7	42g	4,6-Dimethyl (<i>cis,trans</i>)				144.9	147.0	159.6	159.6
8	42h	4,4,6-Trimethyl				156.7	156.7	163.1	163.1

^aReferenced to external tap water.**Scheme 6**

The isotope shift caused by the ^{17}O and ^{18}O nuclei on the frequency of both the symmetric and antisymmetric SO_2 stretching vibrations of 1,3,2-dioxathiane 2,2-dioxides **42** was found to be strongly dependent on whether the heavy oxygen is located in the axial or equatorial position <1988BOC283, 1985CC1073>. The Fourier transform infrared (FTIR) spectra for **42** showed well-resolved vibrations for the isotopomers [^{16}O -1, ^{16}O -2ax, ^{16}O -2eq], [^{16}O -1, ^{17}O -2ax, ^{16}O -2eq], and [^{16}O -1, ^{16}O -2ax, ^{17}O -2eq]. This method permits the distinction between enantiomeric [^{16}O , ^{17}O , ^{18}O]sulfate monoesters of chiral 1,3-diols by IR spectroscopy via cyclization to the isotopomeric mixture of the corresponding 1,3-2-dioxathiane 2,2-dioxides **42** (Lowe's hypothesis) <1991CC1403, 1991PS63>. The vibrational frequencies were consequently *ab initio* MO calculated <1995CC701>: the similarity between calculated and experimental IR spectra was very striking and implied that a computational approach could have demonstrated the feasibility of Lowe's hypothesis prior to carrying out the relevant experiments.

The Raman spectrum of 1,2,3-trithiane has also been published and characteristic bands at 496 and 479 cm^{-1} identified for the S-S-S functionality <1988MI494>.

The absolute configuration of the sulfite center in 1,3,2-dioxathiane 2-oxide derivatives has been assigned empirically based on the combined analysis of NMR, IR, and X-ray data but mainly by their chiro-optical properties <2001CH533>; circular dichroism (CD) and ultraviolet (UV) data for compounds **48–51** studied are displayed in Table 3. The sulfites **48/50** and **49/51** differ from each other only by the S=O conformation. A comparison of their respective CD spectra shows the short wavelength band to be positive for the axial and negative for the equatorial S=O orientation. Thus, the stereochemistry at S-2 proved to be responsible for the sign pattern of the CD curve and, based on the configuration of **48** known from the X-ray study, the absolute stereochemistries in **48** and **50** as well as in **49** and **51** must be the same – this leads to the *SR* absolute stereochemistry for **50** and *SS* for **49** and **51** <2001CH533>.

Table 3 UV and CD data for (*E/Z*)-isomeric 1,3,2-dioxathiane 2-oxides **48–51** <2001CH533>



48

49

50

51

<i>Compound</i>	<i>UV ϵ (λ)</i>	<i>CD $\Delta\epsilon$ (λ)</i>
48	1070 (196) ^a	+10.0 (191) –0.27 (210)
49	1780 (197)	–11.1 (199)
50	1400 (200) ^a	+11.1 (186) –0.38 (204)
51	1870 (196) ^a	–11.1 (195)

^aShoulder.

Finally, it has been shown that sulfuranyl radicals, for example, **52** (cf. Scheme 6), exhibit absorption spectra, which can be detected with ultraviolet–visible (UV–Vis) spectroscopy; absorption maxima were found to be sensitive to the σ - versus π -electronic configurations of these radicals and thereby to be a sensitive guide in the assignment of the electronic structure of sulfuranyl radicals <1985JOC2516>.

9.11.3.3 1,2,4-Trioxanes and Analogs

9.11.3.3.1 Crystal structures

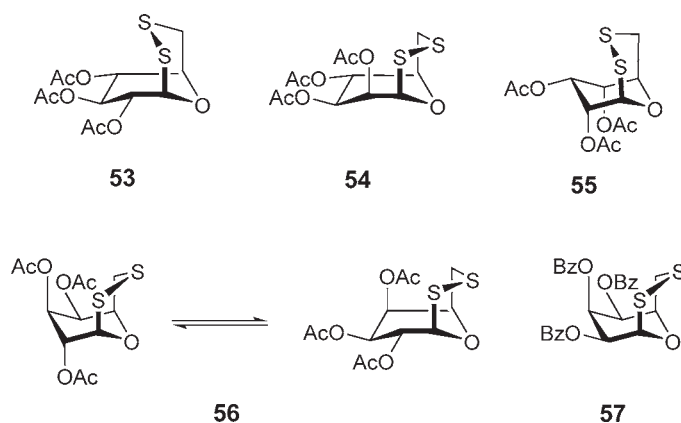
Publication of relevant X-ray structures from 1996 onward has continued, especially due to the continuing strong interest in antimalarial artemisinins. Altogether, ca. 40 structures including the 1,2,4-trioxane ring have been published. Bond and dihedral angles for the preferred conformation of the 1,2,4-trioxane ring vary according to the ring fusion and/or attached substituents. Thus, published structures were classified, continuing on from CHEC-II(1996), as monomeric (**M**) and bearing substituents or even spiro groups, bicyclic (**B**), tricyclic (**T**), bridged tricyclic (**BT**), and artemisinin-like (**A**). For all five groups representatives were found and a comparison of the experimental bond lengths for the 1,2,4-trioxane ring system for the different classes is given in Table 4. They are all unexceptional and deserve no particular comments. More interesting is the conformation of the 1,2,4-trioxane ring in the various structures: the chair is the most stable conformer for structures **M**, **B**, and **T** (slightly twisted in **B**) <2003OBC2859, 2004CEJ1625, 1998H(49)375, 2005BML595, 1977AXB3564, 1997H(44)367>, while the bridged tricyclic and artemisinin-like structures force the 1,2,4-trioxane into the twist boat conformation <2002JOC1253, 2002EJO113, 2002JCX43, 1998TL2969, 1998EJO2897, 2001JME4688, 2003TL3637, 1999TL9133, 2002EJO113, 1997BML2357, 2001BML5, 1997P1209, 1998JCX539, 2000HCA1239, 2001JOC7858>.

Table 4 Experimental bond lengths in some 1,2,4-trioxanes, 1,5,2-dioxathianes, 1,2,4-trithianes, and 1,3,4-oxadithianes (numbering based on 1,2,4-trioxanes)

Conformation (1,2,4-trioxanes)	Class	O(1)–O(2) (Å)	O(2)–O(3) (Å)	C(3)–O(4) (Å)	O(4)–C(5) (Å)	C(5)–C(6) (Å)	C(6)–O(1) (Å)	Reference
Chair	A	1.461	1.434	1.429	1.464	1.538	1.449	2003OBC2859
Twist boat	A	1.469	1.419	1.439	1.379	1.511	1.449	2002JOC1253
Chair	T	1.467	1.430	1.422	1.448	1.534	1.454	2004CEJ1625
Chair	M	1.467	1.419	1.406	1.440	1.527	1.454	1977AXB3564
Twisted chair	B	1.475	1.417	1.412	1.440	1.538	1.407	1997H(44)367
Twist boat	BT	1.474	1.409	1.432	1.391	1.536	1.452	1998TL2969
(1,5,2-dioxathiane)	Class	S(1)–O(2)	O(2)–C(3)	C(3)–O(4)	O(4)–C(5)	C(5)–C(6)	C(6)–S(1)	Reference
Chair	M	1.647	1.453	1.397	1.435	1.534	1.854	1991CJC185
(1,2,4-trithianes)	Class	S(1)–S(2)	S(2)–C(3)	C(3)–S(4)	S(4)–C(5)	C(5)–C(6)	C(6)–S(1)	Reference
Twisted chair	M	1.985	1.457	1.865	1.793	1.466	1.793	2000JOC5514
(1,3,4-oxadithiane)	Class	S(1)–S(2)	S(2)–C(3)	C(3)–O(4)	O(4)–C(5)	C(5)–C(6)	C(6)–S(1)	Reference
Chair	M	2.052	1.829	1.430	1.438	1.547	1.798	2005AJC199

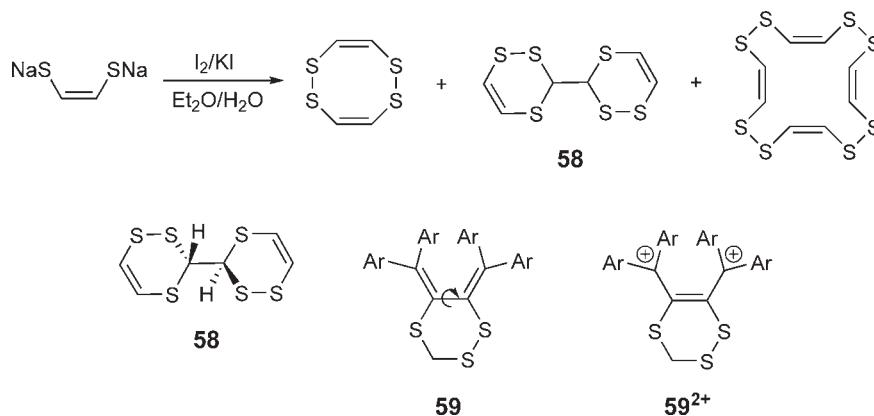
In addition, one 1,5,2-dioxathiane <1991CJC185>, three 1,3,4-oxathiane <2005AJC199>, and two 1,2,4-trithiane structures <2000JOC5514> have also been published and are included in **Table 4** for the purpose of comparison; the latter are monomeric structures and prefer the chair conformation.

A number of 1,6-disulfide-bridged D-hexopyranoses have been synthesized (*vide infra*) and their corresponding triacetates **53–56** and one tribenzoate **57** were studied in detail structurally, both in solution and in the solid state (cf. **Scheme 7**) <2005AJC199>. While in the D-glucosyl triacetate **53** the pyranose ring exists in a boat ($B_{O,7}$) conformation and the dithiane ring in a chair conformation ($^S C_O$), this changes in D-manno- ($B_{O,7}$, $B_{S,O}$) **54**, D-allo- ($^1 C_6$, $^S C_O$) **55**, and D-galacto-triacetate **56** (cf. **Scheme 7**) as well as D-talo-tribenzoate **57** ($^1 C_6$, $B_{S,O}$); D-galacto triacetate **56** proved to be present in two slowly interconverting conformers of approximately equal proportion. For the $^1 H$ NMR solution assignments, the relative size of the vicinal coupling constants ($^3 J_{Hax,Hax} > ^3 J_{Hax,Heq}$, $^3 J_{Heq,Heq}$) and the W-coupling between the equatorial protons in the 6- and 8-positions were examined. In addition, a five-bond coupling between H-1 and one of the protons at C-4 was indicative of the dithiane ring adopting the $^S C_O$ conformation; X-ray work confirmed the conformations within the solid state <2005AJC199>. Additionally, the benzoate analog of **53** was oxidized to the thiosulfinate with the oxygen being positioned axially.

**Scheme 7**

In the dihydro-1,2,4-trithiin series, the solid-state structures of the dimer **58** <1997AXC748> (obtained as a side product during the intramolecular double cyclization of *cis*-disodium ethene-1,2-dithiolate with I_2/KI at $-10^\circ C$ in a

heterogeneous dilute solution; see [Scheme 8](#)) <1996AGE2357, 1997PS457, 1998JOC8192>, the exocyclic tetraaryl 1,3-diene derivative **59** (obtained as a decomposition product of the corresponding 1,3,5-trithiane derivative), as well as the electrochemically synthesized dication **59**²⁺ have been reported <2000JOC5514>. In the dimer **58**, determined to be the *meso*-form, the atoms of the six-membered ring, except sulfur in position 2, are nearly planar with the dihedral angle about the disulfide moiety being reduced to -64.25° from ca. 90° in the strain-free geometry of disulfides. However, the S–C=C–S torsion angle is only 2° , indicating an almost strain-free geometry in this part of the molecule.



Scheme 8

The C(5)=C(6) moiety in **59**²⁺ is completely planar with the two diarylmethyl cation units rotated by dihedral angles of $62\text{--}63^\circ$. Thus the steric repulsion between the two $\text{C}^+(\text{Ar})_2$ moieties is relieved by rotation about the C(5,6)–C⁺ bonds. In **59**, the steric hindrance is so large that the torsion angle of the C=C–C=C unit is 51° and the inner aryl groups are forced to stack face to face. This is one of the very few cases in which the four aryl groups resonate in the ¹H NMR spectrum at different chemical shifts <2000JOC5514>.

9.11.3.3.2 IR studies

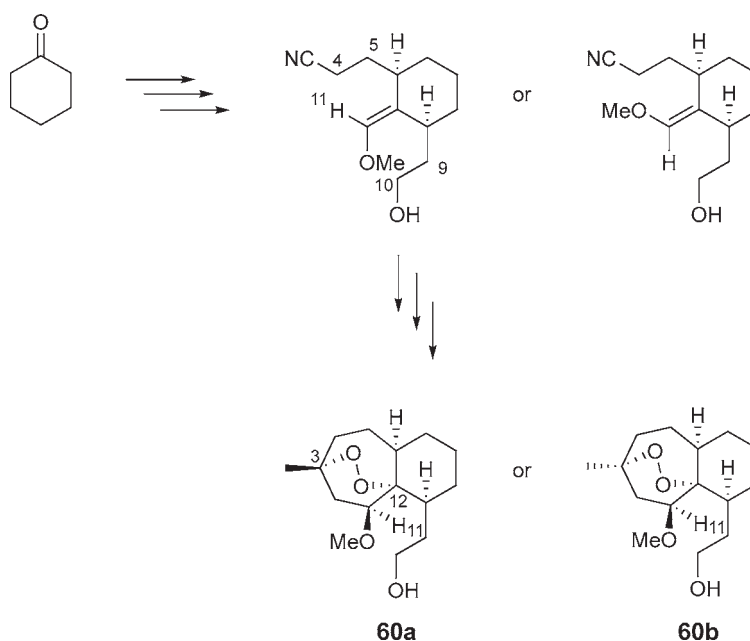
Early IR studies of the vibrational spectrum of artemisinin **17** suggested the peroxy linkage contained therein to be characterized by a frequency at 722 cm^{-1} , but later studies of several 1,2,4-trioxane derivatives proved that the 722 cm^{-1} band of artemisinin must be of nontrioxane origin. A harmonic vibrational frequency analysis at the self-consistent field (SCF) HF/6-31G* level of theory was conducted <1999JST(459)103> on the B3LYP/6-31G* structure <1997CPL(277)234>, which revealed that actually there is no pure O–O stretching mode in artemisinin whatsoever and all the O–O stretching modes are more or less coupled with O–C stretchings. However, even if the experimental band at 722 cm^{-1} cannot be assigned to the O–O stretching motion, it is a characteristic motion of the 1,2,4-trioxane ring in artemisinin **17**. Additionally, also identified as characteristic for the 1,2,4-trioxane ring system in artemisinin is the twisting mode (at 831 and 881 cm^{-1}) and coupled C–O and O–O stretching modes of the O–O–C entities at 1115 cm^{-1} <1997CPL(277)234>.

The vibrational frequencies of hexamethyl-1,2,4-trioxane in both conformations **20** and **21**, analyzed at the DFT B3LYP/6-31G* level of theory on optimized structures, were all real, confirming that the two conformers represent local minima on the potential energy surface <1999JST(459)103>. The O–O vibration was found as almost pure O–O stretching in both chair ($\nu = 829\text{ cm}^{-1}$) and twist boat forms ($\nu = 850\text{ cm}^{-1}$) with frequencies greater than 900 cm^{-1} hardly likely to be related to the motions of the O–O linkage.

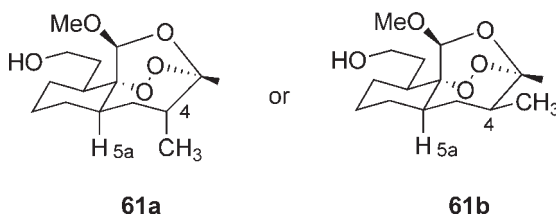
9.11.3.3.3 NMR studies

The definitive assignments of the ¹H and ¹³C NMR spectra of artemisinin **17** and other analogs have been reported. The ¹J_{C,H} coupling constant was employed as a reliable index of the configuration of the substituents on the 1,2,4-trioxane framework and, by dynamic NMR spectroscopy, the barriers to ring interconversion of various 1,2,4-trioxane derivatives were estimated. In addition, a series of strategies has been developed using one-dimensional (1-D) and 2-D NMR spectroscopy for identification of the relative stereochemistry in an assembly of substituted antimalarial

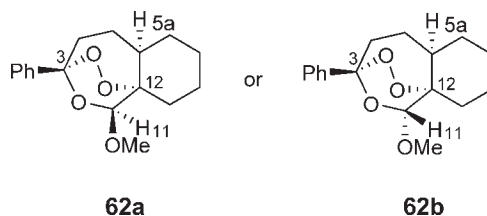
1,2,4-trioxanes <1997SPL241>. The biosynthesis of artemisinin **17** produces a single enantiomer; however, other stereoisomers may have vastly different antimalarial efficacies and so determination and control of the relative and absolute stereochemistries is vital. In the following passages, characteristic examples in accomplishing just that are presented: C-4-unsubstituted 1,2,4-trioxane alcohol **60** and C-4-alkylated analogs **61** are available in six to eight synthetic steps from commercial cyclohexanone (Scheme 9). All have been found to be potent *in vitro* antimalarials. By correlation spectroscopy (COSY) (thereby assigning the involved coupling protons) and 1-D nuclear Overhauser effect (NOE) experiments (H-11 being closer to H-9,10 than H-4,5), the relative stereochemistries were definitively identified. The stereochemistry of the *endo*-peroxide bridge (with a new stereocenter at C-11 as well as the preexisting centers C-5a and C-8a) in **60** was clarified by the ^1H NMR coupling pattern: the acetal proton H-11 appeared at 5.19 ppm as a doublet ($J=1.6\text{ Hz}$) with W-coupling to H-5a, thereby implying that the relative configuration of the trioxane alcohol must be **60a** or **60b**. X-Ray analysis revealed the relative stereochemistry of C-11 to C-3 and C-12 to be that of **60a**. The C-4-alkylated trioxane alcohols **61** have an additional stereocenter introduced by substitution on the seven-membered ring; unfortunately, significant NOEs (expected for **61a**) were not seen in either diastereomer (probably due to the ring interconversion of the seven-membered ring being fast on the NMR timescale) and the stereochemical assignment was left to X-ray crystallographic determination.



Scheme 9



The relative stereochemistry of the two C-11 acetal diastereomers of the simplified 1,2,4-trioxanes **62** was assigned by ^1H NMR spectroscopy: the H-11 proton chemical shifts are similar ($\delta = 5.14$ and 5.20 ppm) (however, only H-11 in **62a** can W-couple to H-5a). In addition, it was determined that in the C-11(β)-methoxy configuration, C-3 and C-11 (^{13}C NMR) are separated by 3 ppm or less and fall above roughly 104 ppm ; in contrast, for the C-11(α) methoxy configuration, the two resonances are separated by ca. 8 ppm and C-11 falls at or below ca. 100 ppm .



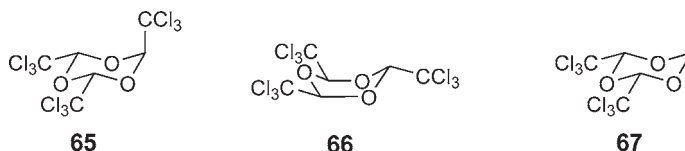
These characteristic ^{13}C resonances were used by the authors [\[1997SPL241\]](#) to assign the acetal stereochemistry in a number of other 1,2,4-trioxanes.

These simple rules for assigning the relative stereochemistry are crucial to ensure correct identification of new analogs in this facet of research.

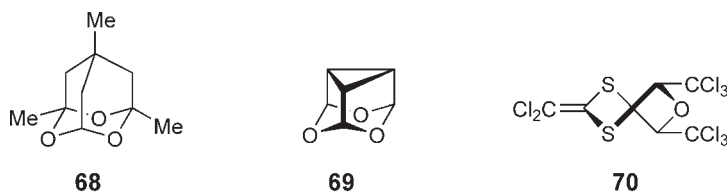
9.11.3.4 1,3,5-Trioxanes and Analogs

9.11.3.4.1 Crystal structures

Both chair and boat conformers of substituted 1,3,5-trioxane derivatives were found in the solid state: while the *cis*- and *trans*-isomers of 2,4,6-tris(trichloromethyl)-1,3,5-trioxane (**63** and **64**), instead of the 2-ax,4-eq,6-eq chair conformer **65**, prefer the corresponding boat conformer **66** [\[1986MI283\]](#), X-ray crystallography of *cis*-bis(trichloromethyl)-1,3,5-trioxane proves the 2-eq,4-eq chair conformer **67** to be predominant [\[1987MI683\]](#). These two compounds both have a strong tendency to lose CCl_3 groups and, as such, molecular ions were not observed by electron-impact mass spectrometry.



The 1,3,5-trioxane moieties in the highly symmetric triheteroadamantane **68** [\[1986CB3842\]](#) and in trioxa-[3]-peristylane **69** [\[2001JOC6905\]](#) reside in ideal chair conformations also. The solid-state structure of one 1,3,5-oxadithiane derivative, 2,6-bis(trichloromethyl)-4-dichloromethylene-1-oxa-3,5-dithiane **70** [\[1986MI851\]](#), has been published; the conformation the molecule adopts is a twist conformer.



Similar conformational preferences have been observed for the corresponding 1,3,5-trithiane derivatives; the normal conformer is the chair, for example, in *trans*-2,4,6-trihexyl-1,3,5-trithiane **71** [\[1995AXC88\]](#), but the twist conformation in *trans*-2,4,6-tris(trichloromethyl)-1,3,5-trithiane **72** with the substituents occupying pseudoequatorial positions [\[1987MI295\]](#) has also been reported. Among the solid-state structures of substituted 1,3,5-trithianes and the 1,3,5-trithiane structure as part of complexes or polycyclic compounds, some rather interesting geometries have been reported. In [Figure 5](#), some characteristic examples are given. Of note are the equatorial position of the highly polar iminotosyl group in **73** [\[1994AXC1821, 1994J\(P2\)1439\]](#), 2,4,6-triaryl-2,4,6-tris(trimethylsilyl)-1,3,5-trithiane with the SiMe_3 groups and the aryl substituents in axial positions adopting a basket-shaped conformation **74** [\[1988J\(P1\)1499\]](#), the silver complex of 1,3,5-trithiane **75** with the trithianes connected to the silver atom through only one sulfur (axial position) with normal bond lengths [\[1993ICA\(207\)263\]](#), the 1,3,5-trithiane $\cdots \text{I}_2$ complex **76** where each iodine bridges two equatorial sulfur lone electron pairs of different 1,3,5-trithiane molecules and each trithiane heterocycle exhibits two iodine contacts ($3.15 \text{ \AA}$) [\[1997LA2151\]](#), and 2-P(=O)OMe₂ and 2-P(=S)Ph₂ in the solid state as chair conformers **77** and **78**, respectively, but with different conformations of the phosphoryl substituent [\[1984T4885, 1988PS183\]](#) ([Figure 5](#)).

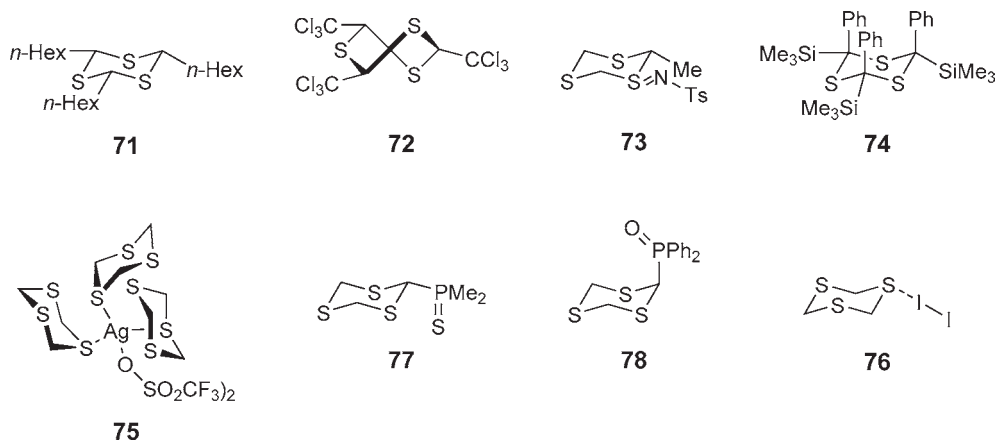


Figure 5 Characteristic examples for 1,3,5-trithianes as part of complexes or polycyclic compounds.

More 1,3,5-trioxane and 1,3,5-trithiane solid-state structures have been published. Chair conformations were evident in monocyclic molecules <1983POL1117, 1984T4885, 1985AXC397, 1985MI333, 1986CB3631, 1986ZNB409, 1986CB3631, 1987MI683, 1987MI675, 1988PS183, 1989IC2499, 1988J(P1)1499, 1992ZNB1736, 1993ICA(207)263, 1993RTC370, 1994AXC1821, 1994J(P2)1439, 1995AXC88, 1996CB451, 1997POL1983, 1997LA2151, 1998S417, 2000J(P2)1777, 2000NCS577, 2001NCS271, 2002NCS597, 2003HCA106, 2003JCX473>, heteroadamantanes <1986ZNB409, 1986CB3842, 2000J(P2)1777>, and peristylane <2004OL1617> (*vide supra*). Also, a few additional twist conformations in solid-state structures have been reported <1986MI851, 1987MI295, 1988MI439, 1989MI183, 2000JOC5514, 2002AXC231>. A comparison of the experimental bond lengths for the 1,3,5-trioxane, 1-oxa-3,5-dithiane, and 1,3,5-trithiane ring systems is given in **Table 5** (M = monomeric; A = adamantane-like). They are all within normal limits and require no particular comment.

Table 5 Experimental bond lengths (Å) in some 1,3,5-trioxanes, 1,3,5-oxadithianes, and 1,3,5-trithianes

1,3,5-Trioxane	Class	O(1)–C(2)	C(2)–O(3)	O(3)–C(4)	C(4)–O(5)	O(5)–C(6)	C(6)–O(1)	Reference
Chair	M	1.420	1.408	1.420	1.407	1.411	1.410	1985MI333
Chair	A	1.437	1.438	1.437	1.438	1.437	1.438	1986CB3842
1,3,5-Oxadithiane	Class	O(1)–C(2)	C(2)–S(3)	S(3)–C(4)	C(4)–S(5)	S(5)–C(6)	C(6)–O(1)	Reference
Chair	M	1.426	1.824	1.818	1.818	1.824	1.426	1987MI675
Twist	M	1.412	1.820	1.756	1.757	1.823	1.400	1986MI851
1,3,5-Trithiane	Class	S(1)–C(2)	C(2)–S(3)	S(3)–C(4)	C(4)–S(5)	S(5)–C(6)	C(6)–S(1)	Reference
Chair	A	1.825	1.824	1.825	1.824	1.825	1.824	2004OL1617
Twist	M	1.851	1.827	1.837	1.834	1.824	1.850	2002AXC231
Chair	M	1.797	1.786	1.784	1.771	1.779	1.860	2003JCX473

The rotational spectrum of 1,3,5-trithiane was measured at 360 K <1984JST(117)247> by laser-desorption spectroscopy <2002JST(612)125> whereby the rotational constants were determined and used to estimate the structure of the skeletal ring under the prevailing conditions. The bond lengths, bond angles, and torsional angles obtained prove the existence of the chair conformer and are in excellent agreement with X-ray crystallographic data and also with the structural parameters as determined by gas-phase electron diffraction (at a nozzle temperature of 466 K) <1989ACS953>.

9.11.3.4.2 IR and rotational spectroscopic studies

Both the sub-millimeter-wave spectrum <1989JSP406> and the pure rotational spectra of 1,3,5-trioxane and of the main ^{13}C and ^{18}O isotopomers <1996ZNA123> have been recorded. These new data enabled the determination of

very accurate rotational parameters and revealed that the molecule is fairly rigid in the vibrational ground state. The Raman and IR spectra of solid 1,3,5-trioxane <2004JMO105> and 1,3,5-trithiane have been recorded also and certain vibrational modes, their intensities, and Raman activities assigned using the MP2 *ab initio* calculation-based chair conformer <2005JMT(713)179>. The effect of the oxygen lone pairs on the C–H bond lengths and frequencies was discussed critically to clarify the effects of oxygen on the vibrational properties. The Raman spectrum of a single crystal of 1,3,5-trioxane was also measured <1984JST(115)129, 1986MI96> and a detailed assignment of the spectrum presented together with a study of the angular dependence of the photon frequencies.

A detailed vibrational band assignment has also been made for 2,4,6-trimethyl-1,3,5-trioxane <2004MI485>; a normal coordinate analysis was carried out in order to obtain the molecular force field of this system based on the C_{3v} point group symmetry (Table 6) and 2-D IR spectroscopy was employed to probe various molecular interactions <2004MI203>. The system dimethyl sulfoxide $\cdots$ 2,4,6-trimethyl-1,3,5-trioxane was examined in order to determine which set of hydrogens (the ring hydrogens or the methyl hydrogens; see Figure 6) interacts more strongly with the S=O group of dimethylsulfoxide. Therefore, the bending vibrational bands of C–H and CH₃ were investigated whereby it was determined that a selective interaction exists between the two molecules and that the interacting site is between the S=O and the three ring hydrogens which form a cyclic 3H group (79-cyc). Under the same conditions (freon matrix, 77 K), the complexation of 1,3,5-trioxane with ClF and Cl₂ was studied by FTIR spectroscopy <1989JST(196)47>; 1:1 molecular complexes were formed which were characterized primarily by the red-shifted stretching mode of Cl–F (ca. 90–100 cm^{−1}) in the corresponding complexes.

Table 6 Vibrational frequencies of 1,3,5-trioxane and 1,3,5-trithiane

<i>Molecule</i>	<i>Frequencies (cm^{−1})</i>
1,3,5-Trioxane	A ₁ : 3025, 2850, 1495, 1235, 978, 752, 466 A ₂ : 1383, 1242, 1122 E: 3025, 2850, 1481, 1410, 1305, 1178, 1070, 945, 524, 296
1,3,5-Trithiane	A ₁ : 2953, 2892, 1376, 908, 654, 405, 282 A ₂ : 1225, 1180, 753, 142 E: 2953, 2892, 1400, 1218, 1172, 795, 738, 664, 308

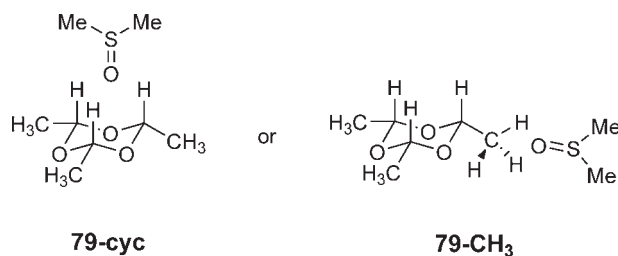


Figure 6 Possibilities of DMSO to interact with hydrogens of 2,4,6-trimethyl-1,3,5-trioxane.

In addition, 22 new optically pumped IR laser transitions of 1,3,5-trioxane were found, six of them were totally assigned and 16 of them only partly <1997MI437>. The absorption and dissociation measurements for the IR multiphoton decomposition of 1,3,5-trioxane have been reported <1987SAA149, 1996MI203> and the equilibrium constants, K_f , for the formation of 1:1 hydrogen-bonded complexes have been obtained by FTIR spectroscopy for 39 ethers (including 1,3,5-trioxane) and three peroxides in CCl₄ at 298 K employing 4-fluorophenol as the reference hydrogen donor and examining the ν_{OH} frequencies for estimating the corresponding pK_{HB} values <1998EJO925>. For the complex 1,3,5-trioxane $\cdots$ HCl, the matrix-isolation method was employed to access the characteristic H–Cl stretching vibration at 2580 cm^{−1} <1989JPC279>. The effect of pressure on the IR spectrum of 1,3,5-trioxane was studied in the range of 500–4000 cm^{−1} in order to follow the pressure-induced flattening of the molecule <1984MI173, 1984JA502>; the integrated intensities of three isolated, nonoverlapped bands (A₁ ring stretch, E CH₂ rock and twist) were analyzed on the basis of simple models and show clearly that 1,3,5-trithiane is flattened at ca. 50–60 kb.

Also, the C–S vibration of 1,3,5-trithiane has been studied intensively <1983MI431, 1984PS231, 1996SPL697>. Both the IR and Raman spectra were recorded with FT instrumentation and vibrations assigned to the C–S and C–H modes based on the calculated force constants (Table 6). The assigned chair conformer was found to be retained when 1,3,5-trithiane was adsorbed on silver sol surfaces and the structure determined by surface-enhanced Raman scattering <1991JST(243)307>. Adsorption occurs through the sulfur atoms parallel to the silver surface and shifts in the C–S and C–H vibrations were readily understood on the basis of hyperconjugation between the sulfur electron lone pairs with the antibonding orbitals of the adjacent C–H bonds. This adsorption process was also studied by photoelectron spectroscopy, thermal desorption spectroscopy, and low-energy electron diffraction, with the same result in each case <1994MI2063>.

9.11.3.4.3 NMR studies

The proton chemical shift of 1,3,5-trioxane ($\delta_{\text{exp}} = 5.00$ ppm) was successfully estimated ($\delta_{\text{theor}} = 4.93$ ppm) by a theoretical model (CHARGE5) <1998J(P1)1751>. This model considers steric, electrostatic, and anisotropic influences by certain terms. The single, usually nonoverlapped sharp ^1H NMR signal in the middle of the spectral region, permitting facile integration, is employed as an internal reference in the quantitative determination of aspirin, phenacetin, and caffeine mixtures <1986MI147>; the corresponding ^{13}C NMR line at ca. 93 ppm is used similarly for the quantitative analysis of lignins <2001JFA3573>.

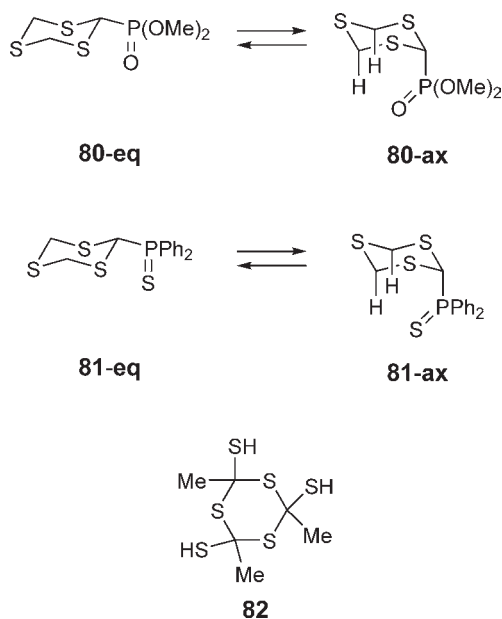
Both the ^1H and ^{13}C NMR spectra of 1,3,5-trioxane, partially oriented in three nematic solvents, were measured and the dipolar coupling constants analyzed and used to obtain information concerning the structure of the six-membered ring <1995MRC831>. As in isotropic media, 1,3,5-trioxane exists in the rapidly interconverting chair conformation with the methylene protons tilted outward from the C_3 symmetry axis by -2.1° . C–H bond lengths (1.11 Å) and H–C–H bonding angles (110.3°) are in excellent agreement with X-ray data (*vide supra*). The dynamic behavior of perdeuterated 1,3,5-trioxane- d_6 , obtained by direct synthesis from deuterated paraformaldehyde <1990JPC8845>, was also studied. The kinetic parameters for the chair–chair interconversion in liquid crystalline solvents yielded a rate constant of $k = 1.5 \times 10^{14} \times e^{(-12.2/RT)}$. In the solid state, 1,3,5-trioxane undergoes a threefold jump about the C_3 symmetry axis; the rate constant of this process was measured ($k = 2.35 \times 10^{18} \times e^{(-19.0/RT)}$). Finally, 1,3,5-trioxane- d_6 was examined as an inclusion compound in urea <1990JPC5391> and in cyclophosphazene <1998MI407> by solid-state deuterium NMR spectroscopy. The six-membered heterocycle undergoes ring inversion at a rate similar to that observed in isotropic solution ($k = 2.7 \times 10^{13} \times e^{(-11.7/RT)} \text{ s}^{-1}$).

A theoretical formalism for calculating dynamic multiple quantum NMR line shapes has been developed and used to calculate the expected line shapes of 1,3,5-trioxane dissolved in liquid crystalline solvents and undergoing ring inversion <1988JCP25>. It was shown that the resulting line shapes can be used to derive the kinetic parameters of the dynamic process.

In the mid-1980s, when the NMR spectroscopy of nuclei other than ^1H became routinely accessible, substance collection and recording were performed in order to create data banks for further assignment purposes. As a result, considerable phenomenological correlations of the NMR parameters were able to be drawn up. ^1H – ^{13}C coupling constants via one to six bonds of a large variety of methyl-substituted polythiaadamantanes, which incorporate the 1,3,5-trithiane moiety, have been measured and the effects of both the sulfur atoms and the methyl substituents on the various parameters were discussed critically <1984CS101>. ^{13}C -enriched 1,3,5-trithiane has been synthesized and both the recorded ^{13}C chemical shift ($\delta = 35.3$ ppm) and the one-bond ^1H – ^{13}C coupling constant ($^1J_{\text{H,C}} = 151.0$ Hz) discussed with respect to the corresponding values in comparable compounds <1984HCA1070>. Finally, the corresponding 2-lithio-1,3,5-trithiane was synthesized and the ^{13}C NMR spectrum recorded at -50°C <1984HCA1083> wherein C-2 was found to be shielded by 8.1 ppm, C-4/C-6 shielded by 0.7 ppm, $^1J_{\text{H,C}}$ reduced in size by 18.0 Hz, but the $^2J_{\text{C,C}}$ coupling constant, contrastingly to the former result, was found to be increased in size by 7.5 Hz.

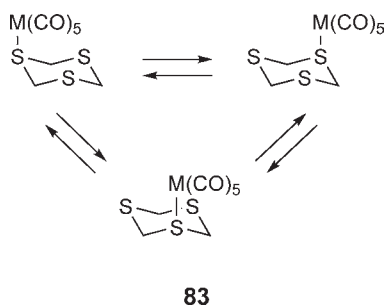
The conformational equilibria of 2-phosphoryl- and 2-thiophosphoryl-1,3,5-trithianes were investigated both experimentally and from the theoretical point of view. The detailed analysis of the ^1H NMR spectrum of 2-phosphoryl-1,3,5-trithiane in CDCl_3 provided clear evidence for the axial position of the dimethoxyphosphoryl group (80-ax, Scheme 10) <1984T4885>. Attractive interactions between phosphoryl oxygen and the axial hydrogens in the 4,6-positions obviously stabilize the axial position of the substituent ($-\Delta G^\circ = 1.43 \pm 0.08 \text{ kcal mol}^{-1}$ <1986JA2000>). The same interactions with the thiophosphoryl sulfur (which is much larger and of lower electronegativity) were expected to be repulsive <1987TL573>; this effect is reflected in the lower $-\Delta G^\circ$ value of the $\text{P}(=\text{S})\text{X}_2$ groups and the remarkable participation of the equatorial conformer 81-eq in the conformational equilibrium.

The trimer 82 of dithioacetic acid has been observed in dilute CD_2Cl_2 solution. The conformation of this species, however, was not determined <1990JA4697>.



Scheme 10

The complete line shape analysis of the variable-temperature ^1H NMR spectra of the $\text{Cr}(\text{CO})_5[\text{W}(\text{CO})_5] \cdots 1,3,5\text{-trithiane}$ complexes provided precise energy barriers for the 1,3-intramolecular shift of the $\text{Cr}(\text{CO})_5$ and $\text{W}(\text{CO})_5$ moieties **83** (Scheme 11) <1983POL1117>. The corresponding 2,4,6-trimethyl-1,3,5-trithiane derivatives yielded the free energy of activation for the 1,3-shifts which proved to be largely dependent upon the skeletal flexibility of the 1,3,5-trithiane ligand. The kinetic parameters of the 1,3-shift in **83** are given in Table 7.



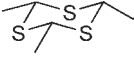
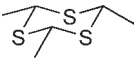
Scheme 11

Similarly, the dynamic behavior of the complex $[\text{Ir}_3\text{Rh}(\text{CO})_6]_2(\mu_2\text{-CO})_3(\mu_3\text{-}1,3,5\text{-trithiane})$ was studied by variable temperature ^1H and ^{13}C NMR spectroscopy and also by 2-D exchange spectroscopy (EXSY) NMR spectroscopy <1994HCA1869>. However, only the apical and basal carbonyl groups are involved in the intramolecular flexibility of the system and not the 1,3,5-trithiane moiety.

9.11.3.4.4 ESR studies

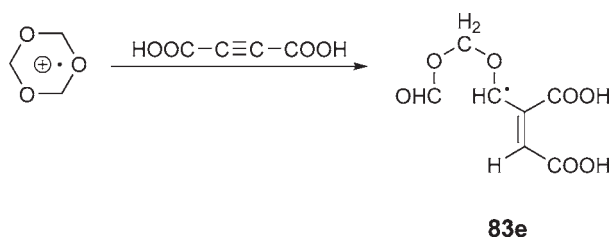
The ESR spectrum of the cation radical derived from 1,3,5-trioxane shows strong coupling to only two protons (160.2 G) and therefore this radical species could be assigned to a structure of C_s symmetry in which there is a planar $\text{C}-\text{O}-\text{CH}_2-\text{O}-\text{C}$ fragment with the remaining oxygen atom displaced from this plane by $0.48 \text{ \AA}$ <1983J(P2)1285>. The CH_2 group in the planar fragment carries high spin density (0.197) compared with only 0.029 and 0.018 for the two other methylenes. The results were supported by MNDO-UHF semi-empirical calculations of the ‘frozen’

Table 7 Kinetic parameters for the 1,3-shift of Cr(CO)₅ and W(CO)₅ moieties in the corresponding 1,3,5-trithiane complexes <1983POL1117>

Complex	E_a (kcal mol ⁻¹)	$\log_{10}A$	$\Delta H^\ddagger$ (kcal mol ⁻¹)	$\Delta S^\ddagger$ (cal K ⁻¹ mol ⁻¹)	$\Delta G^{\ddagger a}$ (kcal mol ⁻¹)
Cr(CO) ₅  83a	18.08 ± 0.65	14.53 ± 0.46	17.58 ± 0.65	6.25 ± 2.08	15.72 ± 0.08
W(CO) ₅  83b	17.47 ± 0.87	13.62 ± 0.63	16.88 ± 0.87	1.76 ± 2.89	16.35 ± 0.01
Cr(CO) ₅  83c	19.26 ± 0.22	13.63 ± 0.14	18.58 ± 0.22	1.60 ± 0.65	18.10 ± 0.03
W(CO) ₅  83d	19.43 ± 0.39	13.32 ± 0.24	18.73 ± 0.39	0.06 ± 1.10	18.71 ± 0.06

^aΔG[‡] calculated at 298.15 K.

geometry of the cation radical (UHF = unrestricted Hartree–Fock) <1984J(P2)511, 1998MI171>. The ESR spectrum of the cation radical of 1,3,5-trithiane was also recorded in freon matrix (CFCl₃ at 77 K) and proved to be almost identical <1988J(F1)4501> to the solution spectrum which shows coupling to two axial protons (0.042 G) but only negligible couplings to the remaining four ring protons (0.009 and 0.002 G) <1984J(P2)407>. Addition of the cation radical to butynedioic acid produced the ring-opened radical **83e** (Scheme 12) which was detected by ESR <1988J(P2)875>. The failure to trap radicals prior to ring opening was attributed to the fast rate of fragmentation – obviously due to the extra conjugation to both the oxygen and allyl moieties in **83e**.

**Scheme 12**

The ¹H chemical shift of H-2,4,6 was found to be an excellent indicator of the rate constant for H abstraction from 2,4,6-trimethyl-1,3,5-trioxane by cumylperoxy radicals <1987DOK413> and the decay kinetics ($k = 3.3 \pm 1 \times 10^3 \text{ s}^{-1}$) of the trioxanyl radicals after pulsed irradiation in aqueous solution have been studied by ESR spectroscopy <1984ZOR2628, 1989MI16>.

9.11.4 Thermodynamic Aspects

Ideal gas thermodynamic properties (ΔH_f° , S° , and $C_p(T)$, $300 \leq T$ (K) ≤ 1500) of 34 cyclic oxygenated hydrocarbons (including 1,2,3-, 1,2,4-, and 1,3,5-trioxane, and 1,2,3- and 1,2,4-trioxene) have been calculated using the PM3 method <1997PCA2471>. Particular correlations of theoretical versus experimental properties were obtained and

employed to estimate values for unknown compounds. In Table 8, these relevant values are given. The standard deviations of PM3-determined ΔH_f° and S° are evaluated as $2.89 \text{ kcal mol}^{-1}$ and $1.15 \text{ cal mol}^{-1} \text{ K}^{-1}$, respectively, and for heat capacities $C_p(T)$ to be less than $0.92 \text{ cal mol}^{-1} \text{ K}^{-1}$. This semi-empirical method is recommended as a convenient and economic alternative to determine ideal gas thermodynamic properties for oxygen heterocycles.

Table 8 Thermodynamic properties of various trioxanes

Compound	ΔH_f° (kcal mol ⁻¹)	S° (cal mol ⁻¹ K ⁻¹)	$C_{p, 300}$ (cal mol ⁻¹ K ⁻¹)
	9.14	73.60	21.90
	-13.05	74.80	23.40
	-38.08	74.68	20.80
	-59.82	74.68	22.00
	-109.62 (-111.35) ^a	70.89 (68.95) ^a	21.71 (19.69) ^a

^aExperimental value.

Using the rigid-rotor harmonic-oscillator approximation on the basis of molecular constants and the enthalpies of formation, the thermodynamic functions C_p° , S° , $-(G^\circ - H^\circ_0)/T$, $H^\circ - H^\circ_0$, and the properties of formation $\Delta_f H^\circ$, $\Delta_f G^\circ$, and $\log K^\circ_f$ to 1500 K in the ideal gas state at a pressure of 1 bar, were calculated at 298.15 K and are given in Table 9 <1992MI121, 1995MI1351>. Unfortunately, no experimental or theoretical data are available for comparison. From the equation $\log k = 30.25 - 3.38 \times I_{\text{pot}}$, derived from known reactivities ($\log k$) and ionization potential (I_{pot}) of cyclohexane, cyclohexanone, 1,4-cyclohexadiene, cyclohexene, 1,4-dioxane, and piperidine, the ionization potential of 2,4,6-trimethyl-1,3,5-trioxane was calculated to be 8.95 eV <1987DOK1411>.

Table 9 Ideal gas thermodynamic properties for 1,3,5-trioxane and 1,3,5-trithiane at 1 bar and 298.15 K <1992MI121, 1995MI1351>

Compound	C_p° (cal K ⁻¹ mol ⁻¹)	S° (cal K ⁻¹ mol ⁻¹)	$-(G^\circ - H^\circ_0)/T$ (cal K ⁻¹ mol ⁻¹)	$H^\circ - H^\circ_0$ (kcal mol ⁻¹)	$\Delta_f H^\circ$ (kcal mol ⁻¹)	$\Delta_f G^\circ$ (kcal mol ⁻¹)	$\log K^\circ_f$
1,3,5-Trioxane	19.557	68.902	56.871	3.587	-111.278	-80.764	14.149
1,3,5-Trithiane	26.581	80.356	64.213	4.813	19.108	31.144	-5.456

Gibbs free energies for the interactions of the ether group in 1,3,5-trioxane (and additionally in 1,4-dioxane) with hydroxyl groups and amide groups have been determined measuring the freezing point temperatures of appropriate ether...carbohydrate/amide mixtures. In simple cases, these group interaction parameters can be employed to predict both the sign and the magnitude of many nonbonded interactions, which are of biological interest <1985MI781>.

A number of solubility studies of 1,3,5-trioxane in various solvents have been published. The best solvent was found to be dichloromethane and deviations from ideal solvation curves were discussed in terms of solute–solvent interactions; the heats of solution are given in [Table 10](#) [<1983CED81>](#). The solubility of 1,3,5-trioxane in water (over the range 20–55 °C) [<1994CED201>](#) and methanol (over the range 65–95 °C) [<1994CED203>](#) was studied and found to exhibit strong deviation from ideal behavior. Quantitative solvation parameters of 1,3,5-trioxane were determined from empirical general solvation equations derived from gas–liquid chromatographic data [<1991JCH\(587\)213, 1993JCH\(644\)95>](#). The solvation of the proton-transfer complex 2,4-dinitrophenol/diethylamine by 1,3,5-trioxane was investigated [<1994JST\(322\)321>](#); extremely strong solvation was construed by a ‘trifurcated’ hydrogen bond of all three ring oxygen atoms with the ammonium ion or phenol proton.

Table 10 Heats of solution of 1,3,5-trioxane in different solvents

<i>Solvent</i>	ΔH_{sol} (<i>kcal mol</i> ^{−1})
Dichloromethane	3.34
Chloroform	3.25
Acetone	3.53
Benzene	5.42
Toluene	6.16
CCl ₄	11.01
Methanol	11.01

The helium I photoelectron spectra of 1,3,5-trioxane in the gas phase (I_p = 10.90, 11.40, 12.47, 12.88, 15.24, and 16.04 eV) have been reinvestigated carefully [<1992MI467>](#). HAM/3 MO calculations were performed to assign the ionization potentials and to identify both the induced effects and through-space/through-bond interactions of the oxygen atoms with the six-membered ring skeleton.

The enthalpy of sublimation of 1,3,5-trithiane was derived from the dependence of vapor pressure on temperature ($\Delta^{\text{g}}_s H^\circ_{\text{m},298}$ = 22.43 kcal mol^{−1}) [<1983MI651>](#). Furthermore, the enthalpies of formation of 1,3,5-trithiane in the solid state (-2.05 ± 0.6 kcal mol^{−1}) and in the gaseous state (20.21 ± 0.6 kcal mol^{−1}) were measured [<2001JOC5343>](#); a theoretical value of the enthalpy of formation was *ab initio* MO calculated as 19.2 kcal mol^{−1}, a value in excellent agreement with experiment. The theoretical study reveals the relevance of through-space lone pair–lone pair electronic repulsion in this sulfur heterocycle [<2001JOC5343>](#) (*vide supra*). The thermal properties of 1,3,5-trithiane between 15 K and the melting point have been determined [<2002MI11>](#), and through this range the solid displays two to three polymorphic forms. The $\text{p}K_{\text{a}}$ value of 2-oximino-1,3,5-trithiane has been estimated from proton chemical shifts in DMSO solution to be 9.98. Finally, the development of polyvinyl chloride (PVC)-based 1,3,5-trithiane sensors for cerium(III) [<2000ANC2391, 2002ANC5538, 2002MI3525>](#) has been published and 1,3,5-trithiane itself has been identified as an environmental organic pollutant in sediment of the eastern Gulf of Finland [<2004MI737>](#).

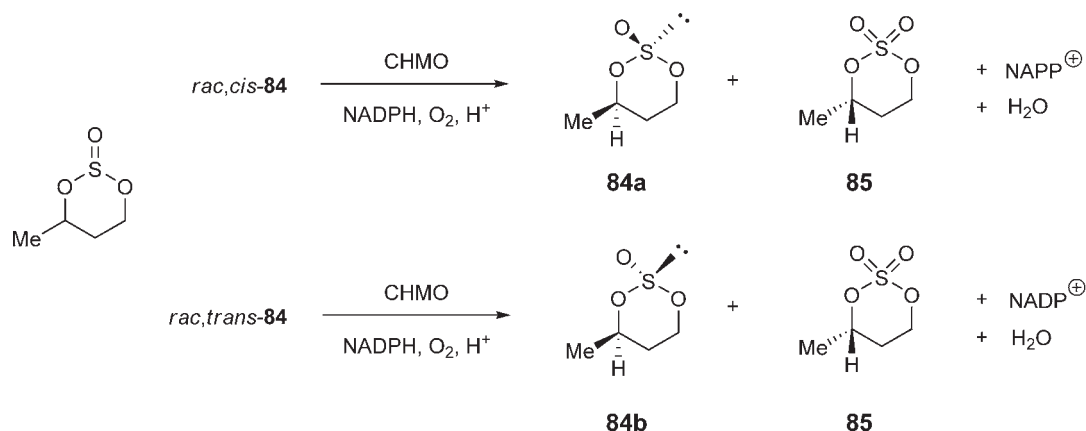
9.11.5 Reactivity of Fully Conjugated Rings

The syntheses and reactivities of fully conjugated rings for these kinds of compounds have not been reported, nor have computations appeared in the available literature.

9.11.6 Reactivity of Nonconjugated Rings

9.11.6.1 1,3,2-Dioxathianes

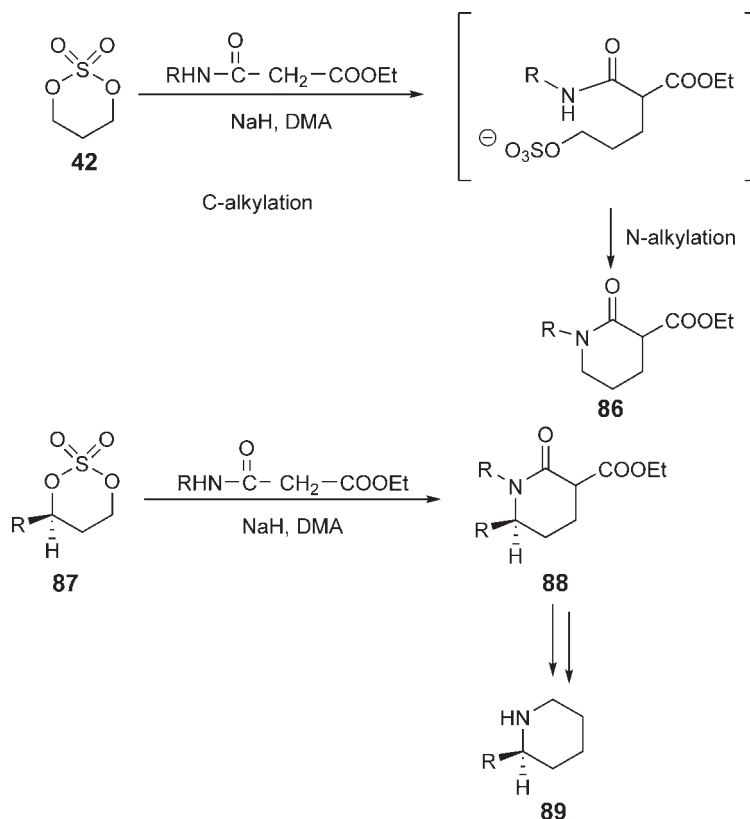
The enzymatic oxidation by cyclohexanone monooxygenase (CHMO) from *Acinetobacter* of 1,3,2-dioxathiane 2-one derivatives **84** to the corresponding 2,2-dioxides **85**, which could serve as an alternative path to other sulfates of special interest, has been published [<1998CC415>](#) ([Scheme 13](#)). The oxygen transfer at sulfur is enantioselective, and, moreover, the diastereomeric 2-oxides **84a** and **84b** can be separated easily by flash chromatography. The resulting 2,2-dioxides **85** are obtainable in satisfactory chemical yield.



Scheme 13

Alternatively, the sulfites can be oxidized to the sulfates **85** in 45 min at 0°C by employing a 350 ppm RuO₄ solution in water, but in only 30% yield <1992NJC107>. Diastereotopically labeled ¹⁷O-sulfates **84** and **85**, obtained by oxidation of diastereoisomeric cyclic sulfites with Ru¹⁷O₄, were shown by application of lanthanide-induced shift reagents on the ¹⁷O NMR signals to be formed with retention of configuration at sulfur <1983CC1392>.

The cyclic sulfites or sulfates thus obtained can be employed as synthetic equivalents of epoxides, which can react with a number of nucleophiles; often, they are more reactive than the oxirane analogs and thus can lead to disubstitution products <1997AHC89, 1994CRV2483>. The cyclic sulfate **42**, for example, has been used as a double electrophile in a [3+3] annulation procedure, which combines C–C–C and N–C–C moieties (Scheme 14)

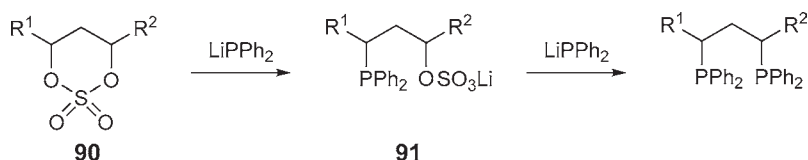


Scheme 14

<2000SL1360>. This reaction involves sequential C- then N-alkylation of the 1,3,2-dioxathiane 2,2-dioxide. C-Alkylation proceeds rapidly at room temperature but the N-alkylation step requires heating to close the ring. By this procedure, chiral nonracemic cyclic sulfates, for example **87** (Scheme 14), were converted into the enantiomerically enriched piperidines **89** with only minimal loss of enantiomeric integrity during the rather complex chemical procedure <2000SL1360>.

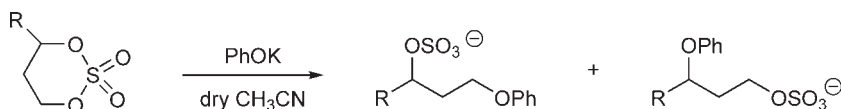
The cyclic sulfates **85** can be reduced easily electrochemically under one-electron transfer conditions to yield a complex product mixture of cyclic ethers, acyclic alkanes, and unsaturated alcohols <1984BCJ3160>. Their alkaline hydrolysis has been studied carefully by *ab initio* MO calculations <1996J(P2)767> and it was found, in comparison with other cyclic sulfates, to be strongly dependent on the ring size <1997J(P1)3173>.

Cyclic sulfates **90** react with LiPPh_2 to form a variety of amphiphilic or water-soluble phosphine derivatives **91** at low temperature <1997CC2385> (Scheme 15). The nucleophilic attack occurs with complete inversion at the stereogenic center of the electrophilic cyclic sulfate **90**. After warming to room temperature and recooling to -70°C , a second LiPPh_2 nucleophile can be added, which exchanges the sulfate group for the second PPh_2 unit <2000AGE575>.



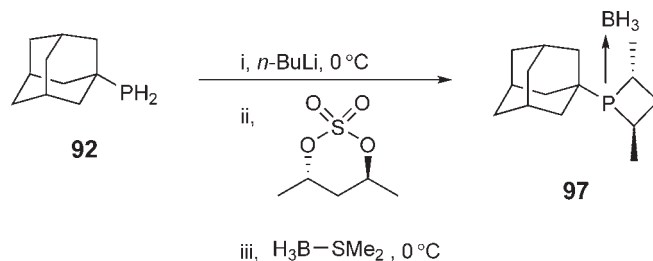
Scheme 15

The six-membered ring of **90** can be opened by nucleophilic attack of PhONa in ethanol <2000RCB1753> or $\text{KS}_2\text{P}(n\text{-Alk})_2$ in methanol/acetonitrile <1998PS137>. Actually, the phenyl sulfate, the expected product of phenoxy attack, was not observed but the phenoxyalkyl sulfate yield was quantitative (Scheme 16) <1990JOC1211>. The regioselectivity of the nucleophilic ring cleavage of **90** and the kinetics of this reaction have been studied theoretically <1983MI361>. Finally, the attack of NaCN at **90** in the presence of a catalyst and in various solvents was studied in detail utilizing an automated laboratory reaction calorimeter <1994IEC814>.



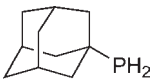
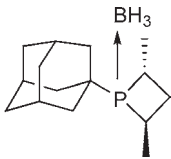
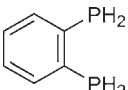
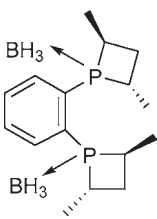
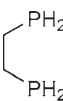
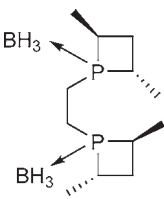
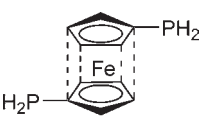
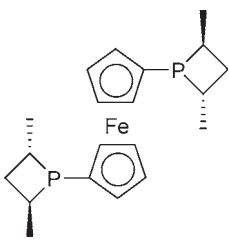
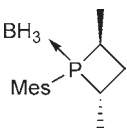
Scheme 16

The preparation of optically active cyclic phosphines was examined starting from optically pure 1,3,2-dioxathiane 2,2-dioxides; 1-adamantylphosphine **92** <2000H(52)905>, 1,2-diphosphinobenzene **93** <1999CEJ1160>, 1,4-diphosphinoethane **94** <2001JOM(624)162>, 1,1'-bis(ferrocenyl)bispophosphinite **95** <1999SL1975>, and mesitylphosphite **96** <1997TL2947> were deprotonated using *n*-BuLi and the resultant dianions treated with an optically pure cyclic sulfate to afford readily the corresponding phosphetanes (cf. Scheme 17 and Table 11), for example, **97** from **92**. Yields were good to excellent and the optically active phosphines were characterized by IR, NMR, high-resolution mass spectrometry (HRMS), and X-ray crystallography.

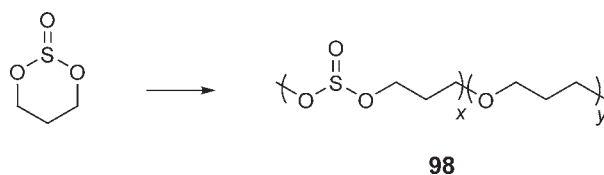


Scheme 17

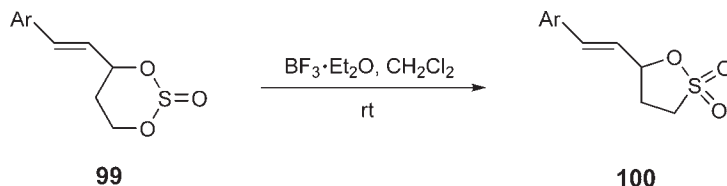
Table 11 Synthesis of optically active cyclic phosphines from optically pure 1,3,2-dioxathiane 2,2-dioxides

Starting material	Reaction product	Reaction conditions	Reference
 92		<i>n</i> -BuLi, 1.1 equiv, 0 °C, 63%	2000H(52)905
 93		<i>n</i> -BuLi, -78 °C, BH ₃ -SMe ₃ , 0 °C, 58%	
 94		<i>n</i> -BuLi, 2 equiv, THF, 25 °C, 1.5 h, BH ₃ -SMe ₂	2001JOM(624)162
 95		<i>n</i> -BuLi, 2.2 equiv, THF, -78 °C/25 °C	1999SL1975
 96		<i>n</i> -BuLi, -78 °C/25 °C, 65%	1997TL2947

The ring-opening, polymerization behavior of 1,3,2-dioxathiane 2-oxide was examined in the presence of cationic inhibitors (e.g., benzyl bromide, BF₃·OEt₂, trifluoromethanesulfonic acid and the corresponding sulfonate) <1995MM7331>, resulting in polymers consisting of sulfite and ether moieties (Scheme 18). The content of the poly(ether) unit varied over the range 30–90% as estimated by ¹H and ¹³C NMR spectroscopy and the corresponding influence of the applied inhibitor on both the chain length and the structure of the polymer was critically examined.

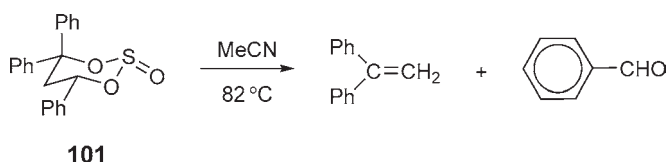
**Scheme 18**

Allylic cyclic sulfites **99** readily undergo rearrangement into the corresponding sultones **100** in the presence of catalytic amounts of boron trifluoride etherate in methylene chloride at room temperature (Scheme 19) <1993TL3367>; yields are better than 50% and the structure of the sultones was proven by ^1H NMR spectroscopy and, in one case ($\text{Ar} = \text{Ph}$), by X-ray crystallographic analysis. The rearrangement of the cyclic allylic sulfites **99** to sultones **100** is accompanied by stereochemical isomerization of the substituents on the carbon skeleton and shows the strong tendency to furnish selectively the thermodynamically more stable *trans*-isomers <1990JOC1823>.



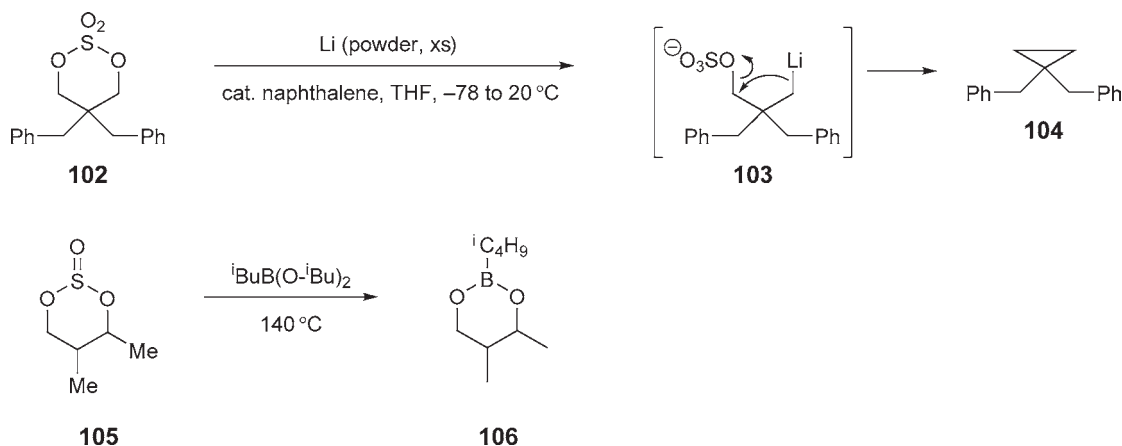
Scheme 19

The decomposition reaction of several phenyl-substituted 1,3,2-dioxathiane 2-oxides, for example **101**, to produce alkenes and carbonyl compounds has been investigated <1986JHC1099>. The reaction occurs readily in polar solvents (reactivity order: methanol > acetonitrile > tetrahydrofuran (THF) > cyclohexane) to produce the corresponding 1,1-diphenylethylenes and benzaldehyde; no styrene could be detected in the ^1H NMR spectrum, indicating that the reaction is highly regioselective (Scheme 20). The decomposition was found to follow first-order kinetics ($E_a = 21.1 \text{ kcal mol}^{-1}$, $\Delta H^\ddagger = 20.4 \text{ kcal mol}^{-1}$, and $\Delta S^\ddagger = -14.0 \text{ eu}$).



Scheme 20

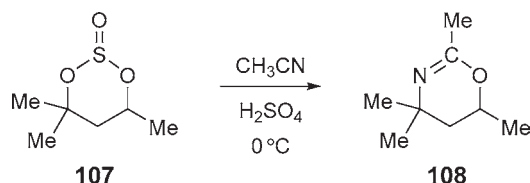
Using the general synthesis of alkyl lithium reagents from dialkyl sulfates, the lithiation of the six-membered sulfate derivative **102** was also attempted (Scheme 21) <1994T3427>. The main process is the γ -elimination of the sulfate from the first-formed γ -functionalized organolithium intermediate **103**. The expected 1,1-dibenzylcyclopropane **104** was isolated in 75% yield.



Scheme 21

Finally, the interconversion of 4,5-dimethyl-1,3,2-dioxathiane 2-oxide **105** into 2-*iso*-butyl-4,5-dimethyl-1,3,2-dioxaborinane **106** has been reported <2000RJO292> (Scheme 21); the reaction is completely stereospecific and demonstrates the higher thermodynamic stability of 1,3,2-dioxaborinanes in comparison to the corresponding 1,3,2-dioxathiane 2-oxides. Employing the same protocol, 2-ethyl(*isobutyl*)-4,5-dimethyl-1,3,2-dioxaborinane was also obtained <1995ZOR146>.

The reaction of sulfite **107** with acetonitrile in the presence of sulfuric acid at 0 °C provided the dihydrooxazine derivative **108** in 80% yield (Scheme 22) <1995KGS275>. The mechanism of this reaction is still unclear because the 4-methyl derivative of **107** also gave the corresponding derivative of **108** as well; however, the yield was only 3%.



Scheme 22

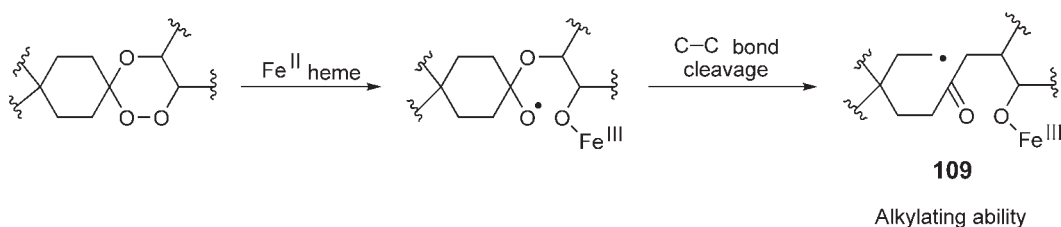
9.11.6.2 1,2,4-Trioxanes

The thermal decomposition reaction of 1,2,4-trioxane, along with others, was studied in toluene solution over a wide temperature range <2000MOL360>. The reaction follows a first-order kinetic law up to ca. 50% peroxide conversion. Only the linear dependence of activation enthalpies and entropies of this unimolecular reaction is reported with a slope of 130.4 °C as the 'isokinetic temperature'.

The copolymerization of 1,2,4-trioxane with the diglycidyl ether of 1,4-dihydroxy diphenyldimethylmethane (catalyzed by BF₃OEt₂ in nitrobenzene) was studied and found to proceed via the tertiary oxonium mechanism <1996MI23>. In the range 30–60 °C, a linear copolymer with high alkali and thermal stability could be obtained <1996JAP2151>. Non-cross-linked condensed polynuclear aromatic resins were prepared using 1,2,4-trioxane and a number of aromatic compounds as monomers at 80–100 °C under acidic catalysis. A mechanism for the polymerization reaction was proposed and the resins obtained were found to be stable up to 400 °C.

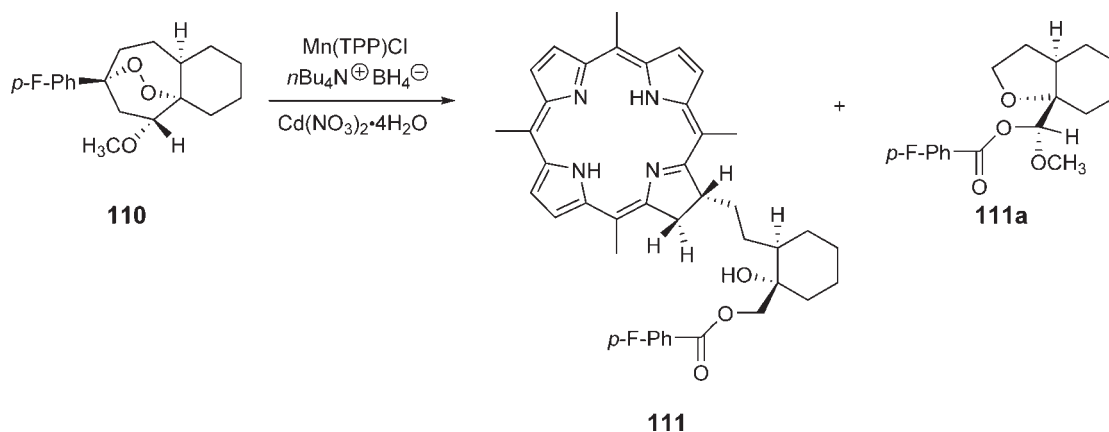
Otherwise, interest continues in the artemisinins: the degradation of artemisinin **17** itself, and of a number of analogs and their reaction with various reagents, has been studied carefully. In order to find potential antimalarial drugs (artemisinin **17** itself is limited by its low solubility and poor oral bioavailability), some interesting reactions have been reported and characteristic examples are now presented.

1,2,4-Trioxane derivatives possessing high antimalarial activity are expected to have alkylating properties after activation of the peroxy bond by iron(II) heme, as established for artemisinin **17** <1997JA5968, 2001AGE1954, 2002CC414, 2002ACR167> and other related 1,2,4-trioxanes <2002JOC609, 1976SCI673>. By reductive activation with Fe(II) heme, studied by FTIR spectroscopy <2001JME3150>, the alkoxy radical is generated which, by subsequent homolysis of one adjacent C–C bond, readily rearranges to the sterically unhindered C-centered radical **109** which effects the alkylation of heme and thereby is responsible for the antimalarial activity attributed to this class of compounds <2003CR153> (cf. Scheme 23). However, it is not yet entirely clear how the free radicals cause the death of the parasite <1998JBC16192, 2001MI122> despite the degradation of artemisinin **17** (induced by cysteine–iron chelates) having been studied in detail <2001HCA928>. The alkylation of heme, studied by the model



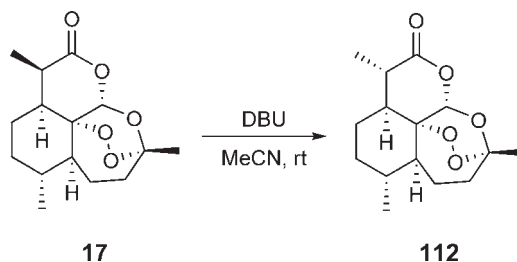
Scheme 23

compound Mn(II) tetraphenylporphyrin (TPP), generated *in situ* from Mn(III) (TPP)Cl and borohydride, was proven by isolation of the covalent adduct **111** between the drug and the macrocycle and a noncoupled drug-derived product **111a** (cf. Scheme 24; **111a** was fully characterized by MS and NMR analysis, **111** only after dehydrogenation of the dihydropyrrole ring) <2002JOC609>. Conversely, pharmacologically inactive analogs of **110** did not react with the heme model. The same result was obtained when studying other polycyclic 1,2,4-trioxane derivatives <2003OBC2859>.



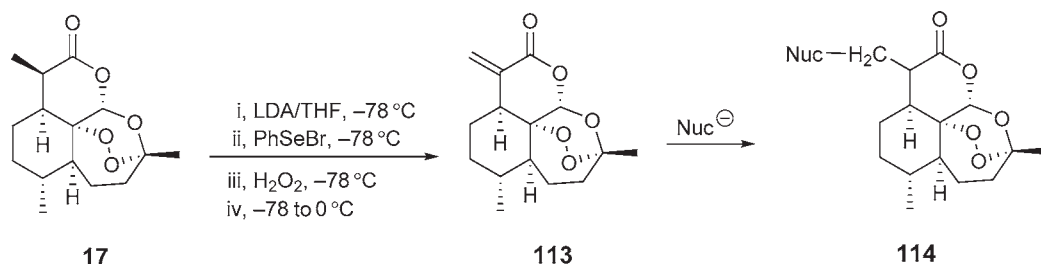
Scheme 24

Epiartemisinin **112** was prepared by epimerization of artemisinin **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature; after 24 h, a 31% yield of **112** had been obtained with the remaining material being unreacted artemisinin **17** (Scheme 25) <2000HCA1239>. Because of the sevenfold lower antimalarial activity of epiartemisinin **112**, it was argued that the α -disposed methyl group hinders complexation of **112** with heme and thereby the formation of the potent radical, the ultimately lethal agent.



Scheme 25

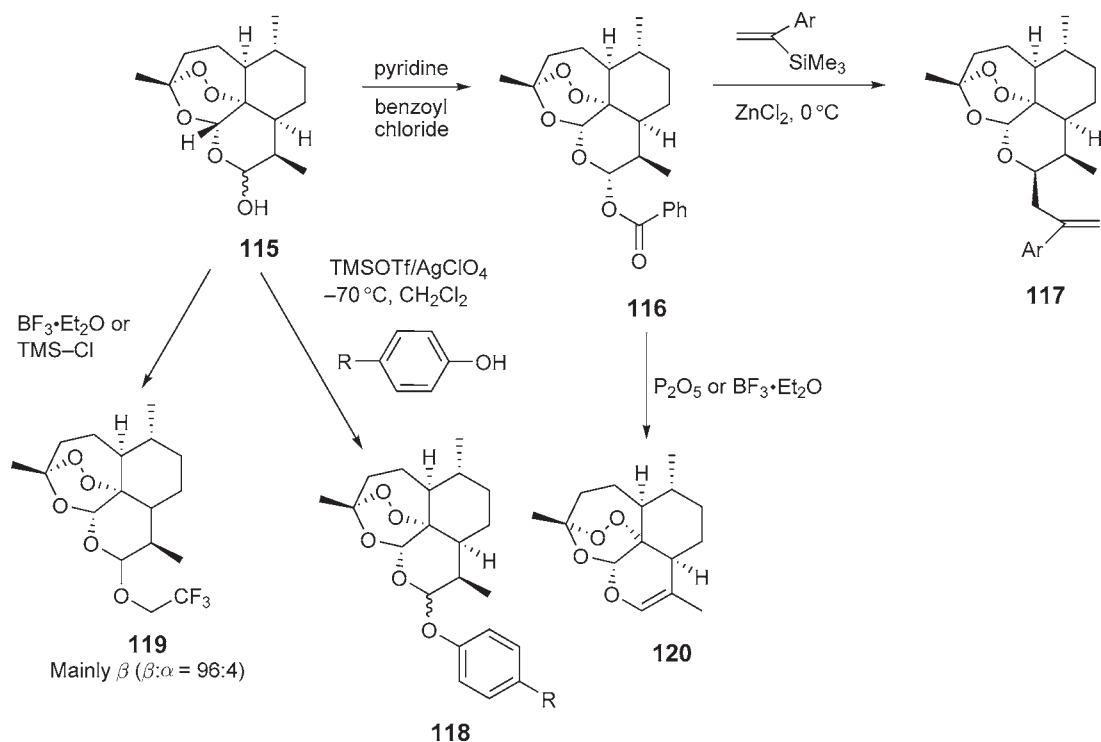
Next, structural modification at C-16, the lactone methyl carbon atom, was studied. First artemisitene **113**, the oxidized form of artemisinin **17**, was synthesized in 73% purified yield by treatment of **17** with lithium diisopropylamide (LDA) in THF at -78°C followed by sequential additions of phenylselenenyl bromide and 30% aqueous hydrogen peroxide solution and finally by raising the temperature to 0°C (Scheme 26) <1997JME633>. Artemisitene **113** reacts readily with nucleophiles to give the corresponding Michael adducts **114** (Nuc = $-\text{CH}_2\text{SPh}$, $-\text{CH}(\text{CN})\text{ferrocenyl}$, $-\text{CH}_2-\text{CO}-\text{ferrocenyl}$, $-\text{N-imidazolyl}$ <1997JME633>, $-\text{CH}_2\text{N}(1,2,4\text{-triazolyl})$, $-\text{CH}_2\text{N}(1,2,3\text{-benzotriazolyl})$, and $-\text{CH}_2\text{N}(\text{benzimidazolyl})$ <2001TL2843>). When organolithium reagents were employed as nucleophiles, pure C-16 derivatives **114** of artemisinin were obtained (Nuc = $-\text{CH}(\text{SC}(=\text{S})-\text{NEt}_2)_2$, $-\text{CH}_2-\text{COPh}$, $-\text{C}(\text{CH}_3)_2\text{COOMe}$ <2001JME4688>); in the case of lithium dithiolates ($\text{LiS}(\text{CH}_2)_n\text{SLi}$), dimeric artemisinin analogs with a linker $-\text{S}(\text{CH}_2)_n\text{S}-$ of various length and flexibility resulted <2001JME4688>. Grignard reagents employed under the same reaction conditions as alternatives to Michael donors yielded only mixtures of products, though with **114** remaining as the main product <2001JME4688>.



Scheme 26

The acidic degradation of artemisitene to the natural product 6,7-dehydroartemisinic acid has also been reported <2001J(P1)2421>.

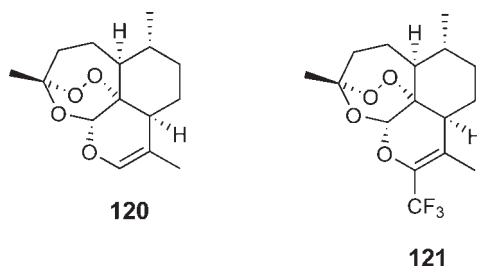
Structural modification at C-10, the lactone carbonyl carbon, was the subject of a number of studies concomitant with the aim of finding drugs of higher antimalarial activity. First, dihydroartemisinin **115**, produced by borohydride-mediated reduction <1989JME1249> of artemisinin **17**, can be treated with benzoyl chloride in pyridine to yield the benzoate **116** in high yield <2001J(P1)2682>. The latter compound reacts readily with a range of allylsilanes at 0 °C in the presence of zinc chloride to form the C-10 deoxycarba analogs **117** of dihydroartemisinin; the configuration at C-10 proved to be β (Scheme 27) <2001J(P1)2682, 2003EJO2098>. The use of TMS-OTf/AgClO₄ as catalyst promotes the efficient C-10 phenoxylation of **115** in good yields and excellent stereoselectivity (TMS = trimethylsilyl; Scheme 27) <1999TL9129, 2001JME58>; the α : β ratio at C-10 ranges from 1:4 to 1:8, respectively, depending on the substituent on the phenoxy moiety of **118**. The stereochemistry of the conversion of dihydroartemisinin **115** into esters and ethers was investigated in detail <2002EJO113, 2003EJO2098>. If the hydroxy group in **115** acts as the nucleophile, α -esters were obtained; when it is activated for displacement, β -esters were the reaction products. The preferred formation of the β -epimer by Lewis acid-catalyzed ether formation could be anticipated on the basis of the anomeric effect <2002EJO113>.



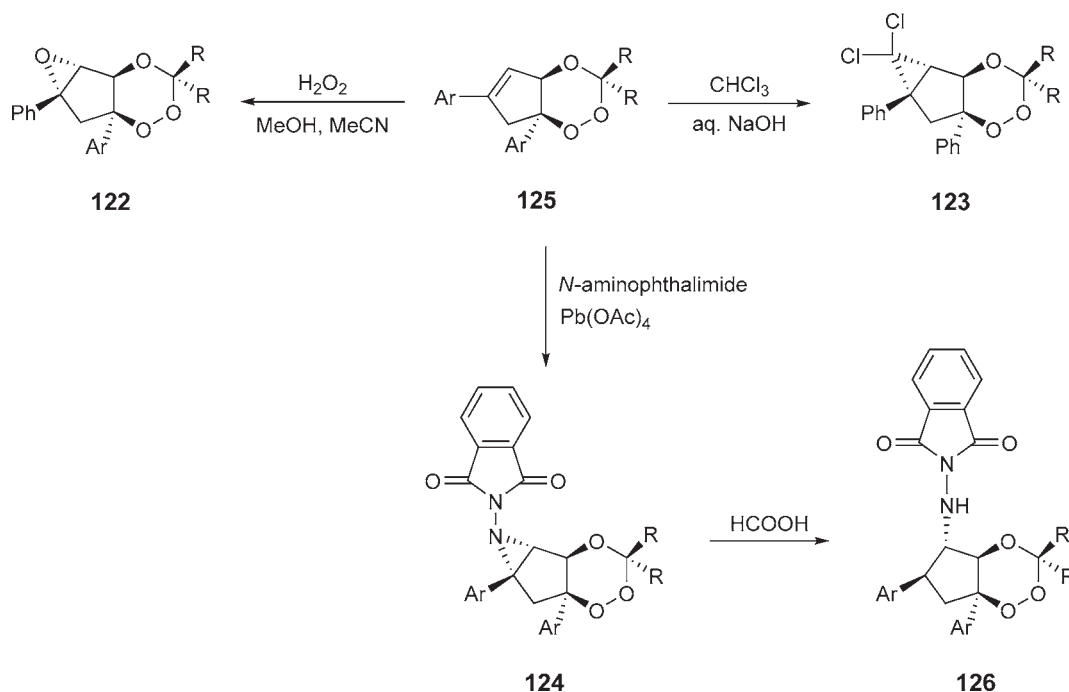
Scheme 27

The corresponding fluoroalkyl ethers **119** (cf. **Scheme 27**) have been prepared by the reaction of fluoroalkyl alcohols with dihydroartemisinin **115** using various methods (with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or TMSCl as catalysts) in moderate to good yields <1998JME4101>.

The comparative reactivities of the glucal **120** (anhydrodihydroartemisinin) of **17**, which can be readily prepared from **116** by reaction with P_2O_5 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and of its trifluoromethyl analog **121**, prepared in high yield from artemisinin **17** with 2 equiv of $\text{TMS}-\text{CF}_3$ in the presence of $\text{TBAF} \cdot 3\text{H}_2\text{O}$ (0.1 equiv) at room temperature, were studied <2002JOC1253>. Both compounds were used to prepare novel lactone ring-contracted artemisinin derivatives with a trifluoromethyl ketone at C-9. These reactions allowed access to a new family of fluorinated artemisinin derivatives with rearranged skeletons <2001TL2125, 2001JOC7858, 2002JOC1253>.



In addition, epoxidation (to yield **122** by using 30% aqueous hydrogen peroxide in methanol/acetonitrile), cyclopropanation (to yield **123** by using chloroform/aqueous NaOH), and amination (to yield **126** via **124** by using *N*-aminophthalimide/lead tetraacetate and exposing **124** to formic acid) of another *cis*-fused bicyclo-1,2,4-trioxane derivative **125** occurs completely at the five-membered ring with *exo*-attack (**Scheme 28**) <1998H(49)375> and leaves the 1,2,4-trioxane moiety intact. The *exo*-configuration of the adducts follows from the almost zero value of the $^3J_{\text{H4a,H5}}$ coupling constants. However, epoxidation, cyclopropanation, and amination did not drastically raise the already high antimalarial activity of the parent compound **125**.



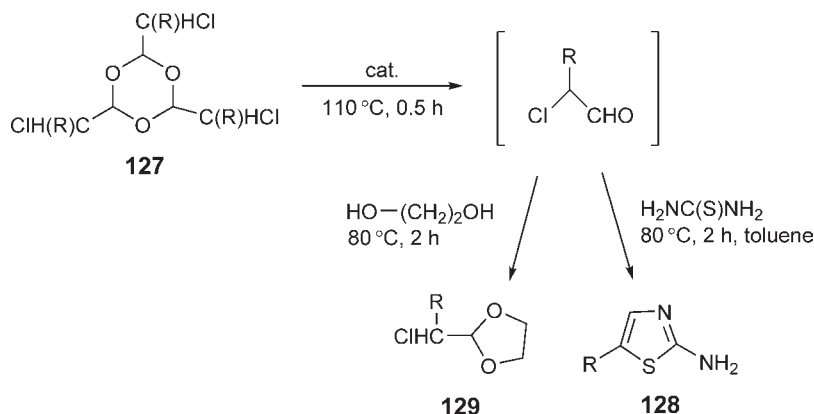
Scheme 28

9.11.6.3 1,3,5-Trioxanes

9.11.6.3.1 Decomposition and novel reactions

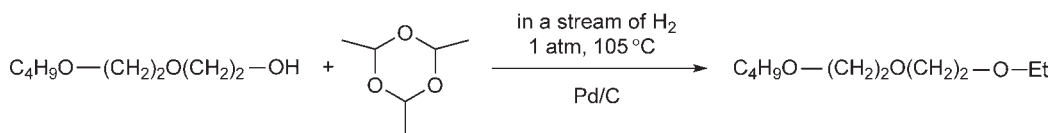
The unimolecular decomposition of 1,3,5-trioxane into formaldehyde has been studied experimentally in the temperature range of 700–800 K under atmospheric pressure <1992JPC295>; the rate constant measured in this temperature range is $k \text{ (s}^{-1}\text{)} = 10^{15.28 \pm 0.06} \exp(-47.5 \pm 2.4 \text{ kcal mol}^{-1} (RT)^{-1})$. The laser schlieren technique was employed to investigate the decomposition in this temperature range, providing formaldehyde to be the sole product <1990CPL(166)491>. A device which easily produces very pure formaldehyde by thermal decomposition of 1,3,5-trioxane (over a wide range of concentrations from sub-ppm to a few thousand ppm) in a stable flow rate has been fabricated <1990MI701>. Formaldehyde or other reactive aldehydes can be readily stabilized as their 1:1 coordination complexes with methylaluminium bis(2,6-diphenylphenoxide), confirmed by ^1H NMR spectroscopy <1990JA7422, 1993JA3943>. As complexes, they react with a number of alkenes to furnish ene-reaction products with excellent regio- and stereoselectivities. 1,3,5-Trioxane, as a replacement for paraformaldehyde, was successfully used for the practical synthesis of chloromethyl esters from the corresponding acid chlorides <2002TL6317>.

Thermal degradation of chloromethyl-1,3,5-trioxanes **127** (Scheme 29) in the presence of catalytic amounts of montmorillonite clay generated α -chloroaldehydes which could be treated *in situ* with thiourea to afford 2-aminothiazoles **128**, or with ethylene glycol to yield the corresponding 2-chloromethyl-1,3-dioxolanes **129** <1994CL2039>. The acidic sites in montmorillonite clays may act as acid catalysts, though the details of the mechanism were not provided.

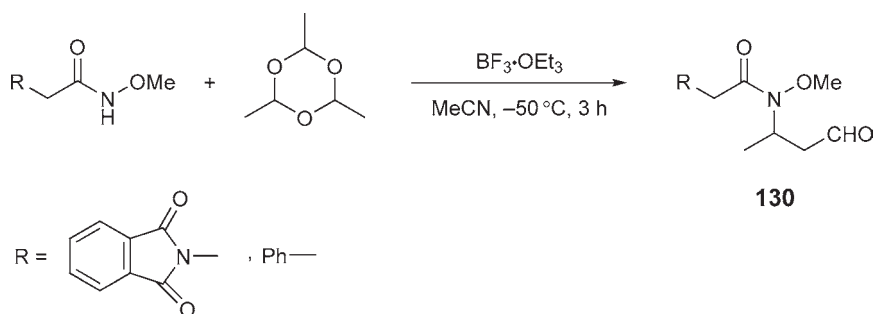


Scheme 29

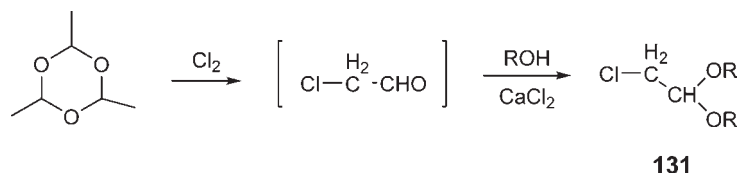
Similarly, 2,4,6-trimethyl-1,3,5-trioxane has been used as an *in situ* source of acetaldehyde for the synthesis of ethyl ethers from the corresponding alcohols (Scheme 30) <2000CL926, 2005BJC456>. The conversion of the alcohol is practically complete. During condensation reactions of amides with acetaldehyde, it was found in some instances that the use of 2,4,6-trimethyl-1,3,5-trioxane was preferable to acetaldehyde, in part because of the tendency of the latter to form aldol side products derived from self-condensation (Scheme 31) <2004TL9007>. The reaction readily proceeded further giving the β -(*N*-methoxy)amido aldehyde **130**. 2,4,6-Trimethyl-1,3,5-trioxane, paraformaldehyde, or acetaldehyde have been employed in the one-pot synthesis of chloroacetaldehyde dialkyl acetals (Scheme 32). The latter are versatile reagents for the synthesis of a range of compounds of biological significance <1991OPP764>. For example, the *in situ* acetalization to yield **131** with simple unbranched alcohols is practically quantitative.



Scheme 30

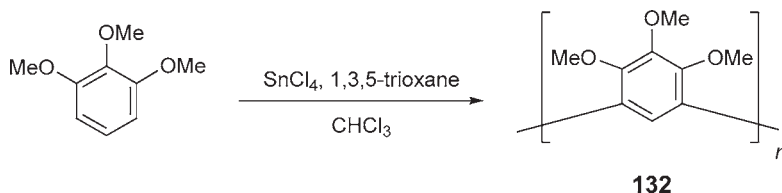


Scheme 31

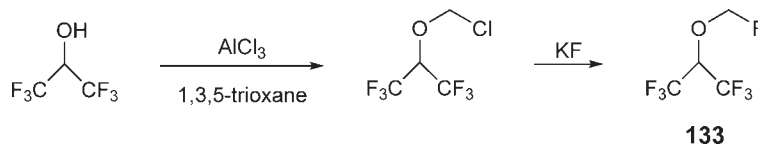


Scheme 32

1,3,5-Trioxane has also been used for the synthesis of methoxyresorc[4]arene compounds **132** (Scheme 33) <2002T2239> and for their monomethyl analogs <2002PSA1293>. The reaction, a template method, affords the calix[4]arene derivatives via the charge-transfer (CT) complex of 1,2,3-trimethoxybenzene and $SnCl_4$. Following synthesis, the complexing properties of the compounds were studied. 1,3,5-Trioxane has also been used as an *in situ* formaldehyde source for the chloromethylation of hexafluoro-2-propanol using $AlCl_3$ as the chlorination reagent (Scheme 34) <2000JFC(106)99>. In the subsequent reaction step, the chlorine is exchanged by fluorine to obtain the inhalation anesthetic sevoflurane **133** in 99.95% purity.



Scheme 33

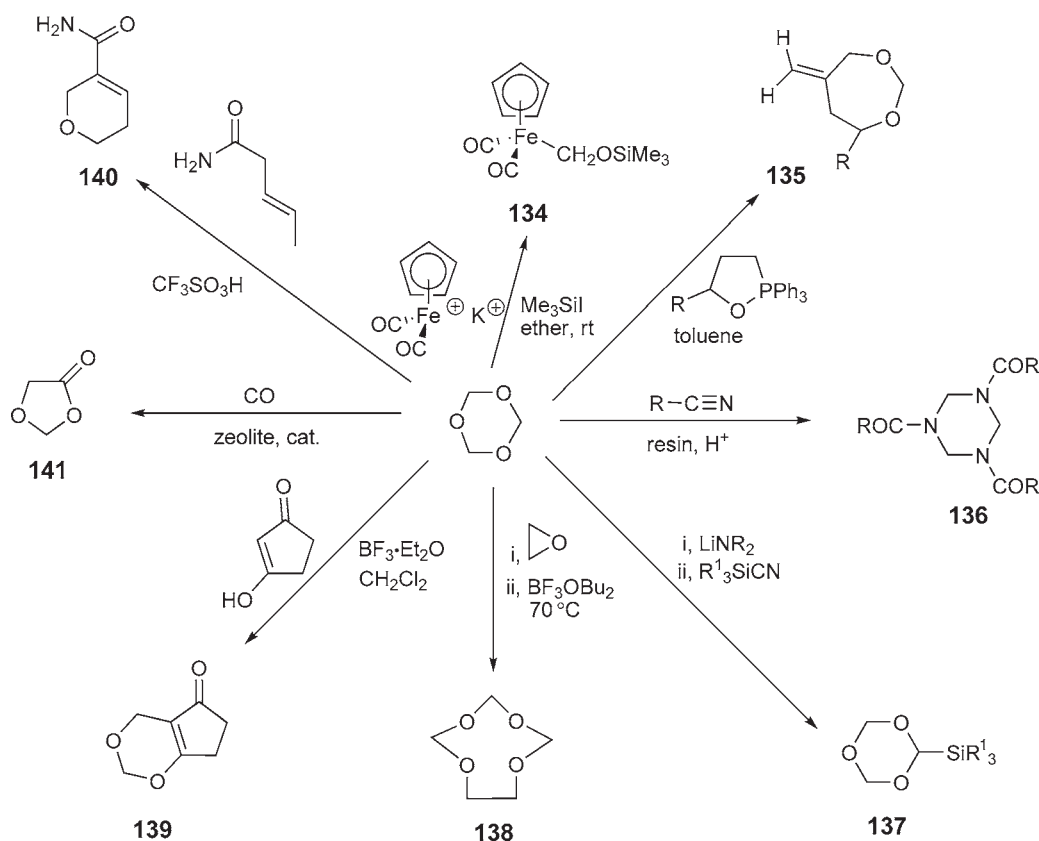


Scheme 34

2,4,6-Tri[2-(*p*-toluenesulfonyloxy)ethyl]-1,3,5-trioxane has been used as a supply of 3 equiv of *p*-toluenesulfonic acid, obtainable by acid-catalyzed decomposition <1998CL823>. The released sulfonic acid can be employed *in situ* as an acid amplifier to enhance the photosensitivity of a chemically amplified photoresistor.

Novel reactions directly between 1,3,5-trioxane and various reagents have been described and are collected in Scheme 35. A convenient *in situ* preparation of the α -siloxymethyl iron complex **134** proceeds via a very reactive

precursor $[\text{CH}_2(\text{I})-\text{OSiMe}_3]$ and has potential synthetic utility for cyclopropanation [<1996SC1371>](#). The reaction of oxaphosphoranes with 1,3,5-trioxane yielded novel seven-membered cyclic vinylidene acetals **135** in almost quantitative yield [<1993TL4233>](#). Representing a new type of synthesis, 1,3,5-triacylperhydro-1,3,5-triazines **136** can be obtained in high yield by the reaction of 1,3,5-trioxane with nitriles in solvents such as chlorobenzene using an ion-exchange resin as catalyst [<1986S643>](#). 1,3,5-Trioxane can be silylated by metalation–silylation reaction in THF with lithium amide and cyanotrimethylsilane; the yield of **137** ($\text{R}' = \text{Et}$) is 60% but methanolysis of 1,3,5-trioxane with $\text{CH}_3\text{OH}/\text{TMS}-\text{Cl}(\text{cat.})$ proceeds slowly with ring opening to $\text{MeO}_2\text{CH}-\text{SiEt}_3$ [<2000SC433>](#). From the reaction of 1,3,5-trioxane and ethylene oxide, novel cyclic formals such as **138** can be isolated and identified [<2001TL271>](#). In addition to **138**, which is not very stable and decomposes by successive elimination of formaldehyde, the corresponding 12- and 15-membered cyclic compounds were obtained as side-products [<1998MI407, 1998CC1809>](#). With 1,3-cyclopentaneone in CH_2Cl_2 in the presence of molecular sieves ($4\text{ \AA}$), 1,3,5-trioxane reacts to form substituted 1,3-dioxins **139** [<1998OS189>](#); with α -alkeneamides, in the presence of $\text{CF}_3\text{SO}_3\text{H}$, condensation is observed to afford the dihydropyran derivatives **140** [<1997TL9057>](#). Carbonylation has been carried out using zeolites and the product isolated was identified spectroscopically as 1,3-dioxolon-4-one **141** [<1997CC1827>](#).



Scheme 35

If a mixture of 2,4,6-tri(1-methylethyl)-1,3,5-trioxane, trimethylsilyl isothiocyanate, and SnCl_2 is stirred for 1.5 h at room temperature, 70% of the corresponding isothiocyanato substituted ether $\text{O}[\text{CH}(\text{CH}_3)\text{NCS}]_2$ is obtained. 2,4,6-Trimethyl-1,3,5-trioxane was converted also into bis(1-isothiocyanatoethyl) ether in similar yield. However, 1,3,5-trioxane was recovered quantitatively under the same reaction conditions [<1987BCJ2289>](#).

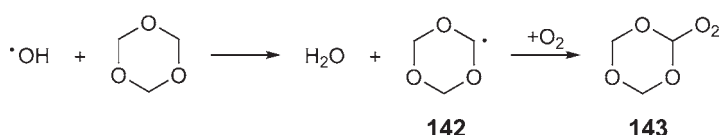
The absolute kinetics of the phenylchlorocarbene (PhCCl) C–H insertion reaction of 1,3,5-trioxane ($\text{R}-\text{H}$) yielding $\text{R}-\text{C}(\text{Ph})\text{HCl}$ has been studied and the rate constant determined ($k = 0.11 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ in benzene at 23°C) [<1998TL9381>](#). DFT calculations have yielded detailed stationary points for the C–H insertion transition states.

New 2-fluoroalkyl thiomethanols $F-(CH_2)_n-SCH_2OH$ can be obtained by reaction of 2-fluoroalkylthiols and 1,3,5-trioxane <1989BSF484>. The former are the starting material for the preparation of novel fluorinated surfactants.

1,3,5-Trioxane has been employed as the formaldehyde source for the synthesis of calixarene derivatives during the cyclization step <1991JOC5527, 2002T2239, 2002PSA1293>. Also, the Mannich reaction of dioxazasilacyclooctane with 1,3,5-trioxane as the formaldehyde source has been reported <1989ZOB483>.

9.11.6.3.2 Free radical reactions

The reaction kinetics for the reaction of hydroxyl radical with 1,3,5-trioxane has been studied using flash photolysis resonance fluorescence <1990JPC1881> and by applying a two-laser photolysis/LiF probe method <1986MI731>. At 296 ± 2 K, the rate constant was found to be $7.9 \pm 0.6 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1}$. The reaction produces an alkyl radical **142**, which, under atmospheric conditions, adds O_2 to form an alkylperoxy radical **143** (Scheme 36) <1998PCA4829>; the corresponding rate constants were also determined. The corresponding activities of $F\cdot$ and $Cl\cdot$ compared with $OH\cdot$ radicals in the same reaction were tested <1998PCA4829>. The rate of hydrogen atom abstraction from 1,3,5-trioxane was studied by generating the abstracting radical from $Br-CCl_3$ both photolytically or by thermal decomposition of 2,2'-azobisisobutyronitrile (AIBN) <1989JPO367> and comparing the results with similar cyclic ethers; both steric and stereoelectronic effects were identified as sources of appreciable influence on the reaction rate. Again the alkyl radical **142** is formed (Scheme 36).

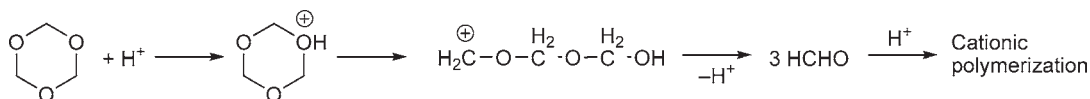


Scheme 36

Finally, the rate constant of the reaction between the cyano radical and 1,3,5-trioxane has been measured over the range of 297–600 K by laser photolysis/laser-induced fluorescence <1993MI1053> and found to ascribe to the formula $k = 1.39 \times 10^{-28} \times T^{4.26} e^{(1333/T)}$. The H-atom abstraction activity rates of $CN\cdot$ and $OH\cdot$ with 1,3,5-trioxane occur with the same mechanism and were correlated; a linear relationship was found with deviations occurring only for those reactions in which dipole–dipole attractive forces and tunneling play a major role.

9.11.6.3.3 Polymerization and copolymerization reactions

The six-membered ring of 1,3,5-trioxane readily opens during cationic polymerization, though the reaction is strongly inhibited in the presence of proton traps <1987MAR535>) (Scheme 37). The complete mechanism <1990MI701, 2001PP21>, the kinetics, and the initial process have been studied in detail <1999PSA4198, 1999PSA483> and reviewed <1989MI123>. The occurrence of hydride-transfer reactions during the cationic polymerization of 1,3,5-trioxane was demonstrated.



Scheme 37

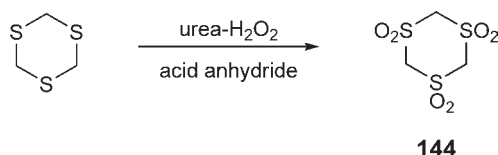
The cationic copolymerization reaction of 1,3,5-trioxane with ethylene oxide was also investigated in detail by employing the full arsenal of NMR spectroscopic methods <1992MI34, 1998MI167, 2000MI1069>. The structures of each of the species arising during the process were assigned precisely and the ^{13}C NMR chemical shifts discussed with respect to the electron density on the various carbon atoms as a parameter for reactivity estimations. With respect to the long-accepted mechanism (the initial formation of 1,3-dioxolane), it was proposed recently that 1,3,5,7-tetraoxacyclononane and 1,3,5,7,10-pentaoxacyclododecane are formed initially, followed by development of 1,3,5-trioxepane (from 1,3,5,7-tetraoxacyclononane), which then finally produces the 1,3-dioxolane <1995IEC2515>.

The copolymerization of 1,3,5-trioxane has been studied with maleic anhydride <1984MI2533>, pentaacetyl glucose <1984PSA3295, 1987PSA3423>, THF, styrene oxide <1987PSA3423>, 1,3-dioxolane <1987PSA3423, 1988PSA511>, and 5-ethyl-5-hydroxymethyl-1,3-dioxane <1990PP30>.

9.11.6.4 1,3,5-Trithianes

9.11.6.4.1 Oxidation of 1,3,5-trithiane and halogenation of derived sulfones

The selective, mild, and safe oxidation of all kinds of sulfides, including 1,3,5-trithiane, to their corresponding sulfones has been accomplished by using either the urea-H₂O₂/phthalic anhydride <1993JPR209> or the urea-H₂O₂/trifluoroacetic anhydride system <1999SC2235, 1999JPR184> (Scheme 38). The sulfones were obtained in nearly quantitative yield (e.g., in the case of 1,3,5-trithiane, **144** was obtained in 97% yield). If 40% peroxy acetic acid (and later, KMnO₄) is employed as the oxidation reagent, the yield decreases to 73% <1986CB3631>. Chlorination and bromination of **144** can also follow in excellent yield (Scheme 39). The exchange of chlorine for fluorine, however, was not successful but the corresponding five-membered ring derivative **146** was obtained in 62% yield. Similarly, the five-membered derivative **148** was synthesized from the bromination product **147**. In the presence of base (e.g., triethylamine), anions **149** and **150** were obtained and were identified unequivocally by X-ray crystallography <1986CB3631>.



Scheme 38

The preparation and characterization of the perfluorinated trisulfone has been achieved via static fluorination of the potassium salt of 1,3,5-trithiane <1994JFC(67)27>; some side products were also obtained and assigned by IR, NMR, and MS. The gas-phase structures of the perfluorinated trisulfones were studied by electron diffraction. Overall, a chair conformation and *C*₃ symmetry for the six-membered ring was found.

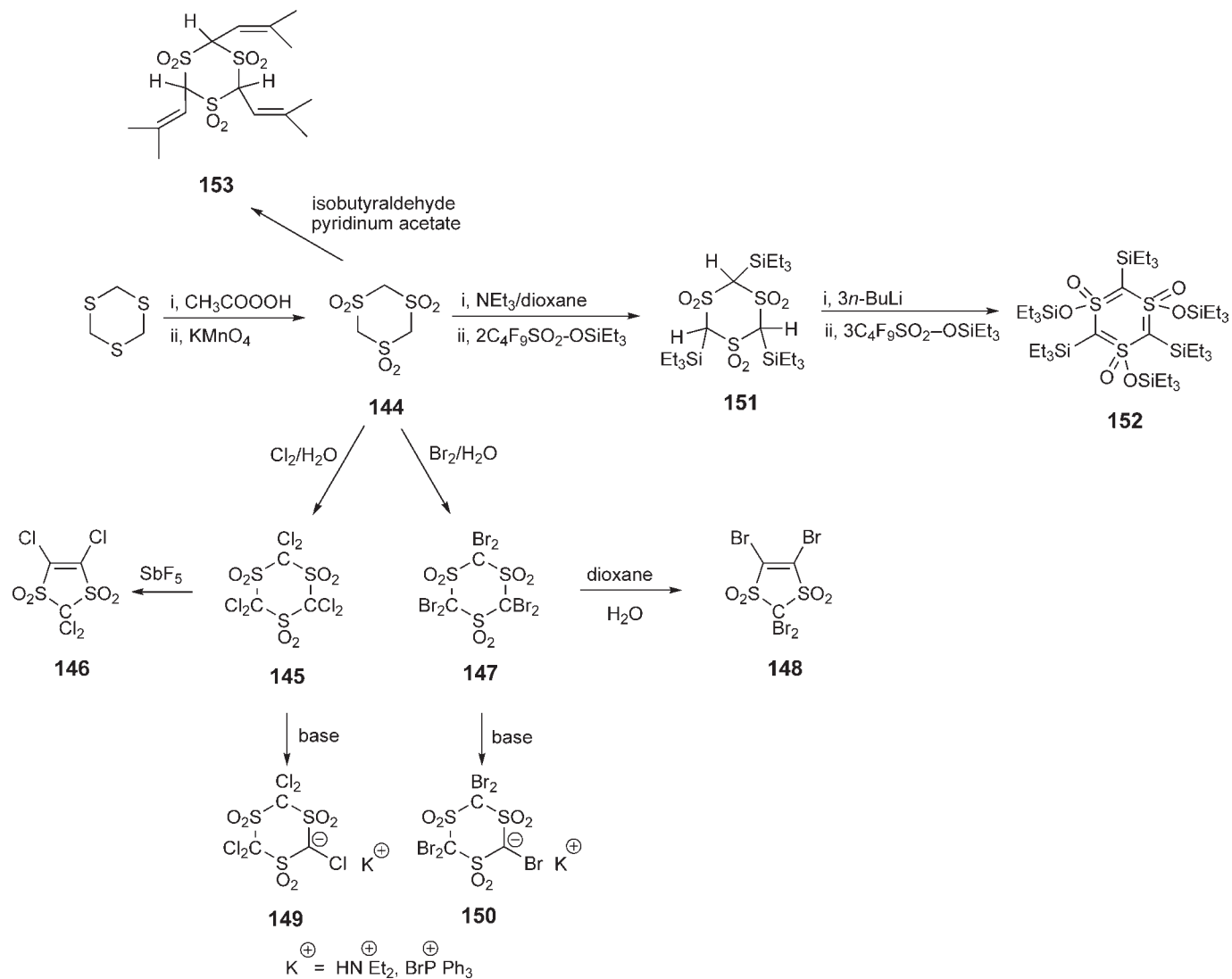
For the trisulfone **144**, the Me₃Si group could also be introduced <1996CB161>; for example, the structure of **151** has been characterized completely (Scheme 39). Metalation of **151** with *n*-butyllithium and subsequent reaction with C₄F₉-SO₂OSiEt₃ afforded a viscous oil, the spectra of which inferred the existence of **152**. Finally, reacting **144** with isobutyraldehyde in the presence of pyridinium acetate as catalyst in benzene with azeotropic removal of the water provided derivative **153** bearing unsaturated substituents (Scheme 39) <1996CB161>.

The hexaoxide **144** can also be synthesized by oxidation of 1,3,5-trithiane with H₂O₂ using ammonium molybdate as oxidation catalyst at room temperature <1993PSA1161>. It reacts further with formic aldehyde to form oligomeric products which are almost insoluble in organic solvents and the structure was, therefore, not further characterized.

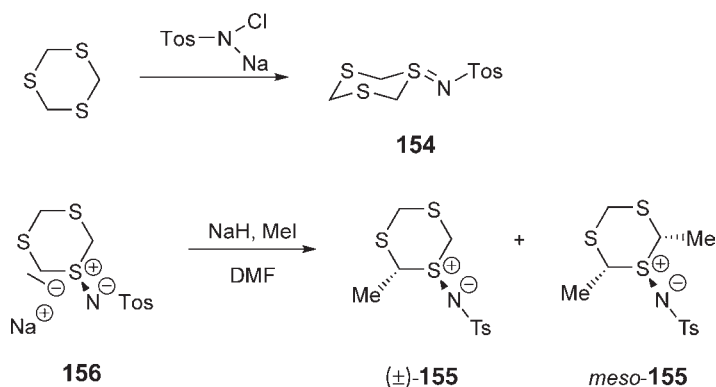
As an analog, 1,3,5-trithiane 1-tosylimide **154** was synthesized by the reaction between chloroamine-T and 1,3,5-trithiane in DMF. After pouring the reaction solution into cold water, the precipitate, recrystallized from acetonitrile, was proven by X-ray crystallography to have the tosylimino group equatorially oriented on a 1,3,5-trithiane chair conformer (Scheme 40) <1994J(P2)1439>. The sodium salt **156** reacted further with NaH/MeI in dimethylformamide (DMF) but delivered a product mixture of (±)-**155** and *meso*-**155**. Thus the authors failed to break the symmetry of **154** and, as part of their asymmetric synthesis program, to deliver enantiomerically enriched products (Scheme 40) <1995J(P1)313>.

9.11.6.4.2 Halogenation and CT complexation

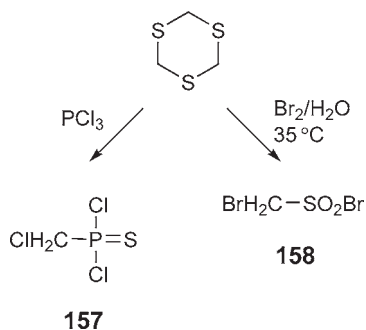
During the chlorination of 1,3,5-trithiane with PCl₃, the heterocycle was destroyed and ClCH₂P(=S)Cl₂ **157** was obtained, but only in 13.9% yield though unequivocally assigned by ³¹P NMR spectroscopy (Scheme 41) <1986ZOB962>. The oxidative cleavage of 1,3,5-trithiane by thionyl chloride is promoted by a catalytic quantity of a Lewis acid (e.g., ZnBr₂ or AlCl₃) and results in the formation of pure S(CH₂Cl)₂ <1992T8065>. This molecule has been successfully employed as a reagent in the straightforward synthesis of thiacycrown ethers with methylene bridges between the sulfur atoms.



Scheme 39



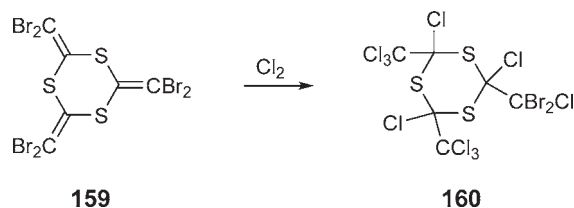
Scheme 40



Scheme 41

The bromination of an aqueous solution of 1,3,5-trithiane provided **158** in 46% yield (Scheme 41) <1983JA6164>. Similarly, 2,4,6-trimethyl-1,3,5-trithiane was able to be brominated delivering the corresponding α -bromoalkane-sulfonyl bromide $\text{CH}_3\text{CH}(\text{Br})\text{-SO}_2\text{Br}$. The latter synthesis is more efficient and occurs in 66% yield <1986JA4568>. Bromomethanesulfonyl bromide proved to be an excellent precursor for the preparation of conjugated dienes from alkenes <1987OS90>.

The mild chlorination of 2,4,6-tris(dibromomethylene)-1,3,5-trithiane **159** yields not the expected addition product but, due to extensive halogen scrambling, 2-(bromodichloromethyl)-4,6-bis(trichloromethyl)-1,3,5-trithiane **160** (Scheme 42) <1990SUL63>. The stereochemistry was not determined and only the gross structure was ascertained by mass spectrometry.



Scheme 42

Finally, the reaction of 1,3,5-trithiane, and also 1,3,5-triselenacyclohexane, with molecular diiodine has been studied <1997POL1983>. In methylene chloride and hot benzene, respectively, solid adducts were isolated whose

structures were solved by X-ray diffraction. The adducts consist of polymer chains in which diiodine molecules bridge 1,3,5-trithiane units in a zig-zag pattern as portrayed in Figure 7. The S $\cdots$ I interchain contacts range from 4.096 to 4.335 Å. The rings are all in chair conformations and the diiodine molecules are bonded equatorially to the sulfur atoms. Both the FTIR and the Raman bands of the I₂ molecule (153–177 cm⁻¹) were employed to indicate the number of differently perturbed I₂ molecules in the polymer units <1997POL1983>. The association constant of molecular iodine and 1,3,5-trithiane in CH₂Cl₂ solution has been determined by ¹³C NMR titration (at 25 °C: $K = 13 \pm 0.7 \text{ dm}^3 \text{ mol}^{-1}$, $\Delta H = -26.38 \pm 0.04 \text{ kJ mol}^{-1}$).

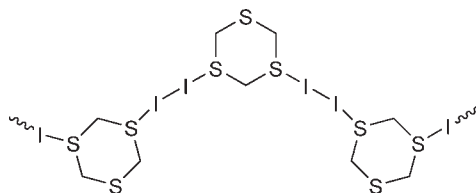


Figure 7 Polymer chains of 1,3,5-trithiane in which diiodines bridge the 1,3,5-trithiane units.

The crystallization and structure of the 1,3,5-trithiane $\cdots$ I₂ complex and the present π - and σ -interactions were studied in detail <1997LA2151>. In addition to the iodine complex, other CT molecular complexes of 1,3,5-trithiane with chloroanil (CA), tetracyanoethylene (TCE), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDBQ) have been synthesized. Solid complexes were separated out and their spectral characteristics (λ_{max}), formation constants (K_{CT}), molar extinction coefficients (ε_{CT}), ionization potentials (IPs) and enthalpy changes (ΔH) for the CT complex formation applying the Van't Hoff equation plots were determined and are presented in Table 12 <1994BCJ2006>. A new band, characteristic for the CT complex and not displayed by any component alone, appears in the 300–550 nm region of the electronic spectra. The formation constants reveal that the formed complexes are weak (stability decreases in the order DDBQ > TCE > CA) and are of the n - π - and n - σ -type, where the sulfur atoms are the donor sites for the CT interaction. The enthalpy changes for the CT complex formation reveal the following order of stability, I₂ > DDBQ > TCE > CA, in agreement with the stability constants and K_{CT} decreasing with the dielectric constant of the solvent. Finally, IR bands of the free donor in comparison with those in the CT complexes support the notion that the CT complexes are of nonbonding structure as can be concluded from the low K_{CT} values as well as the solvent effects <1994BCJ2006>.

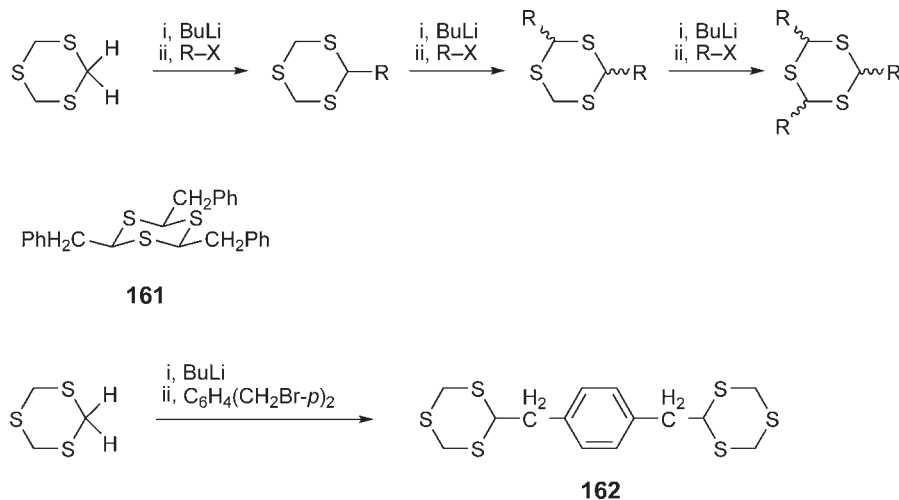
Table 12 Spectral characteristics, formation constants (K_{CT}), and enthalpy changes (ΔH) for CT complexes of 1,3,5-trithiane with various electron acceptors at 25 °C and the ionization potentials of these donors <1994BCJ2006>

Acceptor	Solvent	λ_{max} (nm)	E_{CT} (kJ mol ⁻¹)	IP (eV)	K_{CT} (dm ³ mol ⁻¹)	(ε_{CT} at 10 °C (dm ³ mol ⁻¹ cm ⁻¹))	$-\Delta H$ (kJ mol ⁻¹)
TCE	CH ₂ Cl ₂	463	258.55	8.77	9.5 ± 0.8	260 ± 23	16.6 ± 0.4
	CHCl ₃	460	260.24	8.80	12.9 ± 1.0	233 ± 19	17.6 ± 0.5
	C ₂ H ₄ Cl ₂	467	256.34	8.74	8.7 ± 0.9	269 ± 25	15.8 ± 0.7
I ₂	CH ₂ Cl ₂	317	377.63	8.86	31.2 ± 2.0	13525 ± 869	20.8 ± 0.3
	CCl ₄	314	381.24	8.92	44.3 ± 3.3	11596 ± 869	25.8 ± 0.4
	CHCl ₃	315	380.02	8.90	37.2 ± 3.5	12259 ± 1237	24.6 ± 0.4
	C ₂ H ₄ Cl ₂	318	376.44	8.84	27.6 ± 2.2	16525 ± 878	19.1 ± 0.7
DDBQ	CH ₂ Cl ₂	503	237.99	8.78	15.1 ± 1.4	321 ± 18	16.9 ± 0.4
CA	CH ₂ Cl ₂	410	291.97	8.73	5.9 ± 0.8	289 ± 35	14.6 ± 1.2

9.11.6.4.3 Alkylation

Alkylation of active methylene groups with a suitable electrophile can be accomplished readily and the selective and stepwise alkylation of 1,3,5-trithiane with alkyl halides has been published (Scheme 43) <1993RTC370>. The following alkyl halides, R = *n*-hexyl, benzyl, and *n*-dodecyl, have been employed, and the best alkylation results were obtained in THF with good to excellent yields. Furthermore, the alkylation proceeds with high stereospecificity. In

all cases, *cis*-isomers were obtained; even in the trisubstituted product only traces of the *trans*-isomer were found by ^1H and/or ^{13}C NMR. Crystals of **161** were subjected to X-ray crystallographic analysis and the structure was confirmed to be an all-*cis* configuration (Scheme 43).



Scheme 43

Employing the xylene dibromides (*ortho*, *meta*, *para*) as alkylating reagent under identical reaction conditions, the ditopic 1,3,5-trithianes were synthesized (from *p*-xylene dibromide **162**; cf. Scheme 43) <1993RTC370>. The coordination properties of the alkylated 1,3,5-trithianes were investigated by conductometry.

9.11.6.4.4 Coordination studies of 1,3,5-trithianes

1,3,5-Trithiane readily forms complexes to both ‘soft’ and ‘hard’ metal ions and borderline cases. For complexes where X-ray structural information is available, it appears that utilization of S-donor sites in normal tridentate chelation is never attained; often the ligand is involved in the form of a bridging mode linking two or more separate metal centers. In addition, the 1,3,5-trithiane ring retains the chair conformer which it possesses in the free state.

Another aspect of these complexes concerns fluxional processes in solution (ring interconversion of 1,3,5-trithiane moieties, pyramidal S-inversion, merry-go-round fluxional behavior of carbonyls in the complex, etc.). These have been studied often by 2-D EXSY NMR spectroscopy (e.g., <1983ICA(72)201>).

During the time period covered by this edition, the following metal centers have been studied.

Ruthenium. The X-ray structure of the cluster $\text{Ru}_3(\text{CO})_6(\mu\text{-CO})_3(\mu_3\text{-1,3,5-trithiane})$ has been published <1995OM1992>. 1,3,5-Trithiane binds the three Ru-atoms via interaction of one lone pair on each sulfur atom (A, Figure 8). This compound, and the analog $\text{Ru}_3(t\text{-BuNC})(\text{CO})_8[\mu_3-(\eta^3\text{-1,3,5-trithiane})]$, were studied by variable-temperature ^{13}C NMR spectroscopy whereby it was ascertained that the CO sites exchange via an intramolecular merry-go-round process <1993HCA2936, 1992HCA2227>. The kinetic parameters were also determined. In addition, the structure of $[\text{CpRu}(\text{PPh}_3)_2\text{-1,3,5-trithiane}]^+\text{CF}_3\text{SO}_3^-$ has been published <2003JCX473>; only one equatorial lone pair of electrons from one sulfur atom of 1,3,5-trithiane (B, Figure 8) is coordinated to the ruthenium center.

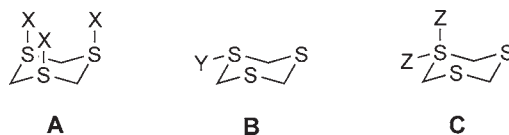


Figure 8 Complexation modes of 1,3,5-dithiane to various metal ions.

Osmium. Only one complex $\text{Os}_6(\text{CO})_{14}(\mu\text{-CO})\text{-1,3,5-trithiane}$ of structure A has been reported, in which the 1,3,5-trithiane ligand was found to cap over a triangular face of the Os_6 skeleton <1993JCD1223>.

Cobalt. In cobalt clusters $\{\text{Co}_3(\text{CO})_6(\mu_3\text{-CR})(\mu_3\text{-1,3,5-trithiane (2,4,6-trisubstituted with alkyl/benzyl substituents, R = Cl, Ph, Me) and Co}_3(\text{CO})_9(\mu\text{-CPh}_3)(1,3,5\text{-trithiane})\}$, 1,3,5-trithiane also unequivocally occupies the axial coordination sites on the three cobalt atoms <1996JCD1875, 1997JOM(548)263>. Additionally, a number of mixed Ru/Co clusters have been published <1992JOM(436)55>. Besides **A**, structure **C** (Figure 8) has also been found for the complex $\text{H}_2\text{Ru}_4(\text{CO})_{12}(1,3,5\text{-trithiane})$.

Iridium. In the iridium clusters $\text{Ir}_4(\text{CO})_{10}(1,3,5\text{-trithiane})$ <1990HCA154>, $\text{Ir}_4(\text{CO})_9(1,3,5\text{-trithiane})$ <1992IC1304> and $\text{Ir}_4(\text{CO})_6(\mu\text{-CO})_3(\mu_3\text{-1,3,5-trithiane})$ <1993JCD1223> and mixed Ir/Rh clusters <1993HCA2913, 1994HCA1869>, the 1,3,5-trithiane moiety caps the triangular basal face of the metal tetrahedron (structure **A**). By variable-temperature NMR spectroscopy, CO scrambling processes involving one, three or four metal centers were studied and the kinetic parameters deduced.

Copper, rhodium. $\text{CuCl}_2(1,3,5\text{-trithiane})$ <1992ZNB1736> and $\text{Rh}_4(\text{CO})_9(1,3,5\text{-trithiane})$ <1984CC1344>, a fluxional butterfly, are **A**-structurally coordinated to 1,3,5-trithiane; the rhodium skeleton of the latter complex is nonrigid in solution.

Silver, iron, platinum. During complexation with $\text{Fe}(\text{CO})_6$, the 1,3,5-trithiane ring was cleaved <1989OM2062>. The X-ray analysis of the Ag(I) complex displayed irregular coordination geometry (mono-, di-, and tricoordination to three different 1,3,5-trithiane molecules) <1983JCD1215>, while platinum was found to prefer bidentate coordination of 1,3,5-trithiane. Solution NMR and other evidence favor the ligand adopting a boat conformation and indicate the occurrence of a fluxional process involving 60° pivots of the ligand about individual S–Pt bonds. Mechanism and activation energies of the dynamic process were presented <1992JCD3497>.

Au(III), Nb(V), Sb(V), Sn(IV), Ta(V), and Tl(IV). 1:1 Complexation of 1,3,5-trithiane with AuCl_3 , SbCl_5 , TaCl_5 , TiCl_4 , SnCl_4 , SnBr_4 , NbCl_5 , and TaCl_5 and 1:2 complexation with TiCl_4 , SnCl_4 , and SnBr_4 were observed <1983ICA(72)201>. Structural assignments in terms of coordination number and metal geometry were based only on IR data. Variable-temperature ^1H NMR measurements of $\text{SnCl}_4(1,3,5\text{-trithiane})_2$ indicated fluxional rearrangements of the heterocyclic ring system <1983ICA(72)201>.

9.11.6.4.5 Miscellaneous reactions

1,3,5-Trithiane has been employed successfully as a reagent for the synthesis of diarylmethanes via the $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ -catalyzed dehydration of electron-rich aromatic compounds <2006TL2291>; this synthesis proved to be very efficient (good to excellent yields were obtained) and facile.

Starting from 1,3,5-trithiane, three novel mono- to trifulvathianes **163–165** have been prepared by (1) formation of the 1,3,5-trithiane anion and (2) reaction with either 4,5-dimethyl-1,3-dithia-2-iminium cation **166a** or the 4,5-dimethyl-1,3-dithia-2-methylthiolium cation **166b** (Figure 9). Spontaneous loss of amine or mercaptan provides

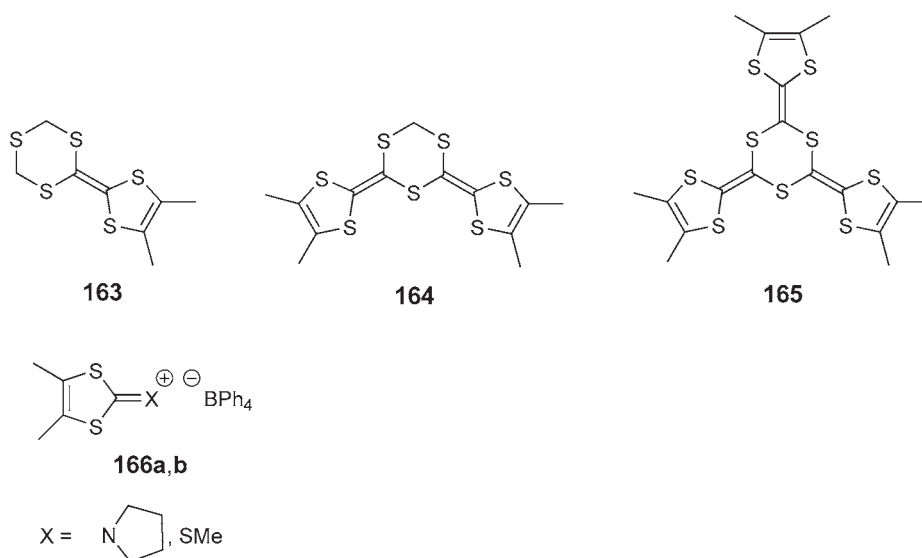


Figure 9 Structures of fulvatrithianes **163–165** prepared from cations **166a** and **166b**.

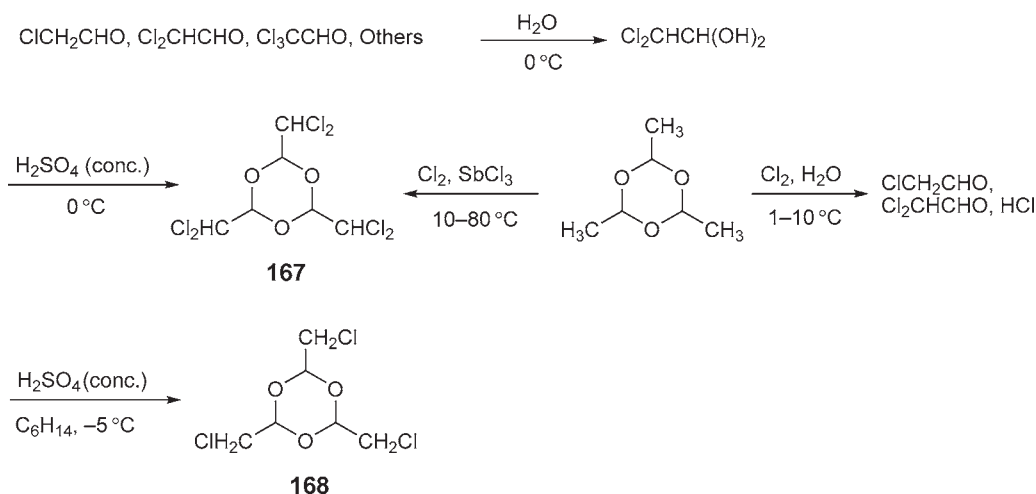
the 2-ylidene monofulvatrithiane **163** and, on repetition of the process, difulvatrithiane **164**. The trifulvatrithiane derivative **165** was obtained in one step from 1,3,5-trithiane with three equivalents of *n*-butyl lithium, presumably generating the 1,3,5-trilithio anion, which afforded **165** upon the addition of cations **166a,b** (Figure 9) <1989JA308>. In the light of the organic superconductor properties of the present compound, both cyclic voltammograms and the ESR spectra of **163**–**165** were scrutinized <1989JA308>. Their relative tendencies to undergo oxidation were determined and the radicals identified by ESR spectra, where not all of the expected hyperfine lines were resolved and spectral simulations were not attempted <1989JA308>.

The role of the isomers of 2,4,6-trimethyl-1,3,5-trithiane as co-initiators in benzophenone-induced photopolymerizations was pursued by studying the primary photochemical reactions by nanosecond laser-flash photolysis <2001JPH133>; it was found that the polymerization efficiency of the co-initiator did not follow the efficiency of photoinduced formation of the initiating radicals; however, detailed mechanisms of the various stages of polymerization were proposed <1998JPH21, 1999MM2173, 2001JPH133>.

Finally, 2,4,6-trimethyl-1,3,5-trithiane was obtained as a minor product by trapping $(\text{CH}_3)_2\text{C}=\text{S}$ by Diels–Alder cycloaddition to dimethylbutadiene <1991T4927>. 2,4,6-Trimethyl-1,3,5-trithiane has been used to supply thioacetaldehyde during vacuum flash pyrolysis <1987JCP60>; both the phosphorescence excitation and the emission spectra of thioformaldehyde were measured using a continuous wave (CW) dye laser and the transitions assigned <1987JCP60>.

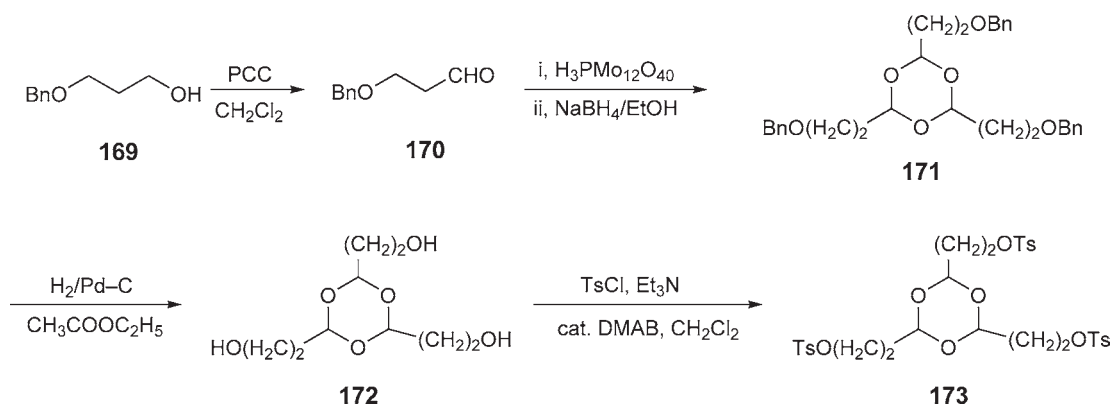
9.11.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Only a sparse amount of material has been published on this topic. Chlorination of 2,4,6-trimethyl-1,3,5-trioxane provided a mixture of chloroaldehydes which could be treated with concentrated sulfuric acid to yield 2,4,6-tri(chloromethyl)-1,3,5-trithiane **168** <1992CL171>. The corresponding dichlorination reaction catalyzed by SbCl_3 at 80 °C (via the previously mentioned chloroaldehyde and hydrolysis to the hydrate) finally yielded the dichloro analog **167** (Scheme 44) <1993SC1289>. Actually, it is chlorination of 1,3,5-trioxane substituents via open-chain reactants that is the process in effect.



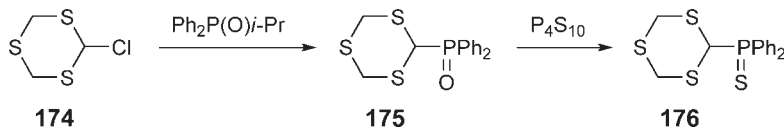
Scheme 44

The hydrolysis of 2,4,6-tri(2-benzyloxyethyl)-1,3,5-trioxane **171**, which was readily obtained as shown in Scheme 45 and which yielded **172** under catalytic hydrogenation, was found as a reaction at the substituents of 1,3,5-trioxane. The latter compound was easily tosylated **173**, isolated, and structurally characterized <1998MI505>.

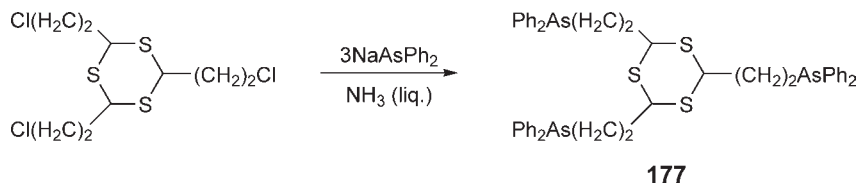


Scheme 45

For 1,3,5-trithiane, reactions of the substituents attached to the heterocyclic ring system have been published. 2-Chloro-1,3,5-trithiane **174** reacts with isopropyl diphenyl phosphine oxide to yield the corresponding phosphine oxides **175**, which were easily converted into the thiophosphoryl analogs **176** upon treatment with phosphorus pentasulfide (Scheme 46) <1987PAC983>. While the position of the phosphoryl group in the 1,3,5-trithiane **175** is exclusively axial, the thiophosphoryl derivative exists in solution as a mixture of axial and equatorial conformers. Furthermore, 2,4,6-tri(2-chloroethyl)-1,3,5-trithiane reacts with sodium diphenylarsenide in liquid ammonia to yield 2,4,6-tri(2-phenylarsinoethyl)-1,3,5-trithiane **177** as fine needles (Scheme 47) <1986JOM(299)51>; at -85°C the yield was larger than 50% and **177** was identified by IR, ^1H NMR, and mass spectra.

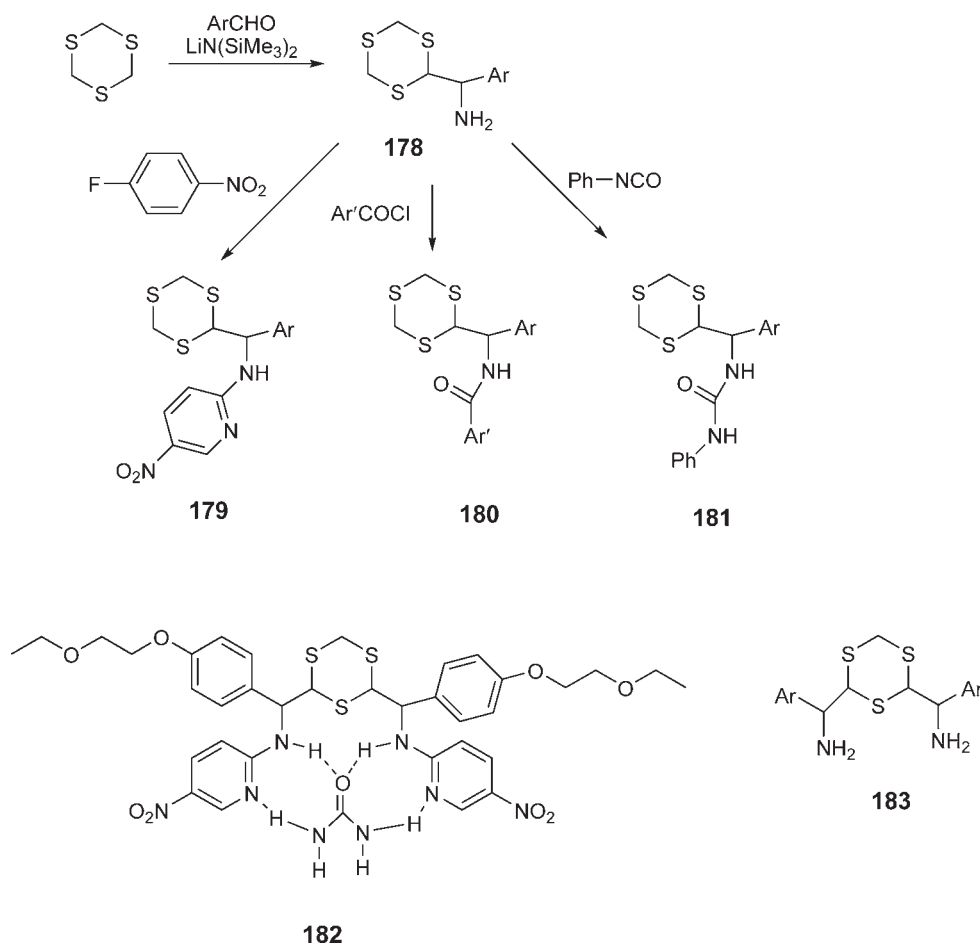


Scheme 46



Scheme 47

Starting from 2-lithio-1,3,5-trithiane, a photolabile scaffold for molecular recognition of urea molecules was synthesized (Scheme 48) <2001OL1841, 2004MI20>. First, the primary amines **178** were obtained by addition to N-silylated benzaldehydes, and these were treated with a number of electrophiles including benzoyl chloride (to yield **180**), phenylisocyanate (to yield **181**), or 2-fluoro-5-nitropyridine (to yield **179**). The host molecule **182** was obtained similarly by starting the syntheses with the corresponding disubstituted 1,3,5-trithiane derivative **183** bearing two primary amino groups which were able to be readily modified. Compound **182** was employable as a photolabile mimic of Hamilton's isophthaloyl bis(aminopyridine) receptor for various urea derivatives <2004MI20>.



Scheme 48

9.11.8 Reactivity of Substituents Attached to Ring Heteroatoms

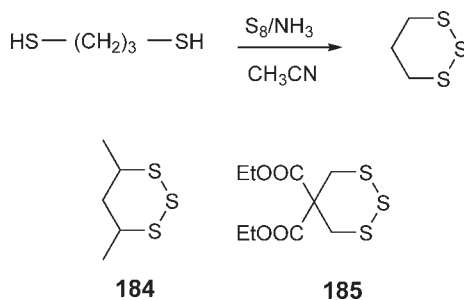
There are no examples of reactions of substituents attached to ring oxygen atoms; compounds with substituents on sulfur atoms other than oxygen (sulfoxides and sulfones) have not been reported and computations have not appeared in the accessible literature. The syntheses and reactivities of sulfoxides and sulfones are covered in the sections concerned with oxadithianes, trithianes, and their derivatives.

9.11.9 Ring Syntheses from Acyclic Compounds

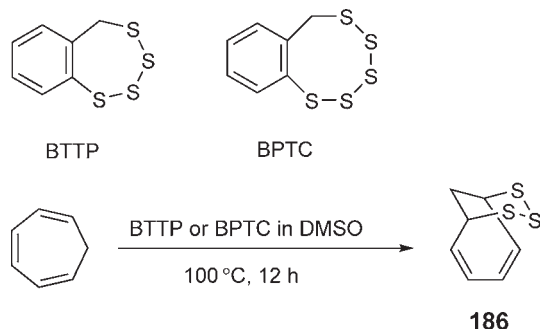
9.11.9.1 1,2,3-Trithianes

1,2,3-Trithiane was synthesized in 38% yield from 1,3-propane thiol using elemental sulfur in liquid ammonia and proved to be very stable (Scheme 49) <1988BCJ1647>. Derivatives of 1,2,3-trithiane were obtained also as side products from other reactions but in each case were solidly identified, for example, **184** from the hydrosulfurization of penta-1,4-diene in DMF <1995J(P1)635> and **185** from the reaction between diethyl bis(*p*-tolylsulfonyloxymethyl)-malonate and tetrasulfide ion <1988ACB620>.

Examination of 5*H*-benzo[*f*]-1,2,3,4-tetrathiepin (BTTP) and 6*H*-benzo[*g*]-1,2,3,4,5-pentathiocin (BPTC) as reproducible sulfurization reagents resulted in the bicyclic 1,2,3-trithiane derivative **186** being synthesized in 50–60% yield from cycloheptatriene by dual attack of the two reagents at 100°C over a course of 12 h (Scheme 50) <1990CL139>.

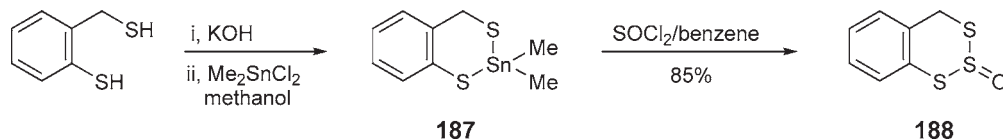


Scheme 49



Scheme 50

The corresponding dithiosulfites **188** can be obtained from dithiols by converting them first into organotin sulfides **187** which are quite stable and insensitive to air, light, and moisture. The latter then react further with thionyl chloride to give the expected cyclic dithiosulfites **188** in excellent yields (Scheme 51) <1993SUL5>.



Scheme 51

9.11.9.2 1,3,2-Dioxathianes

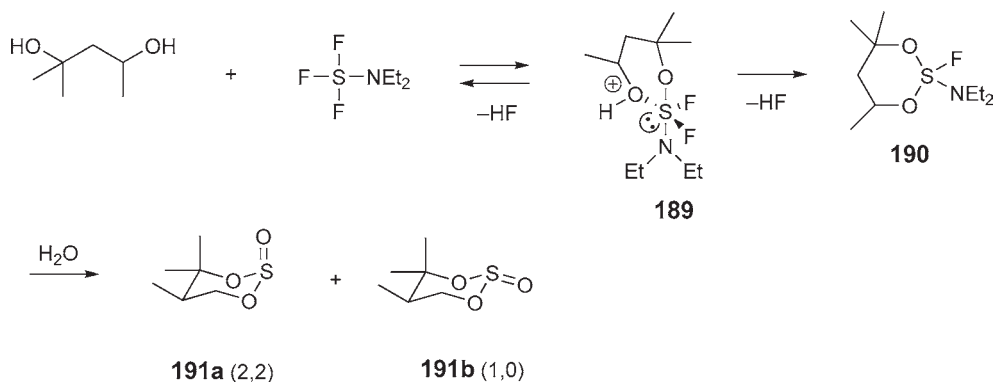
1,3,2-Dioxathiane derivatives can be prepared readily from 1,3-diols and an appropriate sulfuring reagent. The application of $\text{SCl}_2/\text{NEt}_3$ for the synthesis of 1,3,2-dioxathianes, SOCl_2 for the 2-oxides, and SO_2Cl_2 or chlorosulfonic acid or oleum for the synthesis of the 2,2-dioxides has been reported in CHEC(1984). From 1983 onward, a number of publications appeared where thionyl chloride was employed as the sulfuring reagent and both sulfites and sulfates were synthesized (cf. Table 13) <2003EJO2138, 1996TL3525, 2001JA3611, 2001CJC1040, 1997SL22, 1995T11445, 1994TA657, 1993CAR117, 1992CAR193, 1989J(P2)919, 1986IZV2638, 1986JHC1099, 1983CAR21, 1983HCA891>, though chlorosulfonic acid or oleum <1991AP949> and thionyl chloride <1987SAA1355> were also employed as the sulfuration reagents.

The kinetics of the DMF-catalyzed cyclization of 1,3-glycols ($\text{ClCH}_2-\text{C}(\text{R})(\text{CH}_2\text{OH})_2$; $\text{R} = \text{CH}_2\text{Cl}$, Et) with SOCl_2 was also studied quantitatively <1984ZOR1185>; this synthesis proved to be a complex two-step reaction with formation of an intermediate (not structurally characterized), with free energies of activation of 62.3 and 65.8 kcal mol^{-1} , respectively. Diethylaminosulfur trifluoride (DAST) has been employed as an alternative sulfuring reagent and the reaction of DAST with 2-methylpentane-2,4-diol gave the isomeric sulfites **191** in 80% yield (Scheme 52) <1995J(P2)861>. Semi-empirical calculations for the reaction of DAST with terminal diols show

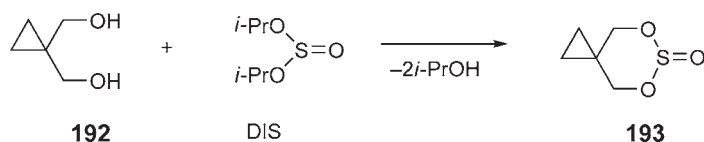
Table 13 Synthesis of 1,3,2-dioxathiane 2-oxide and 2,2-dioxides from 1,3-diols employing SOCl_2 as the sulfurating reagent

Starting material	Reaction product	Reaction conditions	References
		SOCl_2 , CCl_4 , 0°C , 45 min, 91%	2003EJO2138
		SOCl_2 , Et_3N , CH_2Cl_2	1996TL3525
		SOCl_2 , Et_3N , $\text{Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$, THF, 77%	2001JA3611
		SOCl_2 , CCl_4 , 60°C , NaIO_4 , $\text{RuCl}_3\cdot 3\text{H}_2\text{O}$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 25°C	2001CJC1040 , 1988JA7538
		cat., NaIO_4 , 87%	1997SL22
		SOCl_2 , 1.2 equiv, Et_3N , CH_2Cl_2 , 0°C , 10 min $\text{R}^1, \text{R}^2 = \text{Me}$ (79%) $\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph}$ (62%)	2000TL6615

that a cyclic intermediate **189** is favored in free energy <1995J(P2)861>. When SF₄ was used instead of DAST, the corresponding 1,3,2-dioxathiane 2-oxide was also obtained but only in low yield and as a component of a complex mixture <1988ZOB1633>. In the case of 1,1-bis(hydroxymethyl)cyclopropane **192**, the thionyl chloride/base procedure leads to a complicated mixture of products; thus, the corresponding 1,3,2-dioxathiane 2-oxide **193** was synthesized using acid-catalyzed transesterification of the diol **192** with diisopropyl sulfite (DIS) in nonpolar solvents with methanesulfonic acid as catalyst (Scheme 53) <1997SC701>. The reaction proved to be quite general and several other cyclic sulfites were prepared by the same procedure in excellent yields. The transesterification process proceeds also under base-catalyzed conditions (LiO-*t*-Bu, or NaO-*t*-Bu) in most solvents.

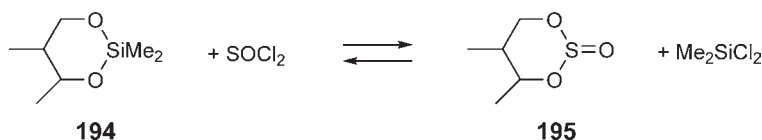


Scheme 52



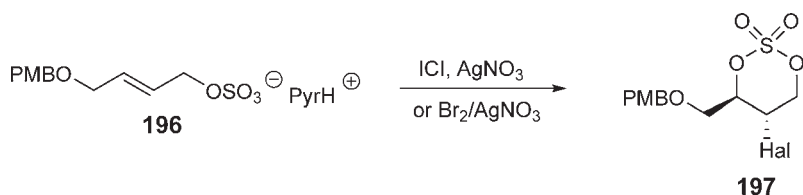
Scheme 53

The mixing of equimolar amounts of thionyl chloride and the silicon ester **194** in an inert gas atmosphere at room temperature was observed to result in a final equilibrium ratio of 25:75 with preference for the thermodynamically more stable 1,3,2-dioxathiane 2-oxide **195** (Scheme 54) <1999CHE755>. The exchange process proceeds stereospecifically.

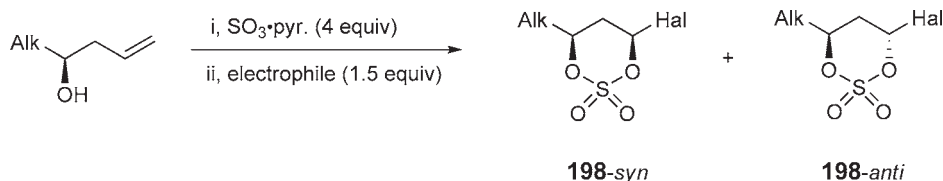


Scheme 54

The synthesis of 1,3,2-dioxathiane 2,2-dioxides by halocyclization has been reported (Scheme 55) <2001OL3557>. 4-(*p*-Methoxybenzyl)oxy-(*Z*)-2-butene-1-pyridinium sulfate **196** was treated with *N*-iodosuccinimide (or, alternatively, with Br₂) to yield the cyclic sulfate **197**; the (*E*)-isomer of the pyridinium sulfate **196** afforded the five-membered ring isomer as the only product. Examining the effect of substituents and (*E/Z*)-isomerism of the starting material, excellent and predictable regioselectivities were obtained for the halocyclization reaction of alkenyl sulfates. The halocyclization of allylic and homoallylic alcohols using an SO₃-pyridine complex together with an electrophile (I₂ or *N*-bromosuccinimide (NBS)) yielded the sulfates **198** with different *syn/anti*-isomeric ratios depending on the solvent (Scheme 56) <2003SC2857>. The best yield (91%) was obtained when CH₃CN was used as the solvent and NBS as the electrophile; the best diastereoselectivity (**198**-*syn*:**198**-*anti* > 100:1) was obtained in the same solvent but by using I₂ as the electrophile. The structures of **198** were characterized by IR and ¹H and ¹³C NMR spectroscopy and, in one case (**198**-*syn*: Alk = cyclohexyl), the complete structure was confirmed by X-ray crystallographic analysis.

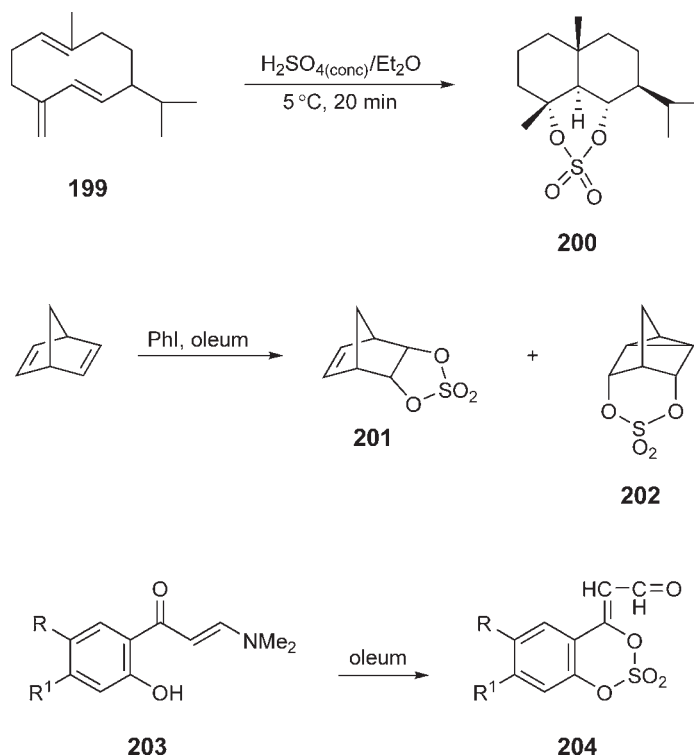


Scheme 55



Scheme 56

Finally, a few miscellaneous methods for the syntheses of 1,3,2-dioxathiane 2-oxides and 2,2-dioxides have been reported. For example, germacrene-D **199** dropped into an ice-cooled mixture of ether and concentrated sulfuric acid causes the precipitation of sulfate **200** as colorless crystals [<1988CPB3161>](#). The formation of the intramolecular cyclic sulfate was proven by IR and ^1H and ^{13}C NMR spectroscopy (Scheme 57). The treatment of 2,5-norbornadiene with PhI/oleum provided a mixture of cyclic sulfates in 72% yield with the six-membered structure **202** being preferred (Scheme 57) [<1986ZOR450>](#). Finally, a few 1,3,2-benzodioxathiins **204** were synthesized from the enaminones **203** by reaction with oleum or chlorosulfuric acid [<1991AP949>](#).

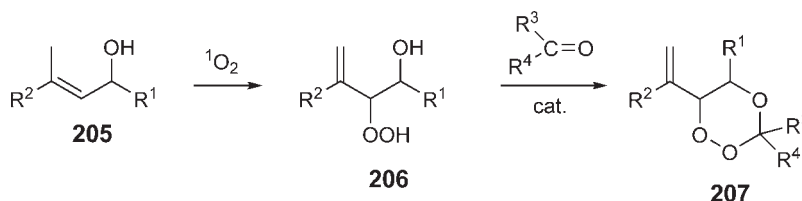


Scheme 57

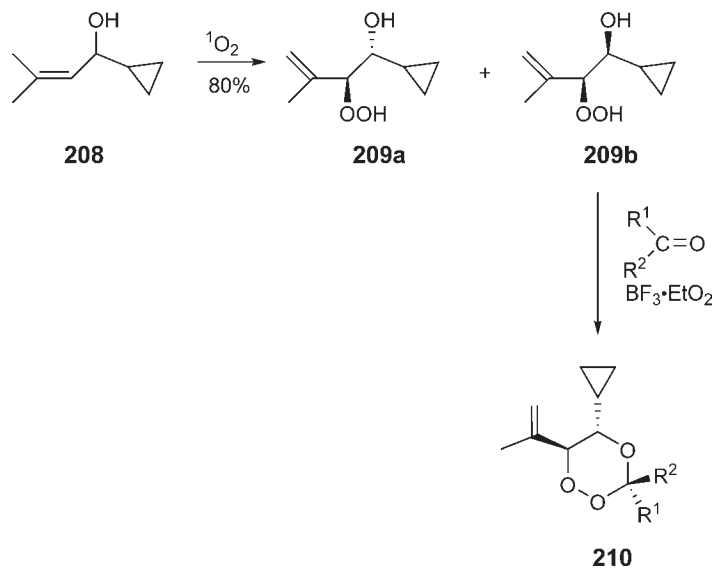
9.11.9.3 1,2,4-Trioxanes

Due to the unabated interest in the antimalarial activity of artemisinin **17** and its derivatives, the synthesis of 1,2,4-trioxanes has been studied intensively; a comprehensive overview is given in CHEC-II(1996). Developed methods have been applied continuously and a survey of synthetic paths from 1996 onward is presented below.

9.11.9.3.1 By photooxidation of allylic alcohols and subsequent ring closure with carbonyl compounds
The best synthetic method for the introduction of the peroxy group into the β -position of a preexisting hydroxy substituent, or vice versa, is by the addition of singlet oxygen to the C=C bond of allylic alcohols **205** followed by cyclization to the 1,2,4-trioxane ring system **207** with carbonyl compounds under acidic catalysis (**Scheme 58**) <1990TL6901, 1991CC947, 2005S2433, 2006T10615>. By the photooxidation of chiral allylic alcohols, hydroperoxides **206** in good yields and moderate diastereoselectivity were obtained, for example, from the cyclopropyl allyl ether **208** a 62:38 mixture of **209a**:**209b** was obtained. Subsequent treatment with 1–20 equiv of acetone yielded 41% of the 1,2,4-trioxane derivative **210** (**Scheme 59**). The 1,2,4-trioxane derivative from the minor hydroperoxide diastereomer could not be isolated <2005S2433>. By this procedure, a family of mono-, bi-, spiro-, and bispirocyclic 1,2,4-trioxanes was produced <2001H(54)607, 2001TL3997, 2002OL4193, 2005BML595, 2002BML1913, 2004BMC5745, 2005S2433, 2005TL205>, and these are collected in **Table 14**.



Scheme 58

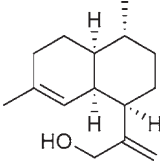
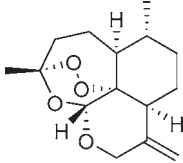
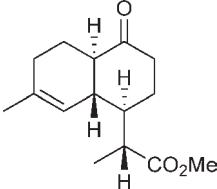
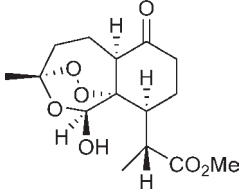
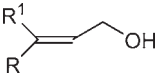
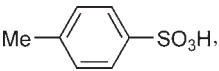
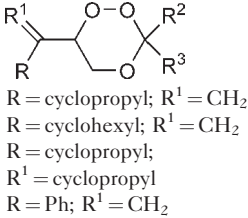
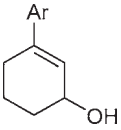
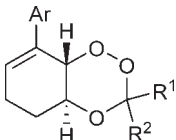
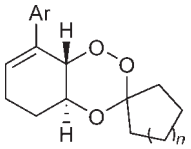
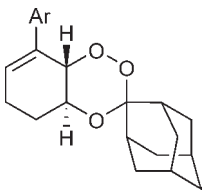
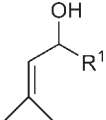
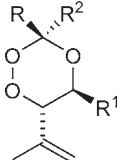
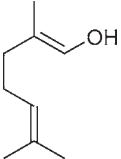
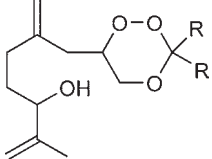


Scheme 59

In a complementary manner, the allylic hydroperoxide **211** (2,3-dimethylbut-1-en-3-yl hydroperoxide) reacted with a large variety of carbonyl compounds to give new 1,2,4-trioxane derivatives **213** affording several further functional group manipulations (**Scheme 60**) <1997TL635>.

An XeCl excimer 308 nm radiation system has been described as a useful tool for these kinds of synthetic organic photochemical reactions <2003PPS450>.

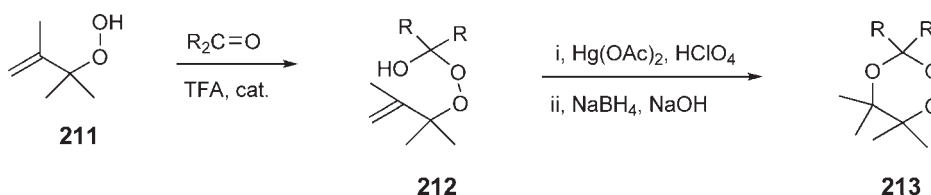
Table 14 Synthesis of 1,2,4-trioxane derivatives by photooxidation

Starting material	Reaction condition	1,2,4-Trioxane derivative	Reference
	i, O ₂ , rose bengal, 500 W tungsten lamp, CH ₃ CN/CH ₂ Cl ₂ , -23 °C ii, TFA, O ₂ , CH ₃ CN, -23 °C, rt, 35%		2001TL3997
	i, O ₂ , methylene blue, <i>hν</i> , 0 °C ii, TFA, O ₂ , rt		2001H(54)607
	i, O ₂ , methylene blue, <i>hν</i> , MeCN, 0 °C ii, aldehyde/ketone,  CH ₂ Cl ₂ , rt, 2 h	 R = cyclopropyl; R ¹ = CH ₂ R = cyclohexyl; R ¹ = CH ₂ R = cyclopropyl; R ¹ = cyclopropyl R = Ph; R ¹ = CH ₂	2004BMC5745
	i, O ₂ , methylene blue, <i>hν</i> , MeCN, 0 °C ii, aldehyde/ketone, HCl _(conc) (cat.), CH ₂ Cl ₂ , 0 °C, 3–6 h		2005TL205
			2005S2433
			2005BML595
	i, ¹ O ₂ ii, R, R ² C=O, BF ₃		2002OL4193
	i, O ₂ , <i>hν</i> , -10 °C ii, R ₂ C=O		2002BML1913

(Continued)

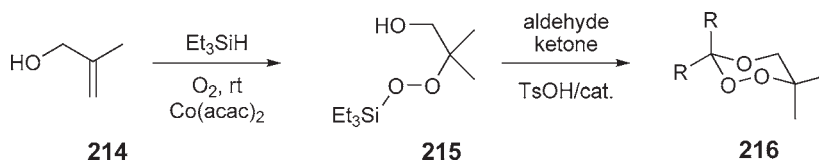
Table 14 (Continued)

Starting material	Reaction condition	1,2,4-Trioxane derivative	Reference
	i, CH ₂ Cl ₂ , RCHO, TFA, -78 °C ii, CH ₂ Cl ₂ , <i>N</i> -iodosuccinimide		2003CR153
	i, air, <i>hν</i> , methylene blue ii, Me ₃ SiOTf iii, EtN , -90 °C		2001JME3054
	i, O ₂ , <i>hν</i> , -78 °C, methylene blue ii, H ⁺ (Amberlyst)		1998EJO2897
	i, O ₂ , <i>hν</i> , CH ₂ Cl ₂ , -78 °C ii, TMS-OTf		1997TA2085

**Scheme 60**

9.11.9.3.2 By hydroperoxidation of allylic alcohols

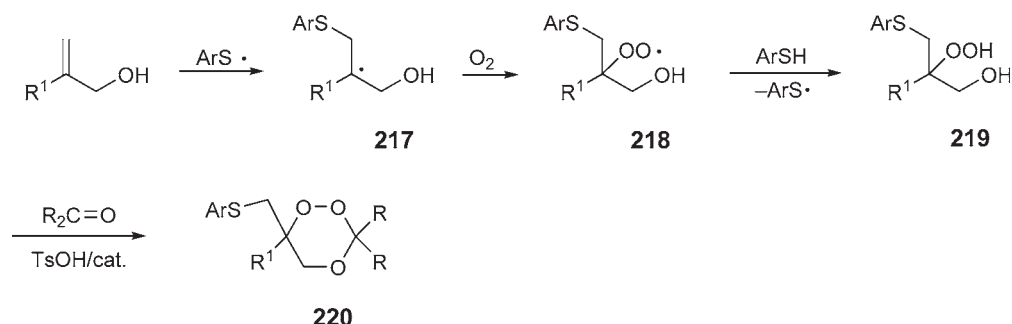
This milder approach to synthesize 1,2,4-trioxane derivatives makes use of the highly regioselective Markovnikov reaction of 2-methyl-2-propen-1-ol **214** with molecular oxygen and triethylsilane using Co(acac)₂ as catalyst (acac = acetylacetonate). The triethylsilylperoxides **215**, thus obtained in high yield, smoothly couple with a range of carbonyl substrates to give the target 1,2,4-trioxanes **216** (Scheme 61) <2001TL4569>. Separate purification of **215** was not required because the one-pot peroxylation/cyclization using crude **215** and the appropriate aldehyde/ketone gave the 1,2,4-trioxanes **216** in yields ranging from 40% to 90%.

**Scheme 61**

9.11.9.3.3 By the thiol–olefin co-oxidation methodology from allylic alcohols

The thiol–olefin co-oxidation methodology starts with the attack of an arylthiyl radical, generated through initiation of AIBN/ $h\nu$, at the double bond of an allyl alcohol. The tertiary carbon radicals **217** obtained trap oxygen to form the peroxy radicals **218**. Finally, hydrogen abstraction from thiophenol produces the α -hydroxy peroxides **219**, which undergo smooth condensation with ketones to generate 1,2,4-trioxane derivatives **220** (Scheme 62) <2004OL3035>.

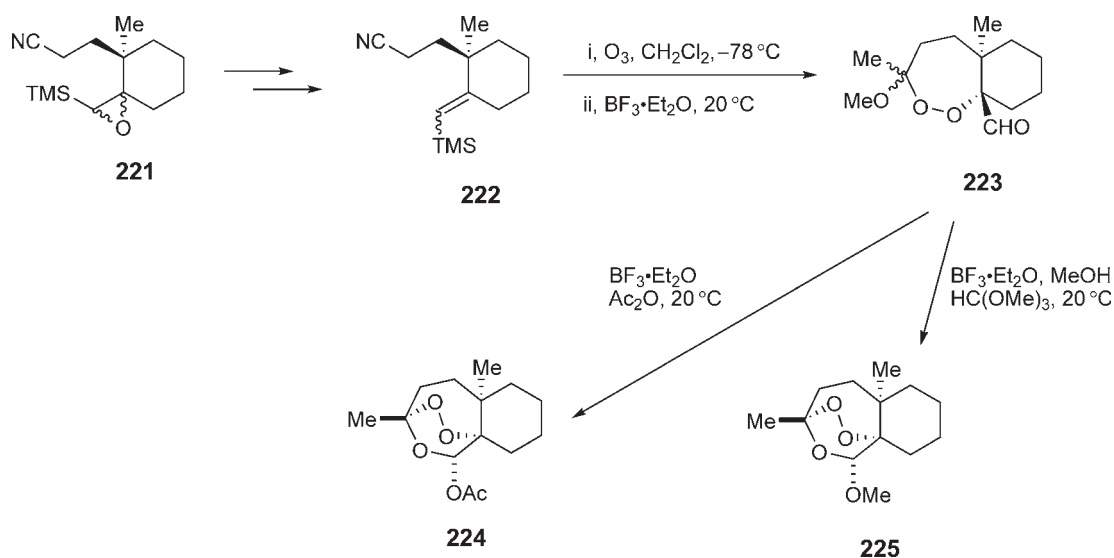
Application of the method to various combinations of ketones and allylic alcohols afforded a rich series of spiro-1,2,4-trioxanes.



Scheme 62

9.11.9.3.4 By ozonolysis of vinylsilanes

Ozonolysis of vinylsilane **222**, synthesized from the corresponding epoxide **221**, followed by treatment with $BF_3\cdot OEt_2$ gave the sensitive peroxide aldehyde **223** which was converted finally into the 1,2,4-trioxane derivative **225** using $HC(OMe)_3$ in methanol in the presence of $BF_3\cdot OEt_2$ in 37% yield based on **222** <1998TL2969, 1998EJO2897>. The structure and stereochemistry of the 1,2,4-trioxane was assigned using the full arsenal of 2-D NMR experiments and by an X-ray crystallographic analysis (Scheme 63). By treating **223** with Ac_2O and $BF_3\cdot OEt_2$, the corresponding acetate **224** was obtained; its stereochemistry is the same as **225** and both exhibit the same relative configuration as in artemisinin **17**. However, both the synthetic 1,2,4-trioxanes are completely devoid of antimalarial activity.

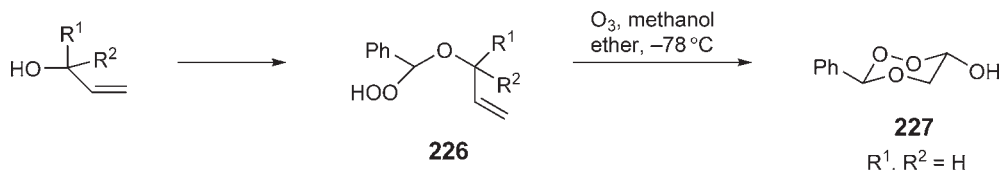


Scheme 63

(+)-Artemisinin **17** and a number of analogs for structure–activity relationships were synthesized by employing ozonolysis as the key ring-closing procedure <1996JME2900, 1996JME4149, 1997BML2357, 2002JME4321, 2006CRV2990>.

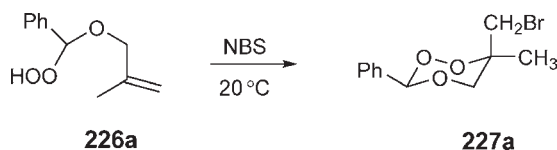
9.11.9.3.5 By cyclization of unsaturated hydroperoxy acetals

Ozonolysis of unsaturated hydroperoxy acetal **226**, readily obtained by trapping carbonyl oxides with primary unsaturated allylic or homoallylic alcohols <1997J(P1)5>, with ozone in methanol/ether at -78°C gave the 6-hydroxy-1,2,4-trioxane derivatives **227** almost quantitatively and as a single isomer (structure confirmed by 1-D NOE spectroscopy; see **Scheme 64**) <1997JOC4949>. In the case of substitution ($\text{R}^1, \text{R}^2 = \text{H}, \text{Me}$ or Me, Me), a mixture of two and three isomers, respectively, were obtained, all completely assigned by ^1H NMR spectroscopy <1997JOC4949>.

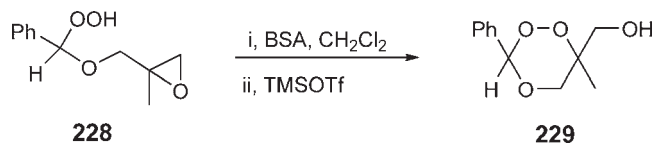


Scheme 64

Alternatively, with the unsaturated hydroperoxy acetals **226** in hand, *N*-halogenosuccinimide-mediated cyclizations were conducted. Treatment of **226a**, for example, with NBS in CH_2Cl_2 gave the corresponding 1,2,4-trioxane **227a**. The obtained yields were rather low (15–36%) and two stereoisomers (ca. 4:1) were obtained, though only the major isomer was isolated and assigned stereochemically as **227a** (**Scheme 65**) <1997J(P1)5>. Furthermore, the electrophilic cyclization of unsaturated hydroperoxy acetals was studied <1996TL463>. Their autoxidation and the acid-catalyzed cyclization of the related hydroperoxides **229** (**Scheme 66**) <1997TL8753> were also examined (cf. **Table 15**).



Scheme 65

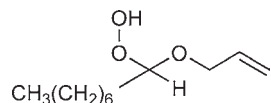
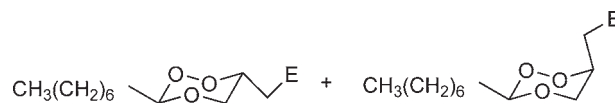
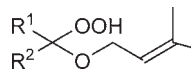
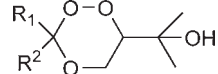


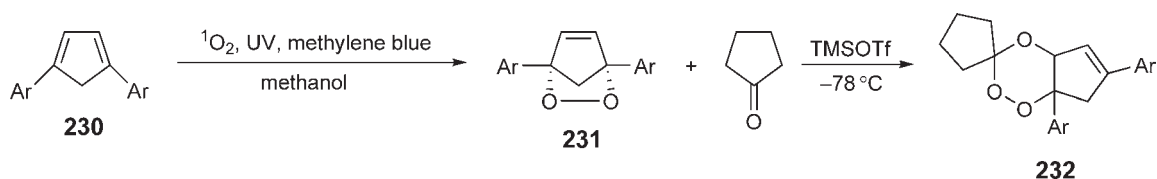
Scheme 66

9.11.9.3.6 By acid-catalyzed reaction of *endo*-peroxides with carbonyl compounds

In CHEC-II(1996), it was shown that *endo*-peroxides, obtained by dye-sensitized photooxygenation of readily available dienes (or enes, in which case the corresponding oxetanes are formed), react on acid catalysis with aldehydes and ketones to afford the corresponding *cis*-fused bicyclic 1,2,4-trioxanes in high yield. A typical synthesis is given in **Scheme 67** <1997HCA2440>. Due to the prochiral nature of the *endo*-peroxide **231** and the steric requirement of the cations resulting therefrom, the reaction proved to be diastereoselective. In order to clarify this reaction, a number of chiral ketones were studied <1997HCA2440> and up to four diastereomers in various relative yields were obtained and stereochemically assigned by NMR and X-ray crystallography. On the basis of this protocol, a large variety of substituted 1,2,4-trioxane derivatives were produced from 1996 onward and characteristic examples are given in **Table 16**.

Table 15 1,2,4-Trioxane synthesis from unsaturated hydroperoxyacetals

Starting material	Reaction conditions	1,2,4-Trioxane derivative	Reference
 <chem>CH3(CH2)6C(OOH)(OCH2CH=CH2)C1OCCO1</chem>	i, <i>n</i> -BuLi; ii, I ₂ -78 °C, THF, 20% i, KH; ii, I ₂ 0 °C, rt, THF, 24% i, <i>t</i> -BuOK/I ₂ 0 °C, CH ₂ Cl ₂ , 19% i, <i>t</i> -BuOK/I ₂ , 18-C-6 rt, C ₆ H ₆ , 22% i, Cs ₂ CO ₃ /I ₂ rt, THF, 12% i, Hg(OAc) ₂ cat. HClO ₄ ; ii, HgBr rt, CH ₂ Cl ₂ , 85% i, Hg(OAc) ₂ ; ii, HgBr rt, CH ₂ Cl ₂ , 64%	 <chem>CH3(CH2)6C(OOH)(OCH2CH=CH2)C1OCCO1E</chem> 10 : 1 7 : 1 4 : 1 6 : 1 10 : 1 1.5 : 1 10 : 1	1996TL463
 <chem>R1C(OOH)(OR2)C1OCCO1C=C</chem>	i, DBPO/TBHP benzene, O ₂ dry, rt ii, Triphenylphosphine	 <chem>R1C(OOH)(OR2)C1OCCO1C=C</chem>	1997TL8753



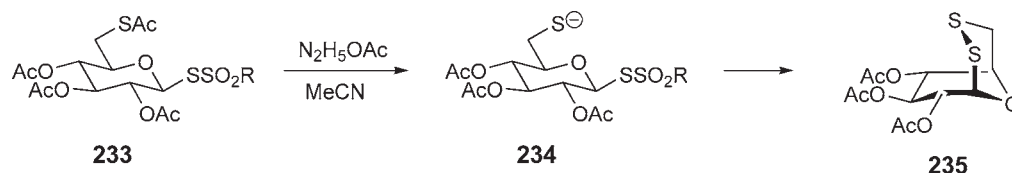
Scheme 67

Table 16 Synthesis of 1,2,4-trioxane derivatives by acid-catalyzed reaction of *endo*-peroxides with carbonyl compounds

Starting material	Reaction conditions	Products	Reference
	i, $^1\text{O}_2, h\nu$ ii, TBDMSOTf iii, Et_3N		1998JME952
	i, $^1\text{O}_2, h\nu$ ii, Me_3SiOTf iii, PhCHO		1997H(44)367
	i, $^1\text{O}_2, h\nu$, TPP, CH_2Cl_2 , 5°C ii, $\text{O}=\text{C}_6\text{H}_{10}=\text{O}$, Me_3SiOTf , CH_2Cl_2 , -78°C		2004CEJ1625
	i, $^1\text{O}_2, h\nu$, methylene blue, -78°C ii, TBDMSOTf, CH_2Cl_2 , -50°C	 $\text{R}^1 = \text{OMe}; \text{R} = \text{H}$ 25% yield (85% ee) $\text{R} = \text{OMe}; \text{R}^1 = \text{H}$ 15% yield (85% ee)	1999TL9133
	i, TMSOTf, CH_3CHO , -78°C	 67% yield, diastereomerically pure	1998EJO2833

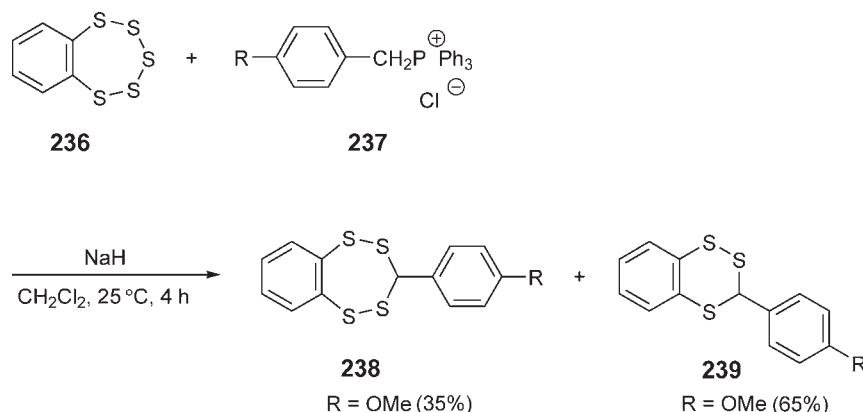
9.11.9.4 1,3,4-Oxadithianes and 1,2,4-Trithianes

The 1,3,4-oxadithiane derivatives (1,6-disulfide-bridged D-hexopyranoses, for example, **235**) were synthesized by intramolecular cyclization of the thiosulfate **233**, achieved through selective deacetylation of S-6 by action of hydrazinium acetate (via **234**; see Scheme 68) <2005AJC199>. The yields of the disulfides were ca. 65% and the best yields and highest reaction rates were obtained for the benzenethiosulfates ($\text{R} = \text{Ph}$). Besides the α -D-glucopyranoside derivative **233**, the D-manno-, D-galacto-, and D-talopyranoside analogs were also cyclized by the same procedure.



Scheme 68

In addition to the dimeric 1,2,4-trithiane derivative **58** (cf. [Scheme 8](#)), isolated as a side product in very low yield and characterized by X-ray crystallography (*vide supra*), 5,6-benzo-1,2,4-trithiin **239** was isolated from the continuous sulfur–carbon displacement reaction of benzopentathiepin **236** <1997H(44)187>. Upon treatment with the phosphorus ylides **237** in CH_2Cl_2 , mixtures of benzotetrathiepins **238** and benzotrithiins **239** were obtained in moderate yields (NaH was deemed the base of choice; cf. [Scheme 69](#)). The new products **238** and **239** were separated easily by high-performance liquid chromatography (HPLC) and the structures characterized by ^1H NMR spectroscopy, whereby the chemical shift of the methine proton was indicative of the cyclic structures that were formed (5.40–5.44 ppm for **238**, but 5.96–6.07 ppm for **239**). The present desulfurization mechanism is complex and is still unclear because likely intermediates have not been isolated or detected directly by spectroscopic techniques <1997H(44)187>.



Scheme 69

9.11.9.5 1,3,5-Trioxanes

The trimerization of formaldehyde is the most important industrial process for the synthesis of 1,3,5-trioxane which is used as an intermediate in the manufacture of polyoxymethylenes. Liquid- and vapor-phase syntheses, solvent-free alternatives, and the application of a variety of catalysts have been studied; also, a number of specially designed reactor systems <1990MI539, 1994MI551, 1994MI415, 1999MI1353> have been employed. The published methods, together with the corresponding references, are given in [Table 17](#). The variation of by-product concentrations (especially formic acid) with reaction time in the synthesis of 1,3,5-trioxane was studied experimentally <1995MI555>; the formation of by-products was found to depend strongly upon reaction time and the concentration of catalysts used while the initial formaldehyde concentration was found to have had little impact.

Both reaction kinetics and chemical equilibria of the formation/decomposition of 1,3,5-trioxane in aqueous formaldehyde solutions were studied by quantitative ^1H NMR spectroscopy <2006MI910>; a virtual reference signal of high stability was generated electronically and employed for the quantification of the small 1,3,5-trioxane proton signal.

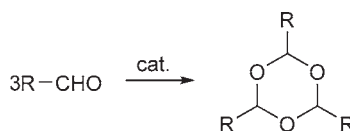
By MNDO calculations, the formation enthalpies of components potentially involved in the cyclization of formaldehyde to 1,3,5-trioxane were determined <2001MI398>. The results suggest that the most favorable

Table 17 Trimerization of aldehydes to 1,3,5-trioxane and derivatives

<i>Aldehyde</i>	<i>Reaction conditions</i>	<i>References</i>
HCHO	Amberlyst-15 cation exchanger H ₂ SO ₄ cat. or tungsten heteropoly acids	1990MI214 1998ZPK981, 2000AGE2102, 2000MI302
CH ₃ CHO	1-Vanado-11-molybdo phosphoric acid, cat., Berty reactor, 110 °C, 0.6–1.1 bar	1994ACL17
R ¹ , R ² = CHCHO	Me ₃ SiCl, rt, solvent free, yield > 89%	2002TL7919
R ¹ , R ² = Me, Me; H, Et; H, <i>i</i> -Pr; Me,	H ₂ SO ₄ , cat., heated glass reactor	1985MI4
(<i>p</i>)- <i>t</i> -BuC ₆ H ₄ CH ₂	HCHO, conc., aq. solution, zeolite cat. (SiO ₂ /Al ₂ O ₃ ca. ≥ 805)	1996NKK290
RCHO (R = Et, <i>i</i> -Bu)	Zeolite host material, rt, >90% Bentonitic earth, rt, >60%	2002PCB1322 1993TL6857
Cyclohexyl-CHO	[RuCl(H)(Co)(PPh ₃) ₃], CH ₂ =CHSiMe ₃ , benzene, rt	2004MI105
	i, HNTf ₂ , Et ₂ O, rt, 0.5 h	2001SL1851
	ii, Cyclohexyl-CHO, –78 °C, 2 h	
	iii, Stirred at –78 °C, 15 min	
	iv, HCl/THF, >95%	
(CH ₃) ₂ CHCHO	ZnCl ₂ , 90 °C, 83%	1987BCJ2289
(CH ₃) ₂ CHCHO	Ionic liquids, rt, 1 h, >90%	2005CCL299
RCHO (R = Me, Et, Pr, Bu, C ₅ H ₁₁ , C ₆ H ₁₃ , C ₇ H ₁₅ , C ₈ H ₁₇ , cyclohexyl, <i>i</i> -Pr,	MeReO ₃ , rt to –30 °C, 1–4 h, 80–99%	1998S417
(<i>E</i>)-Me(CH ₂) ₄ CH=CH(CH ₂) ₂ , PhCH ₂ , Ph(CH ₂) ₂ , MeCH(Me)CH ₂ , MeCH ₂ CH(Me), Me(CH ₂) ₂ CH(Me), <i>t</i> -Bu, CH ₂ =CH(CH ₂) ₈)		
TosOCH ₂ CH ₂ CHO	12-Phosphomolybdic acid	1998CL823
Ph(CH ₂) ₂ CHO	Acetyl/triphenylphosphonium bromide CH ₂ Cl ₂ , 1 h, 38%	2001T6181
	MeOH, 5 min, 95%	
RCHO (R = Me, Et, <i>n</i> -Pr, <i>i</i> -Pr, <i>n</i> -Bu)	[P(2-py) ₃ W(CO)(NO) ₂](BF ₄) ₂ , rt, 24 h, 86–96%	2002TL1051

formation and decomposition in concentrated aqueous acid solutions of formaldehyde is a reaction path involving cyclization of onium polyoxymethylene cations with five or more CH₂O units and heterocycle opening by the hydroxonium ion forming the cation HO(CH₂O)₂CH₂O⁺H₂.

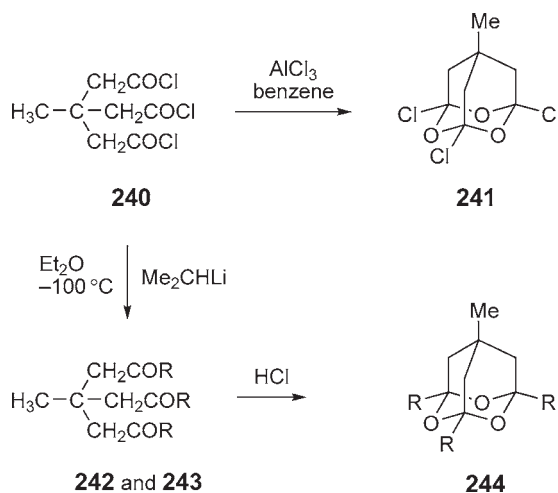
Various other 2,4,6-trisubstituted-1,3,5-trioxanes obtained by cyclotrimerization of the corresponding aldehydes have been reported (cf. **Scheme 70**; **Table 17**); common catalysts employed were, besides protic acids, zeolites, bentonitic earth, Lewis acids, heteropoly acids, organic metal oxides, and ion-exchange resins. When X-ray structures were reported, the chair conformer with the substituents in equatorial positions was always found (e.g., <1998S417>). Also, the trimerization of acetaldehyde and propionaldehyde in the presence of SO₂ has been reported <1983ZOB1787> wherein the aldehydes and SO₂ initially form C·T complexes. In the case of acetaldehyde, the corresponding enthalpy and entropy of complexation were determined to be –15 kJ mol^{–1} and –32 J mol^{–1} K^{–1}, respectively.

**Scheme 70**

When testing the activities of the *Earias insulana* pheromones *E*10 and *E*12–16 (*E,E*)-Me(CH₂)₂CH=CH–CH=CH(CH₂)₈–CHO) and analyzing various samples by ¹H NMR spectroscopy, it was discovered that these pheromone aldehydes spontaneously trimerize to the corresponding 2,4,6-trisubstituted-1,3,5-trioxane derivatives, which are stable and attain a *cis,cis*-geometry <1984JEL421>.

The synthesis of 2,4,6-tri(2-bromo-1,1-dimethylethyl)-1,3,5-trioxane as a major by-product during the synthesis of 3-bromo-2,2-dimethyl-propanal from the corresponding primary alcohol has been reported <2000JPR100>. The 1,3,5-trioxane derivative formed suitable crystals for X-ray analysis where a chair conformer with the three substituents all in equatorial positions was found.

2,4,9-Trioxaadamantane **241** containing the 1,3,5-trioxane moiety can be synthesized simply by cyclization of the tricarboxylic acid chloride **240** in benzene in the presence of AlCl₃. In the case of triketones **242** (R = Me) and **243** (R = Bu), the corresponding trioxaadamantanes **244** were available by treating them at low temperature with HCl or formic acid in diethyl ether (Scheme 71) <1983CB1345>. The ¹H NMR spectra of the C_{3v} symmetric trioxaadamantanes could be interpreted completely by spectral simulation. They are among the few cases where only geminal couplings (–12 to –12.5 Hz) and long-range W-couplings (2.2–3 Hz) play a major role in structural determination.



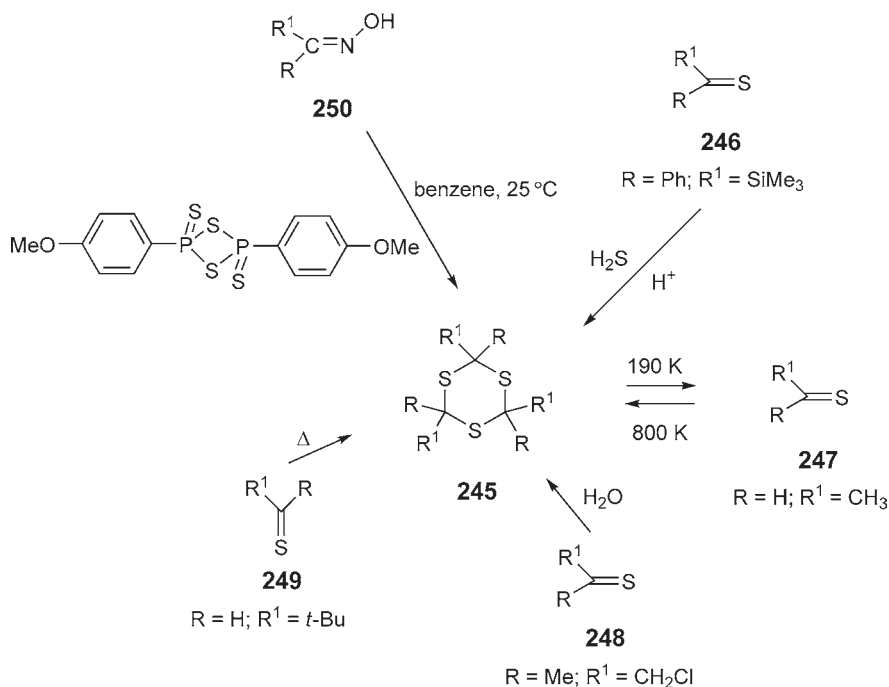
Scheme 71

9.11.9.6 1,3,5-Trithianes

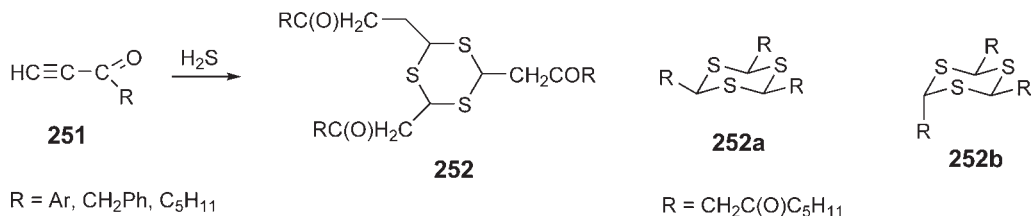
1,3,5-Trithiane is best prepared by passing H₂S through the mixture HCHO/HCl; substituted derivatives are obtained from similar reactions with appropriate aldehydes or ketones. Since the publication of CHEC(1984), a number of novel methods to prepare substituted 1,3,5-trithianes have been published.

Several substituted 1,3,5-trithiane derivatives have been synthesized by trimerization of the corresponding thio-carbonyls (Scheme 72); for example, the acid-catalyzed reaction of the blue phenyl trimethylsilyl thioketone **246** (R = Ph, R¹ = SiMe₃) gave two major, colorless products which were assigned by NMR in solution and by X-ray crystallography to be the *cis*- and *trans*-isomers of 2,4,6-tris(trimethylsilyl)-2,4,6-triphenyl-1,3,5-trithiane <1988J(P1)1499>. The temperature-dependent equilibrium of the pink thioacetaldehyde **247** (R¹ = Me, R = H) and its trimeric 1,3,5-trithiane derivative was studied in detail (Scheme 72) <1983PS185>. Also, hydration of 1-chloro-2-propanethione **248** (R = Me, R¹ = CH₂Cl) yields 2,4,6-trimethyl-2,4,6-tri(chloromethyl)-1,3,5-trithiane in almost quantitative yield <2000RJC917> and heating of the pink *t*-BuCHS **249** gave the isomeric tri(*t*-butyl)-1,3,5-trithiane isomers <1983JA1683, 1986JA2985>.

In a similar manner, the reaction of *p*-tolualdoxime **250** in anhydrous benzene at 25 °C with Lawesson's reagent yielded triaryl-1,3,5-trithiane **245** (R¹ = *p*-tolyl, R = H) <1984SL223>. Another interesting method has been published starting from acetylenic ketones <1989ZOR2022, 1991ZOR559>: ethynyl arylketones **251** react readily with H₂S in methanol at 20 °C with AcONa as catalyst to yield the corresponding 1,3,5-trithiane derivatives **252**. In the case of R = C₅H₁₁, the reaction products were isolated and assigned as the *cis*- and *trans*-isomers **252a** and **252b** by ¹H NMR spectroscopy (Scheme 73).



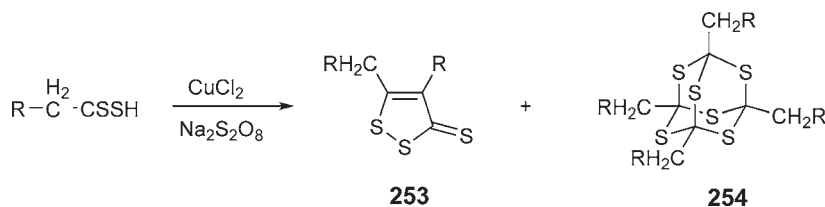
Scheme 72



Scheme 73

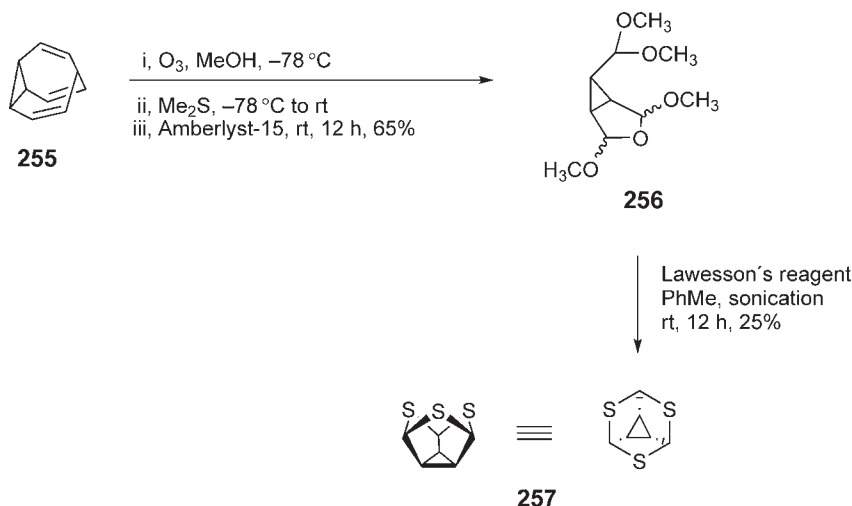
The high-temperature thiation of thiophosgene with elemental sulfur leads to a multitude of primary, secondary, and tertiary reaction products [\[2000SUL23\]](#); the product mixture was separated and assigned by gas chromatography–mass spectrometry (GC–MS), including the unequivocal identification of 2,2',4,4',6,6'-hexachloro-1,3,5-trithiane.

Finally, it is to be mentioned that, along with dithiolethione derivative [253](#), hexathiaadamantane [254](#) which contains 1,3,5-trithiane ring moieties has been synthesized from dithiocarboxylic acid derivatives by reaction with CuCl₂ and Na₂S₂O₈ in water [\[1986IZV1206\]](#) (Scheme 74). Structure [254](#) was assigned unequivocally by ¹³C NMR spectroscopy and MS.



Scheme 74

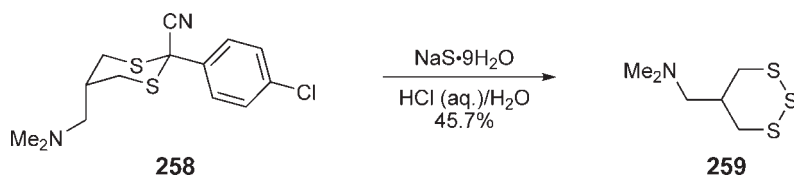
The aesthetically pleasing and topologically novel trithia-[3]-peristylane **257**, also containing the 1,3,5-trithiane moiety, has been synthesized (Scheme 75) <2004OL1617>. Bullvalene **255** was subjected to ozonolysis, the solution further treated with Amberlyst-15 resin, and the cyclic acetal **256** isolated in 65% yield. Finally, **256** was treated with Lawesson's reagent under sonication, resulting in trithia-[3]-peristylane **257** which was isolated in 25% yield. ^1H and ^{13}C NMR spectra ($\delta = 3.81/61.2$ ppm and $5.46/66.0$ ppm, respectively) and the X-ray structure of **257** revealed the nearly C_{3v} symmetric structure. The helium I photoelectron spectrum of **257** displayed peaks at 8.1, 8.2, and 9.5 eV (assigned to transitions of ionizations from the electron lone pairs on the sulfur atoms) followed by a broad band between 10.1 and 10.4 eV <2004OL1617>.



Scheme 75

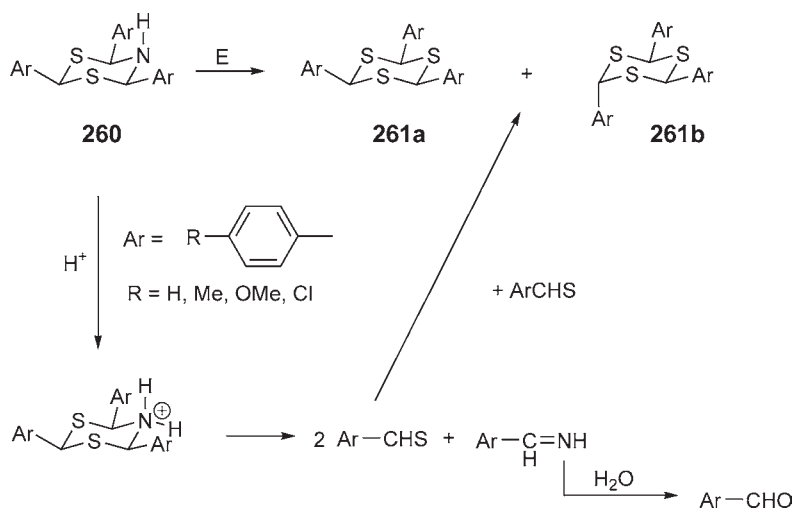
9.11.10 Ring Syntheses by Transformations of Another Ring

Only a few examples of ring syntheses by transformation of another ring have been published. One example is the synthesis of 5-aminomethylene-1,2,3-trithiane **259** from the corresponding 1,3-dithiane derivative **258** <1992MI1623> (Scheme 76). The conformation of the substituent on the 1,2,3-trithiane ring, however, was not determined.



Scheme 76

It was discovered that 2,4,6-triaryl-dihydro-1,3,5-dithiazines **260** react with electrophilic reagents such as *p*-TosOH, CF_3COOH , HCl , $\text{BF}_3 \cdot \text{OEt}_2$, I_2 , ICl , or IBr in inorganic solvents at room temperature to afford the α - and β -isomers of 2,4,6-triaryl-1,3,5-trithianes **261a** and **261b** in good yields (Scheme 77) <1983CL1503>. The 1,3,5-trithiane isomers were formed via ArCHS arising from fragmentation of the N-protonated starting material **260**. In fact, thiobenzaldehyde could be trapped in the presence of 2,3-dimethylbutadiene in acetonitrile at 80°C (Scheme 77).



Scheme 77

9.11.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Reports on the syntheses of six-membered ring systems with three oxygen and/or sulfur atoms are rather limited (compared to the more common analogs with one or two heteroatoms only) and are covered already in [Sections 9.11.9 and 9.11.10](#). Often, only one really successful synthetic path has been described or the derivatives obtained were simply by-products. Thus, the close scrutiny of various synthetic strategies for obtaining certain trioxane/dioxathiane/oxadithiane/trithiane derivatives is not meaningful.

9.11.12 Important Compounds and Applications

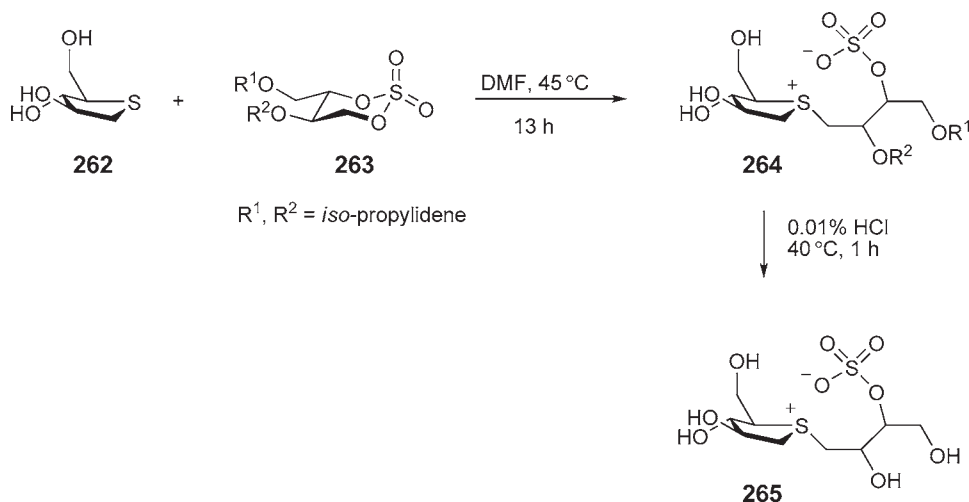
The most important peroxide belonging to the 1,2,4-trioxane family is a natural product, obtained from *Artemisia annua*, which is a very potent antimalarial drug having low human toxicity. The compound, artemisinin, originates from research on traditional Chinese medicinal practice. Its antimalarial activity is associated with the presence of the 1,2,4-trioxane ring in the molecule and, because of this, several efforts have been made to synthesize both it and other structurally variable 1,2,4-trioxane analogs for systematically improving behavioral aspects such as enhancement of aqueous solubility and attenuation of lipophilicity. Both these aspects should be in an optimal range for potent biological activity. Some of the analogs are equally, or even more, potent [\[2006AGE2082\]](#) than the natural product and its derivatives. Also, there has been intensive effort in the elucidation of the peroxide-specific mode of action (*vide infra*). Several reviews [\[2001MI122, 2001MI255\]](#) and a QSAR for the classification and prediction of antibacterial activity of diverse groups of drugs [\[2002JCI869\]](#) have been published. Highly significant models for the prediction of antimalarial activity have been developed from QSAR confirming the role of both molecular hydrophobicity and hydrogen bonding in controlling antimalarial activity.

The direct analysis of artemisinin from *Artemisia annua* L. by HPLC, GC [\[2006JCH\(1133\)254\]](#), and HPLC–ESI–TOF MS (ESI=electrospray ionization; TOF=time-of-flight) [\[2006JCH\(1118\)180\]](#) has been reviewed and a comparative study of assessment technologies for the extraction of artemisinin from the same natural product was published [\[2006JNP1653\]](#).

Derivatives of 1,2,4-dioxathiane, 1,2,4-oxadithiane, and 1,2,4-trithianes have not received such attention, though a few derivatives were synthesized and studied structurally (*vide infra*). 5-(*N,N*-Dimethylamino)-1,2,3-trithiane is by far the most thoroughly investigated representative of the 1,2,3-trithiane series because of its commercial use as an insecticide. The chemical and biological properties of naturally occurring 1,2,3-trithianes were reviewed in 1990 [\[1990SR257\]](#). It should also be mentioned that among the volatile compounds, generated from the thermal degradation of alliin and deoxyalliin (two important nonvolatile flavor precursors present in garlic), alkyl-substituted

1,2,3- and 1,2,4-trithiane derivatives were isolated and analyzed by GC and GC–MS <1994MI281, 1994JFA146, 1988MI223>; the same was reported from the thermal interaction of 2,4-decadienal and the flavor precursors of garlic <B-1994MI61> and from the decomposition of allyl isothiocyanate or phenethyl isothiocyanate <B-1998MI152>.

Salacinol **265**, a new type of α -glucosidase inhibitor isolated from an antidiabetic herb, was synthesized for the first time by the coupling reaction of 1,4-*epi*-thio-D-arabinitol **262** and the 1,3,2-dioxathiane derivative of an erythrol **263** after deisopropylidenation of the intermediate **264** (Scheme 78) <2000TL6615>. In addition, a diastereomer of salacinol was synthesized and the stereochemistry at the sulfonium center was determined to be *S*.



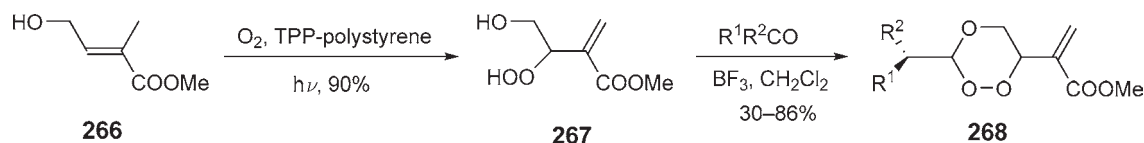
Scheme 78

1,3,5-Trithiane itself has been found among the volatile sulfurous compounds of Shiitake mushrooms extracted from the homogenate of fresh mushrooms <1986JFA830> and 2,4,6-triethyl-1,3,5-trithiane was identified among the flavor compounds in the steam distillate of onions <1992MI459> analyzed by GC and characterized by GC–MS. Other than that, 1,3,5-trioxane derivatives are not found that often in natural products as their sulfur analogs. Only 2,4,6-trimethyl-1,3,5-trithiane has been found among the volatile components of cork used for the production of wine stoppers <1994MI401> and identified by GC–MS analysis as a component of the wine distillate made from Muscat grapes (pisco) <1990JFA1540>.

9.11.13 Further Developments

9.11.13.1 1,2,4-Trioxanes

Photooxygenation of the ester alcohol **266** led to the allylic hydroperoxide **267** which could be converted into a series of 1,2,4-trioxane derivatives **268** ($\text{R}^1/\text{R}^2 = \text{Adamantan}$, cyclo-Hex, cyclo-Pent, Me/Me and Et/H) by BF_3 -catalyzed peroxyacetalization <2006LOC247> (Scheme 79); the adamantane derivatives were characterized by X-ray diffraction and proved to be of moderate antimalarial activity.



Scheme 79

A variety of polymer matrices were studied for their suitability in solvent-free photooxygenation reactions <2006JMOC(A, 251)41> which involve the photochemical activation of O₂ into ¹Δ_g-dioxygen. The reaction was applied to the synthesis of mono- and spirobicyclic 1,2,4-trioxanes.

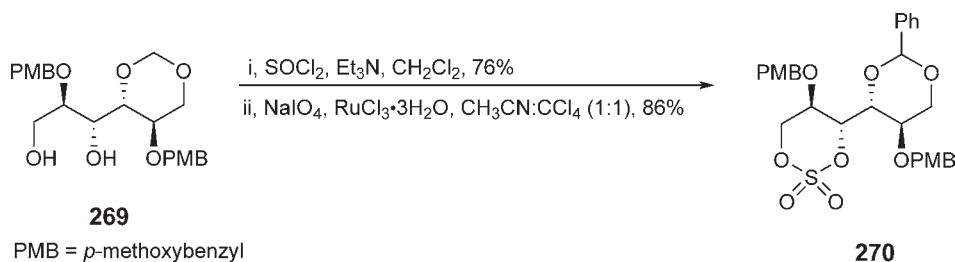
The singlet oxygen ene addition to chiral allylic alcohols and subsequent peroxyacetalization was also applied to the synthesis of diastereomerically pure 3-β-naphthyl-substituted 1,2,4-trioxanes <2006T10615>.

6-(1-Arylviny)-substituted 1,2,4-trioxanes decompose under mild basic conditions to deliver 3-aryl-1-hydroxybut-2-en-2-ones [Ar-C(=CH₂)-C(=O)-CH₂-OH] <2006S3485>; the latter react very efficiently with amines and thiols to give the Michael adducts.

Finally, a review of recent scientific and patent literature on therapeutically promising anticancer 1,2,4-trioxanes derived from artemisinin was published <2006MI1665>.

9.11.13.2 1,3,2-Dioxathiane 2-Oxide and 2,2-Dioxides

The X-ray structure of (4*S*)-4-[(1*S*)-1-(dimethylamino)-2-phenyl-ethyl]-1,3,2-dioxathiane 2-oxide has been published <2006AX(E)0425>; the 6-membered ring forms the chair conformer with the S=O in an axial and the substituent in an equatorial position. Further, the (phenylsulfonyl)difluoromethylation of 1,3,2-dioxathiane 2,2-dioxide derivatives <2007AG(E)786>, the reaction of phosphanes with enantiomerically pure 1,3,2-dioxathiane 2,2-dioxides <2006OM2607> and the coupling reaction of salacinal derivatives with a number of diastereomeric 1,3,2-dioxathiane 2,2-oxides <2006BMC500> were studied, and the cyclic sulfites **270** were synthesized by treatment of the diols **269** with thionyl chloride/triethylamine and subsequent oxidation with NaIO₄/RuCl₃ <2007JOC180> (Scheme 80).



Scheme 80

9.11.13.3 1,3,5-Trioxanes

A number of new technologies for 1,3,5-trioxane production were published <2006SC1927, 2006MI22, 2006MI336, 2006MI70, 2006MI88> and the compound itself employed for the synthesis of diarylmethanes <2006TL2291>, resorcin[4]arenes <2006TL3991> and *para-tert*-butylcalix[8]- and [9]arenes <2007CC975>, 2,4,6-trimethyl-1,3,5-trioxane worked successfully as an acetaldehyde source in the [4+2] benzannulation reaction <2006JOC5249>.

The principal photochemical reaction of the 1,3,5-trioxane radical in freonic matrices at 77 K was studied carefully by ESR spectroscopy <2006MI259>, and the molecular interactions of 2,4,6-trimethyl-1,3,5-trioxane with *n*-alkyl acetates <2006MI1664> and various carbonates <2006JCED69> and of 1,3,5-trioxane in the formaldehyde-water-1,3,5-trioxane mixture <2006MI910> were quantified as well.

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Biographical Sketch



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9.12

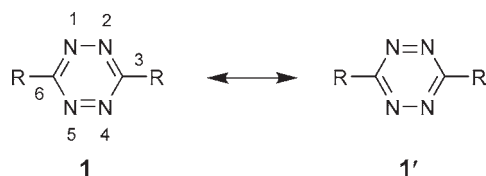
1,2,4,5-Tetrazines

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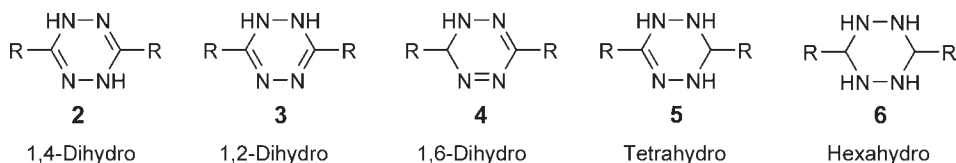
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9.12.1 Introduction

The parent 1,2,4,5-tetrazine (**1**: R = H), for which two degenerate Kekulé structures **1** and **1'** can be drawn, was first synthesised by Hantzsch and Lehmann in 1900 <1900CB3668>.



In addition to the fully unsaturated system **1**, dihydro-1,2,4,5-tetrazines **2–4**, tetrahydro-1,2,4,5-tetrazines **5**, and hexahydro-1,2,4,5-tetrazines **6** are also known.



The literature on 1,2,4,5-tetrazines **1–6** is well documented in CHEC(1984) by Neunhoeffer <1984CHEC(3)531>, in CHEC-II(1996) by Sauer <1996CHEC-II(6)901>, in the *Science of Synthesis* by Bohler <2006SOS(17)585>, and in the *Houben-Weyl Methods of Organic Chemistry* <1998HOU(E9c)870>. Several shorter and annual reviews have been published <1996PHC(8)255, 1997PHC(9)268, 1998PHC(10)275, 1999PHC(11)276, 2000PHC(12)294, 2001PHC(13)296, 2002PHC(14)310, 2003PHC(15)339, 2006SOS(17)585>. Interest in the chemistry of 1,2,4,5-tetrazine derivatives has stimulated research on annelated 1,2,4,5-tetrazines and a review dealing with the chemistry of such species has appeared, covering the period 1981–2000, including information about biological activity and industrial applications <2001JHC541>.

This chapter will describe the new developments in the field of 1,2,4,5-tetrazine chemistry from 1995–2006, with emphasis on theoretical methods, experimental structural methods, synthesis of novel 1,2,4,5-tetrazine derivatives, and applications of 1,2,4,5-tetrazines in organic synthesis.

9.12.2 Theoretical Methods

The Freedericksz transition in the nematic and smectic C phases of 3-*n*-heptyl-6-(4-*n*-hexyloxyphenyl)-1,2,4,5-tetrazine has been studied. In both phases, the threshold voltage and the switching times were measured. In the smectic C phase, two thresholds have been observed which can be explained by an asymmetric chevron structure <1996MH131>.

A coordination-induced switch between the singly occupied and the lowest unoccupied molecular orbitals in 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine has been studied <1996J(P2)1197>. The molecular and electronic states of 1,2,4,5-tetrazine have been studied by vacuum ultraviolet (VUV) absorption, near-threshold electron energy-loss spectroscopy, and *ab initio* multireference configuration interaction (CI) studies. A number of forbidden valence states, both singlet and triplet, together with some Rydberg states have been located <1997CPH(214)191>. The theoretical vertical electronic excitation spectrum of 1,2,4,5-tetrazine has been obtained using the extended similarity transformed equation-of-motion coupled-clusters method compared to previous CASPT2 and MRCI results. In extended-STEOM-CCSD, all types of excitations that occur in *s*-tetrazine, Rydberg transitions, and doubly excited states are obtained in a balanced way from a single calculation. All features in the experimental VUV spectrum up to about 11 eV are assigned to calculated dipole-allowed transitions <2000PCA4553>. The electronic structures of 3,6-diphenyl-*s*-tetrazine, 3,6-bis(4-pyridyl)-*s*-tetrazine, 3,6-bis(3-pyridyl)-*s*-tetrazine, and 3,6-bis(2-pyridyl)-*s*-tetrazine have been investigated by linear dichroism, ultraviolet–visible (UV–Vis) absorption spectroscopy using stretched polyethylene matrices, magnetic circular dichroism spectroscopy, and quantum-chemical calculations. The electronic transitions predicted by time-dependent density functional theory (TD-B3LYP/6-31G* DFT), using molecular geometries determined by X-ray crystallography, are in excellent agreement with the observed transitions <2000CPH(254)135>. In order to gain new insight into the nature of aromaticity and conjugation, a novel procedure for constructing a localized fragment molecular orbital (MO) basis set has been developed by a three-step procedure: (1) attainment of each subcanonical fragment molecular orbital (FMO) basis set from a specific double bond fragment and its fragment molecule; (2) the localization of the canonical FMOs; (3) the superposition of all sublocalized FMO basis sets <2000PCA1736>. An MO multicenter bond index involving $\sigma + \pi$ electron population has been proposed as a measure of aromaticity. It is related both to the energetic and the magnetic criteria. The index is applied to linear and angular polycyclic hydrocarbons with benzenoid rings, to hydrocarbons including nonbenzenoid rings, to monocyclic azines, benzoazines, and other heterocyclic compounds with five-membered rings <2000PCP3381>. *Ab initio* electron-correlated calculations of the equilibrium geometries, dipole moments, and static dipole polarizabilities have been reported for benzene and 12 heteroaromatic six-membered rings including 1,2,4,5-tetrazine. Geometries and dipole moments agree well with available experimental microwave determinations. The polarizabilities are in reasonable agreement with the fragmentary experimental data available. Uncoupled Hartree–Fock (HF) calculations indicate that as much as half of the polarizability comes from the σ -electrons <1996IJQ421>. The effect of using a realistic model for the electrostatic forces on the calculated structures of molecular crystals has been explored by

using atomic multipoles derived from a 6-31G** wave function and tested on 40 rigid organic molecules containing C-, H-, N-, and O-atoms, including nucleic acid bases, azabenzenes, and other simpler molecules. The distributed multipole electrostatic model, plus an empirical repulsion–dispersion potential, was able to reproduce successfully the lattice vectors and available heats of sublimation of the experimental room temperature structure in most cases <1996JPC7352>. *Ab initio*-calculated azole, azine, and benzoazole heats of formation are within 0–4 kcal mol⁻¹ of experimental results for isolobal reaction schemes. The *ab initio* heats of formation have been compared with calculated semi-empirical (modified neglect of diatomic overlap (MNDO), AM1, PM3) heats of formation. It has been found that the MNDO method systematically underestimates all nitrogen heterocyclic heats of formation while the AM1 method overestimates azole and underestimates azine heats of formation. The PM3 method performs well on azoles and benzazoles, but underestimates azine heats of formation. The PM3 method is the most accurate semi-empirical method for calculating nitrogen heterocyclic heats of formation. Correction terms for the semi-empirical azine heats of formation are suggested, which bring semi-empirical values into agreement with experimental results <1997JMT(393)9>. Geometric parameters for 3,6-diphenyl-1,2,4,5-tetrazine and some derivatives have been calculated by MNDO/d, AM1, PM3, and *ab initio* STO-3G methods and compared with X-ray structural analysis <2003MI71, 2004MI68>. Structure and energies have been computed using a density functional procedure B3P86/6-31+G** for six azines, their mononitro derivatives, including 3-nitro-1,2,3,5-tetrazine, and the radicals formed by loss of a hydrogen or a nitro group. Relative stabilities within isomeric groups have been compared, and 20 C–H and C–NO₂ dissociation energies presented. The results are viewed as demonstrating the importance of the electron-attracting powers of the ring nitrogens <1998PCA6697>. To clarify the origin of nonplanarity in π -electron heterocyclic conjugated systems, an energy component analysis has been carried out for the ground states using an *ab initio* multiconfiguration self-consistent field (MCSCF) method with the 6-31++G(d,p) basis set. Inspection of the energy components comprised in the total energy reveals that the type of pseudo-Jahn–Teller stabilization is classified into two groups, one in which the stability of nonplanar structure arises from a lowering of the interelectronic and internuclear repulsion energies and the other in which the stability results from a lowering of the electron–nuclear attraction energy. This distinction in energy changes is accounted for in terms of an expansion or contraction of the molecular skeleton and a proximity among nuclei and the electron clouds owing to a folding of the six-membered ring. The theoretical and structural characteristics for 1,2-dihydro- and 1,4-tetrahydro-1,2,4,5-tetrazines are in good agreement with available experimental facts <2001PCA1334>. ‘Difficult’ reaction barrier with self-interaction-corrected DFT has been examined for closed-shell unimolecular dissociation of *s*-tetrazine <2002JCP7806>. Enthalpies of formation and standard state entropies have been calculated for tetrazine, amino- and nitro-tetrazine, and four extended ditetrazines using DFT programs. The derived values have been corrected with the previously derived supplementary set of four parameters and basic geometric structural features of the minimum-energy states of the tetrazine have been summarized <2002JEM71>.

For some six-membered heterocycles, a number of aromaticity indexes, especially magnetic ones, have been calculated. The tables of correlation coefficient between the individual indexes revealed that mutual relationships between them depend on their composition in the set and that some magnetic characteristics may be orthogonal to others <2004JPO303>. Computational studies, MP2(fc)/6-31-G*, B3LYP/6-31-G*, CCSD(T)/6-31G**//MP2(fc)/6-31-G*, and G3(MP2), have been carried out on stability, homodesmotic ring-opening energies, electron distribution (bond orders and lengths, Bird index), and magnetic ring current for 12 azabenzenes including *s*-tetrazine <2004CJC50>. The concerted cycloaddition reactions between ethylene and azines have been studied extensively. For most of these reactions, there are two or more reaction pathways. Upon obtaining the G3(MP2) barriers for all the possible pathways, it has been found that three factors affect the activation energies of these processes. In general, the pathway with the least disruption of the ring aromaticity is favored <2005JMT(723)195>.

Singlet excited-state geometries of a set of medium-sized molecules, including 1,2,4,5-tetrazine, with different characteristic lowest excitations have been studied with two closely related restricted open-shell Kohn–Sham methods and within linear response to time-dependent DFT (TDDFT). The results are compared to wave function-based methods <2003JMT(630)163>.

Complexes of anions with electron-deficient *s*-tetrazine aromatic rings and other binding units have been studied and compared using both high-level MP2/6-311+G** *ab initio* and molecular interaction potential with and without polarization and molecular electrostatic potential calculations, in order to explore the physical nature of the interactions <2003CPL(370)7>.

Electronic properties related to the semiconductivity of monomers and polymers of phthalocyanoruthenium with bidentate bridging ligands, [PcRu(L₂)] and [PcRu(L)]_n, have been investigated using density functional calculations (L = pyrazine, triazine, tetrazine, etc.) <2001JMT(579)169>. The electronic structures of one-dimensional

metallomacrocycles with bidentate bridging ligands, such as $[\text{MacM}(\text{L})]_n$, have been studied using the tight-binding solid-state extended Hückel <2001JMT(543)23>. A series of dinuclear copper (I) complexes with azo or tetrazine bridge ligands have been studied by different density functional methods <2006PCA4021>. The geometrical structure, force fields, and parameters of vibrational-rotational interactions of six-membered azacyclic compounds, including *s*-tetrazine, in the ground and excited states have been estimated using the structural dynamic model of a polyatomic molecule <1997MI227, 2003PCA248>.

The accuracy and reliability of the CIS(D) quantum-chemical method and a spin-component-scaled variant (SCS-CIS(D)) have been tested for the calculation of 0-0 excitation energies of organic molecules (CIS(D) = configuration interaction with single and double excitations). The ground and excited state geometries and the vibrational zero-point correction were taken from (TD)DFT-B3LYP calculations. In total, 32 valence excited states of different character were studied <2004CPH(305)223>.

The complex polarization propagator method has been applied to the calculations of dipole-dipole dispersion coefficients of pyridine, pyrazine, and *s*-tetrazine. These calculations refer to the electronic ground states as well as the first excited states of $\pi \rightarrow \pi^*$ character <2004MI321>. Calculations of static and dynamic polarizabilities of excited states by means of DFT have been performed <2004JCP9795>.

A BKW equation of state in a one-dimensional hydrodynamic simulation of the cylinder test can be used to estimate the performance of explosives. Using this approach, the novel explosive 3,6-diamino-1,2,5,6-tetrazine 1,4-dioxide has been analyzed <B-1995MI378>.

A similarity-transformed equation-of-motion coupled-cluster (STEOM-CC) study of excited states <1997JCP6812> has been applied to calculate the vertical excitation spectra and various 0-0 transitions of selected azobenzenes <1999SAA539>.

A comparative study has been performed on electronic spectra of tetrazine, using on one hand density functional linear response theory and on the other multifunctional second-order perturbation theory, in order to establish the accuracy that the density functional-based methods can give for excitation energies and energy surfaces for excited states <1999MP859>.

The ground and first excited states of *s*-tetrazine have been studied using the complete active space self-consistent field (CASSCF) and the second-order multiconfigurational perturbation theory (CASPT2) *ab initio* methods <1995JCP7048>.

The vertical electronic spectrum of *s*-tetrazine has been studied using multiconfigurational wave functions and second-order perturbation theory to include effects of dynamic electron correlation. In all, 47 excited states have been characterized, comprising both valence (singlet and triplet) and Rydberg states <1999MP603>. A series of equation-of-motion coupled-cluster (EOM-CC) calculations of the vertical excitation energies of *s*-tetrazine have been performed. Single and double excitations have been included fully, and a noniterative approximation has been used to estimate triple excitation effects <1996JCP9859, 1997JCP6051>. Vertical ionization energies have been calculated with partial third-order electron-propagator theory. Extensive reordering of final states is produced by correlation corrections to Koopman's theorem results <1996JCP2762>. Spin-restricted open-shell coupled-cluster theory of excited states has been extended to the treatment of excited states of high-spin-open-shell molecules <2000JCP4027>. Single-reference coupled-cluster singles and doubles theory has been combined with low-order perturbation theory to treat ground-state electron correlation <1999JCP10815>. The implementation of the linear response function for singlet excited states for the coupled-cluster models CCs, CC2, and CCSD is based on the derivation of excited-state response functions as derivatives of excited-state quasi-energy Lagrangians <1998JCP9237>. The diagonalization manifold in STEOM-CC theory has been extended to include doubly excited determinants <2000JCP494>. Static polarizabilities, polarizability anisotropies, second hyperpolarizabilities, and an analysis of the vibrational effects for these polarizabilities of azabenzenes, including *s*-tetrazine, have been calculated in the frame of DFT <2000JCP6301>. The structure and energetics of van der Waals complexes of argon with azabenzenes, including *s*-tetrazine, using the second-order Möller-Plesset perturbation theory combined with a well-balanced basis set <2005JCP154302>, and van der Waals vibrational states and the structure of vibronic spectrum have been studied by *ab initio* methods <2006JCP044310>. Rotational distribution following van der Waals molecule dissociation has been measured <2005JCP074311>. *Ab initio*, second-order, Möller-Plesset perturbation theory calculations of quadrupole and octupole moments have been reported for 36 different monocycles, including 1,2,4,5-tetrazine, with good agreement with the limited experimental and computational data available <1999PCA10009>.

The linear and nonlinear optical properties of donor-acceptor π -electron chromophores having conjugated bridges varying in aromaticity and electron excessivity have been investigated using intermediate neglect of differential overlap (INDO/1) semi-empirical Hamiltonian methods <1997JA6575>.

Potential energy surface, van der Waals energy spectrum, and vibronic transitions in an *s*-triazine–argon complex have been studied by *ab initio* methods <2006JCP044310>.

Quasi-particle P3 calculations produce better accuracy than outer valence Green's function (OVGF). An application of the photoelectron spectrum of *s*-tetrazine illustrates the ability of the P3 method to predict correct final-stage orderings <1997IJQ291>.

Quadratic response theory in combination with self-consistent field (SCF), MCSCF, and coupled-cluster electronic structure methods have been used for calculation of excitation energies and transition dipole moments between excited electronic states <2000PCP5357>. The excited state polarizabilities for *s*-tetrazine are given by the double residues of the cubic response functions <1997CPH(224)201>.

Linear optical and SHG coefficients of a number of 'push-pull' porphyrins have been analyzed using a semi-empirical INDO/screened approximation (INDO/S) Hamiltonian and singles-only CI. The results suggest strongly that large nonlinear optical (NLO) responses may be obtained by (1) minimizing the dihedral twist of phenyl substituents with respect to the porphyrin plane and (2) replacing the homoaromatic phenyl ring by electron-excessive or -deficient heteroaromatic rings such as pyrrole or tetrazine <1998CM753>.

The utility of a frozen-density embedding scheme within DFT for the calculation of solvatochromic shifts has been reported <2005JCP094115>. *Ab initio* calculations of spin–spin coupling constants have been carried out for a series of five- and six-membered heterocyclic compounds, including 1,2,4,5-tetrazine, using both equilibrium experimental X-ray structures and molecular mechanics optimized structures. The relationship between neighboring atom electronegativities, net charges on the carbon atoms, bond orders, and the magnitudes of $^1J_{C-H}$ have been investigated. The 4-31G and 6-31G basis sets have been found to be adequate to reproduce the general trends in $^1J_{C-H}$ <1995JMT(339)245>.

Harmonic and anharmonic frequencies of *s*-tetrazine have been compared using the B3LYP density functional method and medium-size basis sets <2004PCA4146> and DFT with the B97-1 exchange–correlation functional and a triple- ζ plus double polarization (TZ2P) basis set <1996JPC6973, 2004PCA3085>.

Vertical and adiabatic excitations of the *s*-tetrazine molecule, small clusters with water molecules, and a single *s*-tetrazine molecule within 60 water molecules using periodic boundary conditions have been studied using DFT-based methods <2004PCA2044>.

TDDFT has been applied to calculate vertical excitation energies of *s*-tetrazine, both in the gas phase and in aqueous solution. Results in the gas phase show that the model density functional (PBE0) provides accurate excitation both to valence and to low-lying Rydberg states. At the same time, the experimental solvent shifts in aqueous solution are well reproduced when the solute and the first solvation shell are embedded by a continuum solvent <2000CPL(330)152>.

For the *s*-tetrazine–water cluster, a linear orthodox hydrogen-bond arrangement is predicted in both ground and excited states with small structural and energetic differences, and a bifurcated hydrogen-bond isomerization is anticipated. For the *s*-tetrazine–water solution, a mixture of two hydrogen-bonding arrangements has been found in both ground and excited states, resulting in small magnitudes of absorption and fluorescence solvent shifts <2004JCC1487>.

Electronic structure aspects related to the semiconducting properties of monomers and polymers of phthalocyanoirone with bidentate bridging ligands, $PcFe-L_2$ and $[PcFe(L)]_n$, have been investigated from density functional calculations (L = pyrazine, triazine, tetrazine, etc.) The following results have been obtained: (1) an energy analysis in terms of electrostatic interactions, Pauli repulsions, and occupied/virtual orbital interactions shows that the Pauli repulsion is the origin that the axial ligands (L) prefer to be located toward the aza positions of the macrocycle; and (2) the intrinsic semiconducting properties depend on the frontier band. The valence band is composed largely by the transition metal d_{xy} orbital. The conduction band in tetrazine is composed of π^* -orbitals <2001IJQ170>.

9.12.3 Experimental Structural Methods

9.12.3.1 X-Ray Diffraction

Characteristic features of the molecular geometry and electron density distribution in the crystals of 3,6-dimethoxy-1,2,4,5-tetrazine and 3-phenyl-1,2,4,5-tetrazine have been studied by X-ray structural analysis and quantum-chemical (RHF and MP2) and molecular mechanics (MM3) calculations. An unusual shift of the maxima of the deformation

electron density from the N–N bonds toward the center of the heterocycles was found, which may be interpreted as a ‘bending’ of the corresponding bonds. This ‘bending’ was confirmed by calculations of characteristics of the electron density distribution within the multiple model [<1995IZV2337>](#). In *trans*-3,6-dibenzyl-1,2,4,5-tetrazine with crystallographic inversion symmetry, there is an angle of 84.73(4)° between the phenyl and tetrazine planes. Close contacts between H-atoms on each phenyl group with the phenyl ring in adjacent molecules (3.353 and 3.382 Å) give rise to weak layers parallel to the *bc* plane, but there are no intermolecular π -interactions [<2002AXEo699>](#). In 3,6-di-2-pyridyl-4-[(2-pyridyl)carbonyldiazenyl]-(2-pyridyl)methyl-1*H*-1,2,4,5-tetrazine, the tetrazine ring adopts a boat conformation. The structure is stabilized by strong intramolecular and weak intermolecular N–H···N hydrogen bonds [<2001AXEo1237>](#). 3,6-Di-2-pyridino-1,2,4,5-tetrazine diperchlorate has a crystallographic center of symmetry. The pyridinium ring makes a dihedral angle of 26.4(3)° with the mean plane of the central 1,2,4,5-tetrazine plane. The perchlorate anions link the cations to form a chain structure through C–H···O close contacts and N–H···O hydrogen bonds [<2001AXEo127>](#). 3,6-Bis(3-pyridyl)-1,2,4,5-tetrazine forms with trimesic acid a hydrogen-bond-mediated self-assembly, which generates one-dimensional multicompartmental arrays in the solid state. The directional intermolecular hydrogen bonding between 3,6-bis(3-pyridyl)-1,2,4,5-tetrazine and trimesic acid molecules uses O–H···N and C–H···O interactions, together with intramolecular C–H···N hydrogen bonding, to build up the one-dimensional network structure [<2005MCL147>](#). Despite the demands of stronger hydrogen-bonding interactions present in the crystal structures of 6,6'-diphenyl-3,3'-bi-1,2,4,5-tetrazine and 6-phenyl-1,2,4,5-tetrazine-3-carbaldehyde benzoylhydrazone monohydrate, T-shaped and shifted π -stacked arrangements of aromatic moieties are preferred, leading to herringbone and/or π -stacked crystal-packing motifs. In both these compounds, the crystal packing is in accordance with the theory of arene–arene interactions being dominated by electrostatics [<1996AXC936>](#). The nature and the energy of the intermolecular bifurcated N–H···N hydrogen bond in the crystal of 3-amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine were studied by analyzing the electron density distribution based on X-ray diffraction data. In contrast to two-center hydrogen bonds, the total energy of the N–H···N interaction is virtually independent of the geometric parameters of two contacts and is determined only by the nature of the interacting atoms [<2005RCB924>](#).

3,6-Bis(2-chlorophenyl)-1,4-dihydro-1,2,4,5-tetrazine forms a chain-like structure in the solid state, stabilized by N–H···N and N–H···Cl hydrogen bonds. A contribution from weak interactions to the strong hydrogen-bond network is observed [<2004AXCo57>](#). In 3,6-di(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine [<1996AXC1841>](#), *N*-(2-methoxyphenyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1-carboxamide [<2006MI103>](#), 3,6-diethyl-*N,N'*-bis(3-methylphenyl)-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxamide [<2004AXEo1065>](#), 3,6-dipropyl-*N,N'*-di-*o*-tolyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxamide [<2005AXEo1622>](#), 1-acetyl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine [<2004JCX207>](#), 3,6-diphenyl-1,4-bis(*p*-tolylsulfonyl)-1,4-dihydro-1,2,4,5-tetrazine [<2005AXEo1026>](#), 1-isobutyl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine [<2004JCM408>](#), 1-isobutyl-3,6-bis(4-chlorophenyl)-1,4-dihydro-1,2,4,5-tetrazine [<2005AXEo3276>](#), ethyl 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1-carboxylate [<2005AXEo1637>](#), propyl 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1-carboxylate [<2005AXEo2431>](#), diethyl 1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate [<2005AXEo3664>](#), and 11 1-acyl 3,6-disubstituted-phenyl-1,4-dihydro-1,2,4,5-tetrazines, prepared from the corresponding tetrazines and anhydrides or acid chlorides, the central 1,4-dihydro-1,2,4,5-tetrazine ring has a boat conformation and is not homoaromatic. Atoms N-1 and N-4 deviate from the plane of the ring by 0.454 6(33) Å and 0.378 6(33) Å, respectively [<2006MI103>](#).

On the other hand, in dipropyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate [<2003AXEo281>](#) and diphenyl 3,6-bis(4-chlorophenyl)-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate [<2005AXEo1552>](#), the central tetrazine ring adopts a twist conformation, while in 3,6-bis(*p*-chlorophenyl)-1,4-bis(*p*-tolylsulfonyl)-1,4-dihydro-1,2,4,5-tetrazine the tetrazine ring is essentially planar [<2005AXEo3152>](#).

The crystal structures of 3,6-bis(pyridin-3-yl)-1,2,4,5-tetrazine, 3,6-bis(pyridin-4-yl)-1,2,4,5-tetrazine, and 3,6-bis(pyrazin-2-yl)-1,2,4,5-tetrazine have been reported. The packing arrangements of these three compounds are affected by a subtle interplay of competing weak forces, most notably π – π -interactions and C–H···N hydrogen bonding. In most instances, the tetrazine···phenyl/pyridyl interaction is the dominant intermolecular interaction. This is affected by intramolecular torsions which depend upon the precise nature of the tetrazine substituents. Interstack arrangements are controlled by C–H···N interactions [<2003CEO82>](#).

The crystal structures of six 3,6-diaryl-1,2,4,5-tetrazines have been determined and their molecular packing has been compared to the supramolecular architecture observed in related carboxylic acid dimers. In the tetrazines, covalent N–N bonds are considered to replace the intermolecular O–H···O hydrogen bonds of the carboxylic acids. In the system investigated, the covalent six-membered ring of the tetrazine was an appropriate replacement for the carboxylic acid synthon. This apparent interplay between molecular and supramolecular units may have applications in the crystal engineering of new materials (**Figure 1**) [<2003HCA1205>](#).

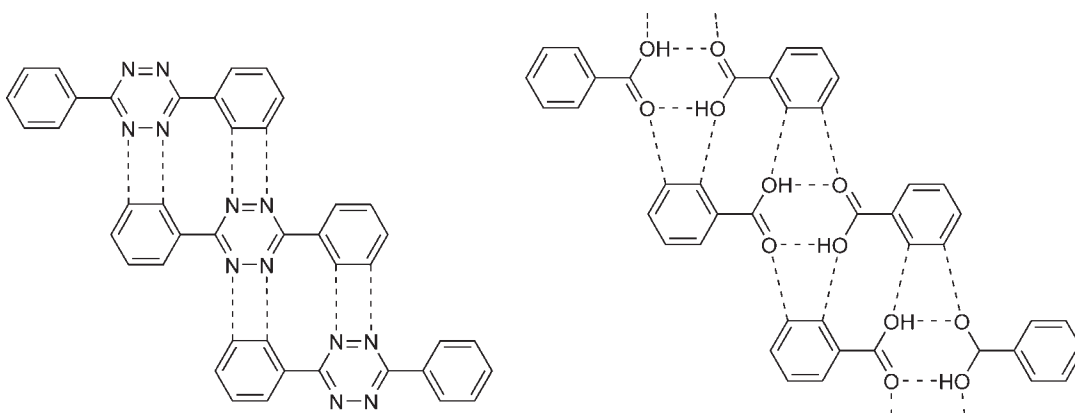


Figure 1

9.12.3.2 Mass Spectrometry

A high-performance liquid chromatographic/atmospheric pressure chemical ionization-mass spectrometric (HPLC/APCI-MS) method has been developed for the determination of the pesticide clofentezine (3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine) in plum-, strawberry-, and blackcurrant-based fruit drinks <1995RCM1441>. The structural characterization and the mass spectrometric behavior of pyridazinofurocoumarins, prepared by the inverse electron demand Diels–Alder reaction between furocoumarinones and 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine, were studied under electron ionization conditions via sequential product ion fragmentation experiments <2004RCM564>.

Broadening and shifts of spectral holes by changing the hydrostatic pressure at 2 K have been measured for 3,6-dimethyl-1,2,4,5-tetrazine probe molecules in durene crystals, both pure and doped with hexachlorobenzene (HCB) at 2 mol%. The HCB molecules act as elastic defects and cause an increase in inhomogeneous broadening as well as the pressure-induced broadening of spectral holes <2002JLU171>. Zero phonon holes have been burned in $S_1 \leftarrow S_0$ absorption bands in organic compounds in an ethanol glass at 6 K. The application of He gas pressure (P) leads to the shift of holes with a frequency coefficient $d\nu/dP$. The mechanisms leading to a matrix-polarity-dependent hypsochromism in *s*-tetrazine correspond to a distance dependence r^{-6} and are deemed to be a multipolar nature <2001PCA9094>. The dependence of frequency, width, and area of spectral holes on pressure has been measured at 1.6 K in the pressure range up to 2.5 MPa for 3,6-dimethyl-1,2,4,5-tetrazine doped with *n*-hexane <1998JCP1830>. An overview of results obtained in isobaric studies of spectral holes in frozen *n*-hexane doped with 3,6-dimethyl-1,2,4,5-tetrazine, along with the theoretical work on the pressure effects, has been described <2001MI221>. The absorption spectrum of *s*-tetrazine in atactic polypropylene has been measured over a range of temperatures for comparison with modeling results, while the information on the geometry and the electronic structure in the ground and excited states was obtained from *ab initio* calculations <1995JA7493>. The electron diffraction patterns of *s*-tetrazine in specific electronic and vibrational states have been calculated for isotropic samples, for molecules that are aligned in high-intensity laser fields, and for orientationally clamped molecules <2003PCA6622, 2004PCA1189>. The time-resolved solvation of *s*-tetrazine in propylene carbonate has been studied by ultrafast transient hole burning <1995JML301>. The spectra of the 0_0^0 bands of *s*-tetrazine and 3,6-dimethyl-*s*-tetrazine in a seeded molecular beam, using optothermal detection, have been reported <1997JCP1318>. 3,6-Dimethyl-*s*-tetrazine in an *n*-heptane lattice has been studied with hole-burning techniques <1996JCP942>. The solvation dynamics of *s*-tetrazine, a nonpolar solute, in propylene carbonate, a polar solvent, have been measured in the temperature range of 190–300 K and the time range 1.5–300 ps by transient hole burning <1995JCP9146>.

Rotational tunneling of monodeuterated methyl groups of 3,6-dimethyl-*s*-tetrazine guest molecules in *n*-octane and tetramethylbenzene crystalline matrices has been characterized by optical spectroscopy, including hole-burning methods <1996JCP9762, 1996MI194>, and quantum-mechanical tunneling involving proton displacement in molecular crystals has been investigated by optical spectroscopy, nuclear magnetic resonance (NMR), and neutron scattering, as well as numerical modeling <B-1997MI(24)369>. The rotational tunneling states of methyl groups are subject to severe symmetry restrictions, which result at sufficiently low temperature in extremely long lifetimes.

These states can be used to store population data and to perform hole-burning experiments. Experiments of this type have been performed with the probe molecule 3,6-dimethyl-1,2,4,5-tetrazine in a series of *n*-alkane host materials <1996MCL97>.

Two-level tunneling systems have been identified in a number of pure and doped molecular crystals. The tunneling dynamics of translation of protons along symmetric hydrogen bonds and hindered rotations of methyl groups has been characterized by a variety of experimental techniques: optical and vibrational spectroscopy, neutron scattering, and proton NMR T_1 relaxation <2002JLU197>. Rotational tunneling of 3,6-dimethyl-1,2,4,5-tetrazine has been investigated by optical spectroscopy, neutron scattering, and numerical modeling with the objective to gain information about the hindering potentials and to test the force field used in the model <1997JLU459>. Pressure-induced shifts of absorption, fluorescence, and phosphorescence lines of organic chromophores embedded in crystalline *n*-alkanes have been measured at 6 K under He gas up to 200 bar. The shifts are reversible (elastic) and linear with the change of pressure P <2003CPH(295)255>.

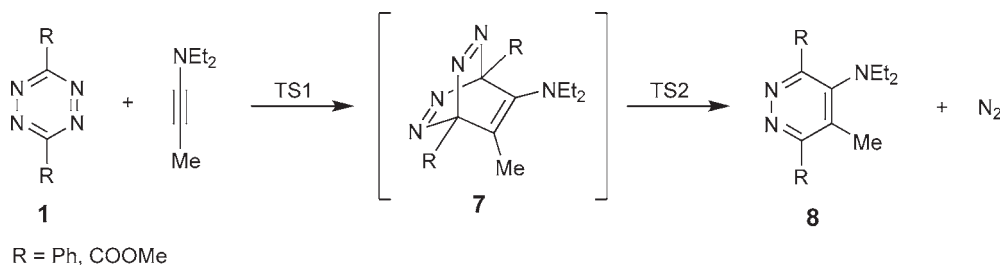
Six symmetrically disubstituted derivatives of *s*-tetrazine have been studied by linear dichroism spectroscopy in the UV-Vis region, magnetic circular dichroism spectroscopy, and theoretical calculations of structures and spectra <1995CPH(200)201>. A detailed discussion of the sensitivity and of the optothermal detection scheme for the study of nonfluorescing excited states of the *s*-tetrazine-argon van der Waals complex has been presented <2000MI183>.

The photoelectron (PE) spectra of tetrahedron 1,2,4,5-tetrazines have been recorded and their conformations have been investigated by *ab initio* SCF calculations. They possess two low-energy conformations, according to *ab initio* HF and Becke3LYP methods. Best results in assigning the ionization potentials have been obtained when the *ab initio* hybrid method Becke3LYP of the density functional has been employed <1997JST(435)157>.

9.12.3.3 Thermodynamic Aspects

The heat capacities of *p*-terphenyl-based crystals that are mixtures with 3,6-diphenyl-1,2,4,5-tetrazine (**1**: R = Ph) have been measured by adiabatic calorimetry below room temperature. The concentration dependence of the apparent entropy of transition for the twist transition of the host *p*-terphenyl crystal shows clearly that the phase transition is of order-disorder <1998MI3359>. Applying the Gaussian 3 (G3) model and its variant G3(MP2) and using the atomization scheme, the heats of formation (ΔH_f) at = K and 298 K have been calculated for 12 monocyclic azines with the general formula $N_n(\text{CH})_{6-n}$, $n = 1-6$. Most of the calculated ΔH_f values are well within $\pm 10 \text{ kJ mol}^{-1}$ of the available experimental data. On this basis, it is concluded that the unfavorable accumulation of component errors found in the Gaussian 2 methods is greatly reduced in the G3 models <2002JSC257>.

Kinetic measurements of the cycloadditions of 3,6-diphenyl-1,2,4,5-tetrazine and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with diethylpropynylamine give $\Delta G^\ddagger = 19.2 \pm 1.0$ and $11.5 \pm 1.2 \text{ kcal mol}^{-1}$, respectively. Stopped-flow UV studies on the reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with diethylpropynylamine show an isosbestic point at 428 nm. This places an upper limit of $11.6 \pm 2.6 \text{ kcal mol}^{-1}$ on $\Delta G^\ddagger$ for loss of N_2 from the putative bicyclic intermediate **7**. Calculations (B3LYP/6-31G(d,p) + ZPVE) of the transition structure for the reaction of 1,2,4,5-tetrazine-3,6-dicarboxylic acid with ethynylamine are consistent with the experimental results for the reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with diethylpropynylamine. This, and several related model systems, reveal two interesting features of the calculated energy surfaces. First, there may be no barrier for the loss of nitrogen from structure **7** and, thus, there may be two sequential transition states (Scheme 1) <2006PCA1288>.



Scheme 1

A new approach to determination of partial rate constants for reactions of conformers has been developed on the basis of constituents of the Gibbs energy of activation for reactions of a series of conformationally heterogeneous substrates. The proposed model allows solving of formal kinetic tasks under conditions of thermodynamic control and in the absence of diastereoisomeric products. The ρ -values and partial rate constants have been determined for the chair and twist conformers of a series of 2-substituted 1,3-dioxacyclohept-5-enes in the model Diels–Alder reaction with 1,2,4,5-tetrazine-3,6-dicarboxylate in two solvents. In dioxane, the chair conformer reacts 3.4 times faster and, in acetone, 1.4 times faster than does the twist conformer <1996RJC477>.

Extensive kinetic studies of normal, neutral, and inverse Diels–Alder reactions observed in [4+2] cycloadditions of some thio- and selenocarbonyl compounds to 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine prove the highly dienophilic activity of the C=S and C=Se bonds. Studies of the solvent and temperature dependence of the reaction rate indicate a concerted mechanism <1998EJO2875>.

Reactions of conformationally nonuniform 2*R*-1,3-dioxacyclohept-5-enes, existing in solution in chair and twist conformations, with 1,2,4,5-tetrazine-3,6-dicarboxylate yield mixtures of diastereomeric products. The diastereoselectivity is influenced significantly by the medium. The maximum selectivity is attained in proton-donor chloroform, and the minimum selectivity in acetone <2000RJC788>.

Pressure and temperature effects on the reaction rate of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with 1-hexene have been investigated. The activation volume ($-26.7 \text{ cm}^3 \text{ mol}^{-1}$, 298.1 K) is in agreement with the conservation of all four nitrogen atoms in the transition state. Densitometry, ^1H NMR, and calorimetric studies of the reaction indicate nitrogen molecule loss by the intermediate just after its formation. Partial molar volumes in acetone of diene (127.2), 1-hexene (127.6), and the resulting adduct ($206.9 \text{ cm}^3 \text{ mol}^{-1}$) have been determined <1999T12201, 1999DOK498>.

The kinetics of the Diels–Alder reactions of di(2-pyridyl)-1,2,4,5-tetrazine with substituted styrenes have been investigated in aqueous media and in organic solvents. The second-order rate constants of this reaction increase dramatically in water-rich media. A decrease in pH accelerates the aqueous Diels–Alder reaction even more. The Hammett ρ -values and also the electronic demand η -values of the reaction are solvent sensitive. In protic solvents, the dipolar character of the activated complex is increased but, simultaneously, hydrogen-bond interactions stabilize the activated complex. These effects are most pronounced in 2,2,2-trifluoroethanol, which shows that the aqueous accelerations cannot be attributed solely to solvent-induced changes of the reaction mechanism <1996JOC2001>.

A theoretical study of the *N*-methylpyrrole cycloaddition reaction with benzene has been performed using the hybrid Becke3LYP/6-31G* DFT method in combination with the AM1 semi-empirical method. The cycloadduct is theoretically transferred to *N*-methylindole, utilizing three different pathways: elimination of acetylene, azomethine addition followed by pyrazole elimination, and the addition of 1,2,4,5-tetrazine, followed by nitrogen and 1,2-diazine elimination. For these three pathways, all the activation energies and the heats of reaction have been evaluated by the Becke3LYP/6-31G*//AM1 theoretical model <1996JMT(370)85>.

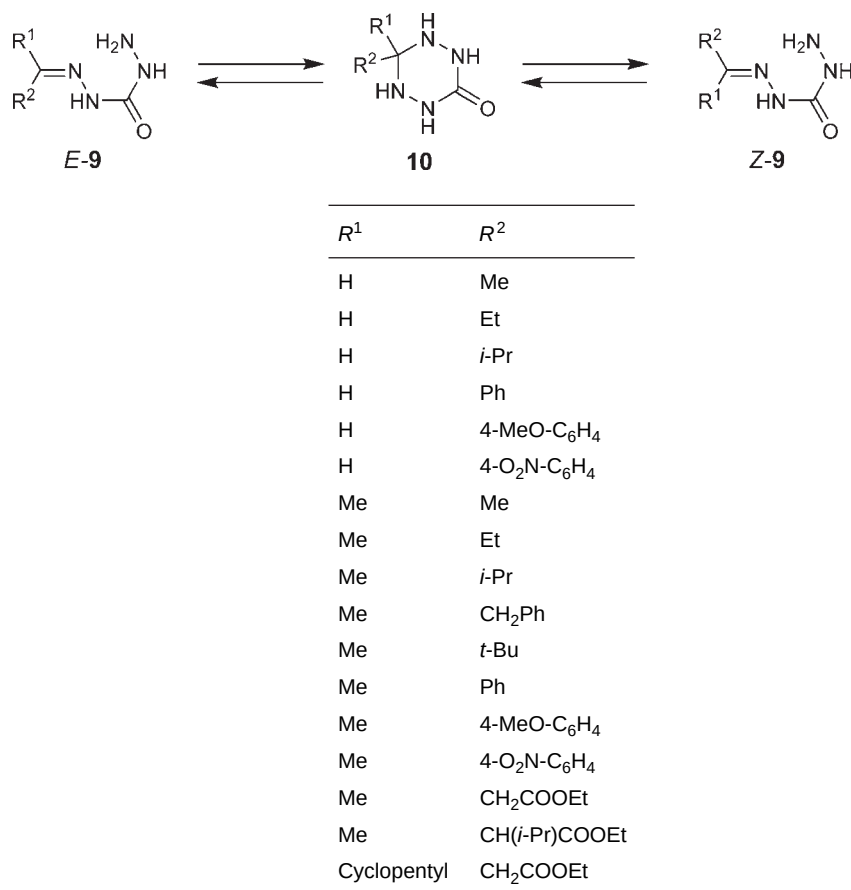
9.12.4 Spectral Characteristics

Using a molecular beam laser spectrometer equipped with laser-induced fluorescence and optothermal detectors, the high-resolution rovibronic spectra of large molecules, such as aniline, tetrazine, and pyridine, were measured. This technique reveals, in a direct manner, the energy transferred to vibrational and rotational degrees of freedom of the ground state after relaxation <1997JPH109>.

9.12.5 Ring–Chain Tautomerism

Monohydrazones **9**, derived from carbonohydrazide and monocarbonyl compounds, exist in solution as tautomeric mixtures of the *E/Z*-hydrazone **9** and hexahydro-1,2,4,5-tetrazine forms **10** (Scheme 2) <1999RJO357>.

In the reaction of 5-hydroxy-3,3,5-trimethylisoxazolidine **11** with derivatives of thiosemicarbazide and thiocarbonohydrazine, 5-thiosemicarbazido(thiocarbonohydrazino)-isoxazolidines **13** are formed. However, ^1H and ^{13}C NMR spectroscopy revealed a tendency of these two types of compounds toward ring–chain and ring–ring conversions in solutions involving the 1,2,4-triazolidine **14** and 1,2,4,5-tetrazine rings **15** (Scheme 3) <2002CHE730>.



Scheme 2

9.12.6 Synthesis of 1,2,4,5-Tetrazines

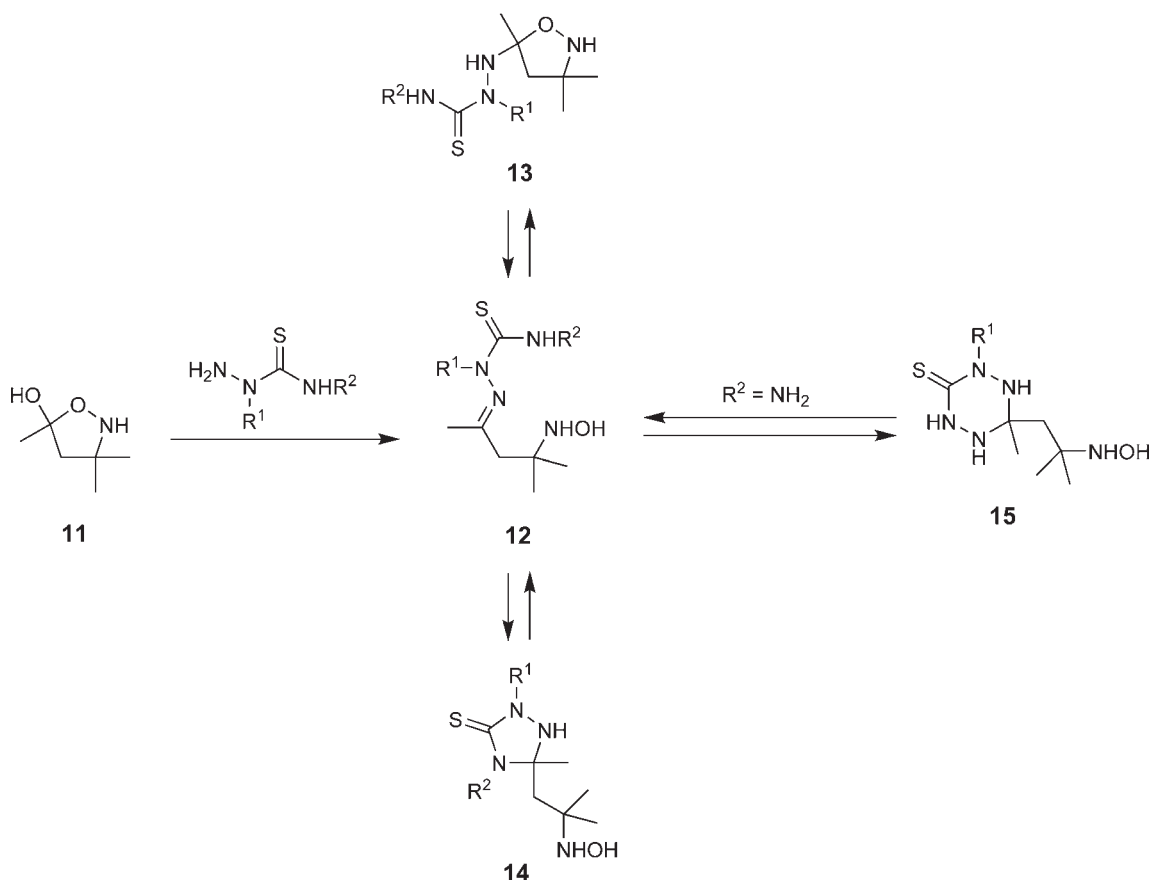
The principal synthetic methods for the preparation of 1,2,4,5-tetrazines, and a summary of the most successful avenues to the heterocyclic system via the dihydro compounds, are described in Neunhoeffer's contribution to CHEC(1984) <1984CHEC(3)531> and Sauer's contribution to CHEC-II(1996) <1996CHEC-II(6)901>. In the meantime, no novel synthetic approach toward the 1,2,4,5-tetrazine system has been published. The discussion in this contribution will focus on the improved synthetic variants, which have been published since 1995.

9.12.6.1 Synthesis of Fully Conjugated 1,2,4,5-Tetrazines

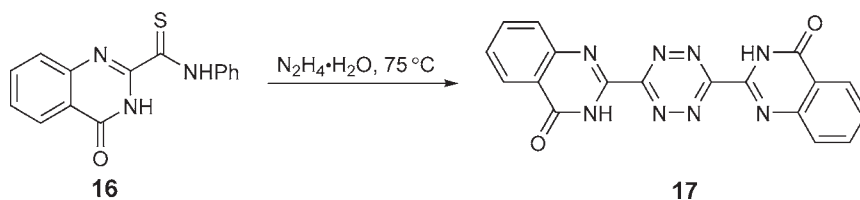
Treatment of 4-oxo-*N*-phenyl-3,4-dihydroquinazoline-2-carbothioamide **16** with hydrazine hydrate led to 2,2'-(1,2,4,5-tetrazine-3,6-diyl)diquinazolin-4(3*H*)-one **17** in 70% yield (Scheme 4) <2004MI3>.

For photochemical studies and investigations on the formation of liquid crystals, 3,6-bis(styryl)-1,2,4,5-tetrazines **21** were prepared in low yields by treatment of cinnamoylhydrazines **18** with Appel reagent in the presence of triethylamine, followed by subsequent oxidation of the intermediate dihydrotetrazines **20** with NBS and air (Scheme 5) <1995JPR641>.

In addition to the previous reports by Huisgen, Sauer, Siedel, and Sturm <1961CB1555, 1962LA146>, some novel examples of thermal transformation of tetrazoles into symmetrical 3,6-diaryl-1,2,4,5-tetrazines have been recently reported. Thus, 3,6-diaryl-1,2,4,5-tetrazines **23–25** were obtained in 41–77% yields by heating 5-aryl-2-trityl-2*H*-tetrazoles **22** in benzonitrile at 150 °C (Scheme 6) <2002RJO1360>.



Scheme 3

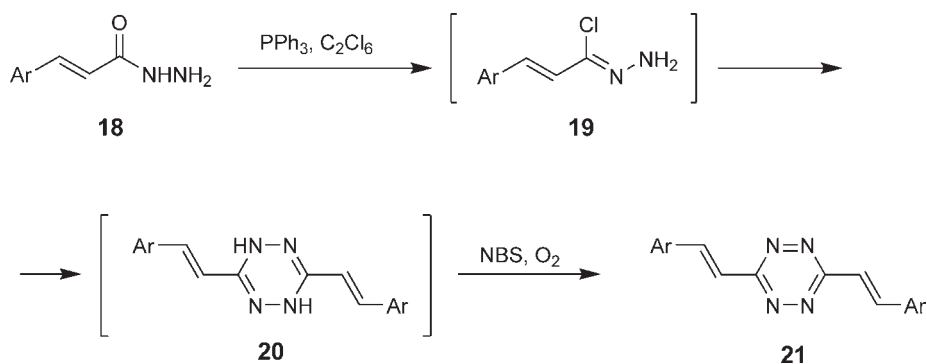


Scheme 4

In order to investigate their electrochemical properties, four novel 1,4-dihydro-1,2,4,5-tetrazines **34–37** were prepared by reacting the corresponding nitriles **26–29** with hydrazine hydrate. Further oxidation of dihydro-1,2,4,5-tetrazines **30–33** with isoamyl nitrite or nitrous acid or hydrogen peroxide gave the fully conjugated compounds **34–37** (Scheme 7) <2003T4761, 2004MI144, 2004NJC387>.

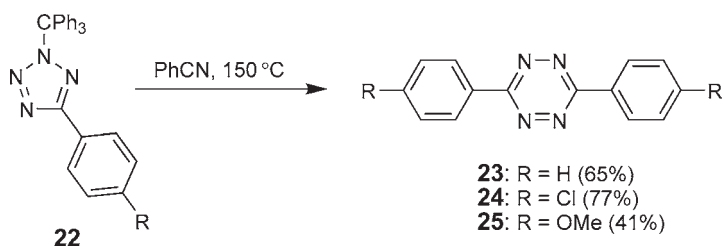
Treatment of *N'*-(benzylidene)benzohydrazonoyl chlorides **38** with titanium tetrachloride in chloroform produced symmetrically substituted 3,6-diaryl-1,4-dihydro-1,2,4,5-tetrazines **2** in moderate yields. The authors suggest that cyclocondensation between two molecules of hydrazonoyl chloride takes place first, followed by elimination of two molecules of an aldehyde during hydrolytic workup. Oxidation of the dihydro-1,2,4,5-tetrazines **2** with nitrous acid afforded the fully conjugated tetrazines **1** in 32–56% yields (Scheme 8) <2000MI37>.

In a similar approach, (3,6-diphenyl-1,2,4,5-tetrazin-1-ium-1-yl)(propyl)amide **43** was obtained in a one-pot reaction by treatment of *N'*-(chloro(phenyl)methylene)benzohydrazonoyl chloride **39** with 1 equiv of sodium azide under phase-transfer conditions, followed by addition of 1 equiv of 1-propanethiol and triethylamine (Scheme 9) <2000JA2087>.



Ar	Yield (%)
Ph	13
4-Hydroxyphenyl	11
4-Dodecylphenyl	7
3,4-Bis(dodecyl)phenyl	7
Pyridin-3-yl	9

Scheme 5



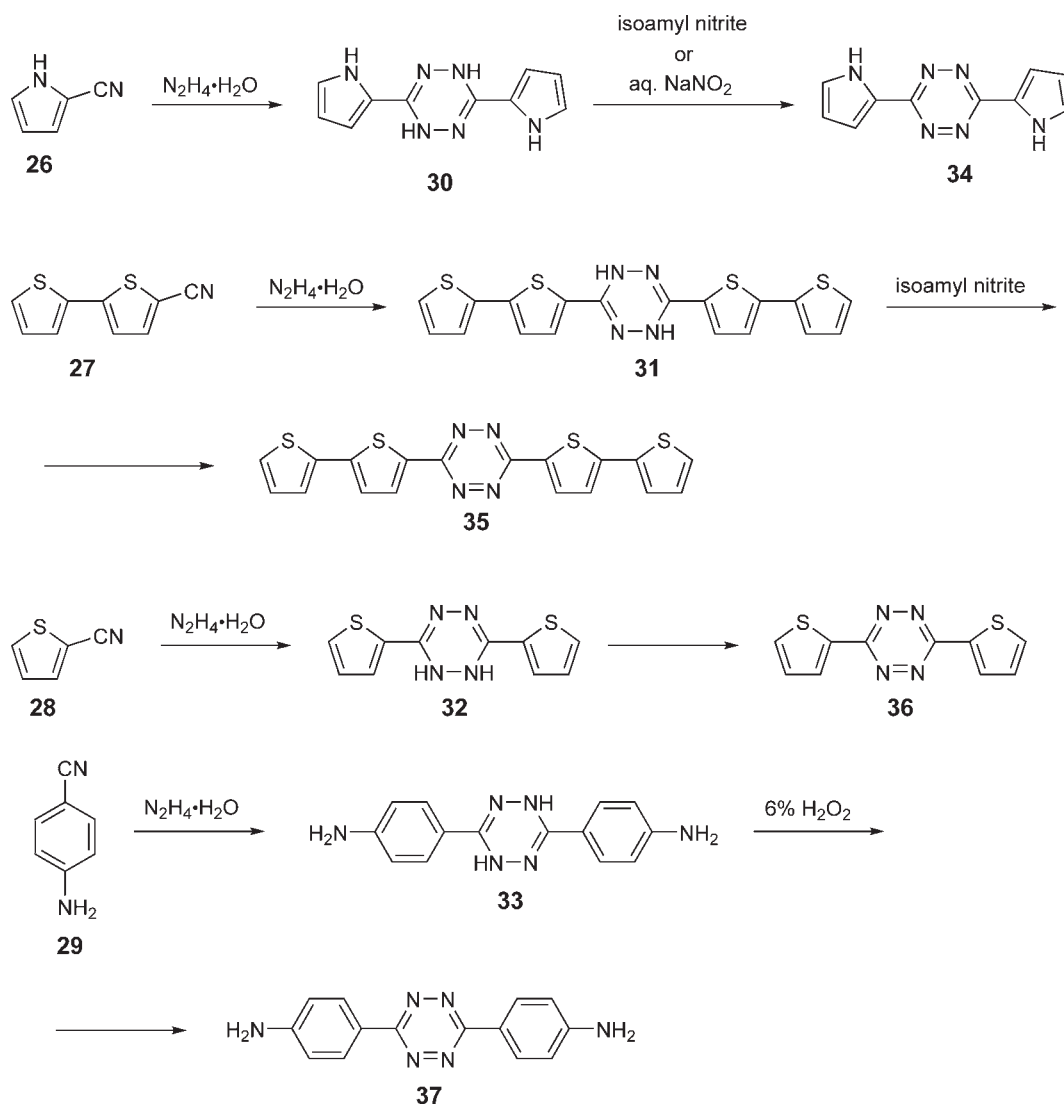
Scheme 6

Recently, Han and co-workers reported a modification of a classical synthesis of 3,6-disubstituted-1,2,4,5-tetrazines **1** from nitriles using an activated catalyst prepared from copper nitrate with excess zinc in the presence of hydrazine monohydrate. It is noteworthy that the corresponding 1,2-dihydrotetrazines **2** were formed as the primary products, which were then air-oxidized during workup to give the fully unsaturated compounds **1** in 20–90% yields (Scheme 10) <1995BK374>.

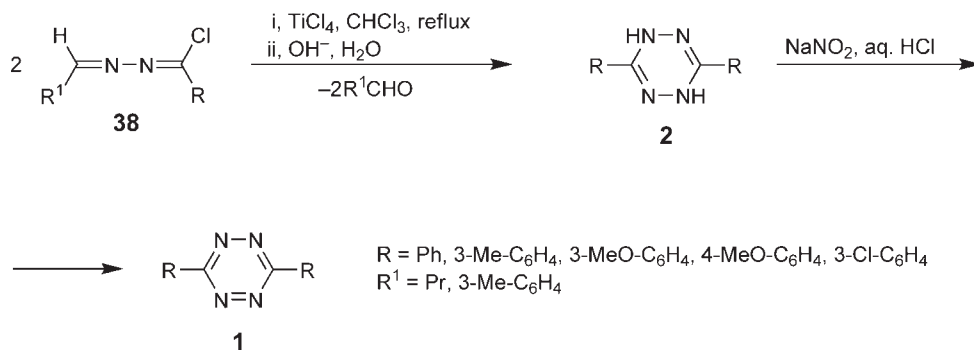
9.12.6.2 Synthesis of Dihydro-1,2,4,5-Tetrazines

Most of the recent preparations of the tetrazine ring have been based on cyclocondensations of nitrile imines with hydrazines and hydrazones. These synthetic studies have been reviewed recently by Farwanah and Awadallah <2005MOL492>.

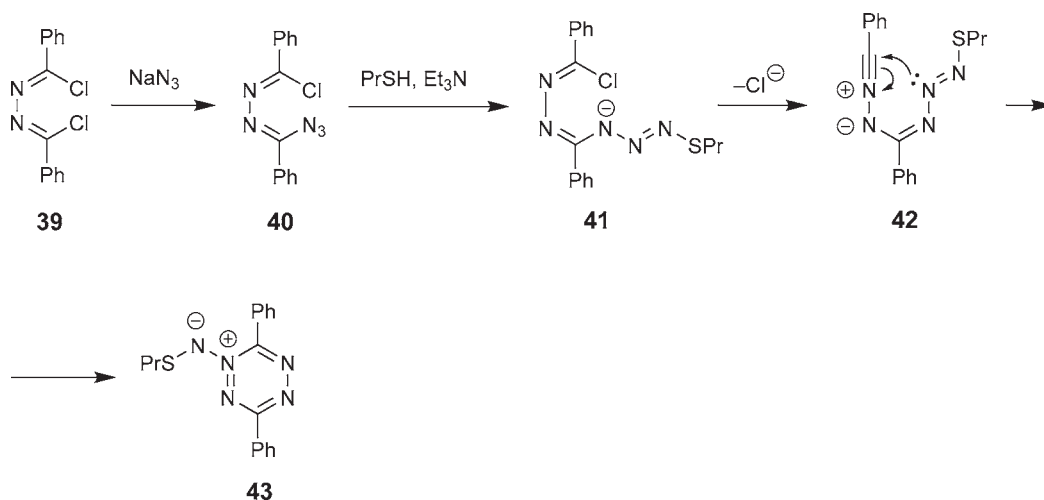
Treatment of hydrazonoyl chlorides **44** with 1,1-disubstituted hydrazines **45** in the presence of a base gave ethyl 1-methyl-2-(1-(2-arylhydrazono)ethyl)hydrazinecarboxylates **47**. Thermal cyclization of **47** in refluxing toluene in the presence of charcoal led to 1,2,3,4-tetrahydro-1,2,4,5-tetrazine derivatives **48** <1998JPR623, 2003HCO307, 2002HCO369, 2003SC1245>. In the case of aldehydes, partial removal of the formyl group also took place to furnish the 1,6-dihydrotetrazines **49** as side products in 22–25% yields (Scheme 11) <2003HCO307, 2003SC1245, 2003ASJ1320>.



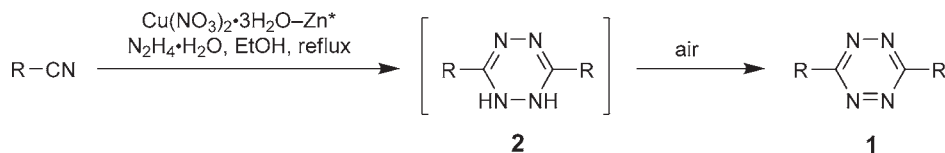
Scheme 7



Scheme 8



Scheme 9



<i>R</i>	Yield (%)
Phenyl	85
3-Methylphenyl	87
4-Methylphenyl	90
4-Bromophenyl	82
4-Chlorophenyl	85
4-Methoxyphenyl	20
Pyridin-2-yl	80
Pyridin-4-yl	87
Benzyl	80

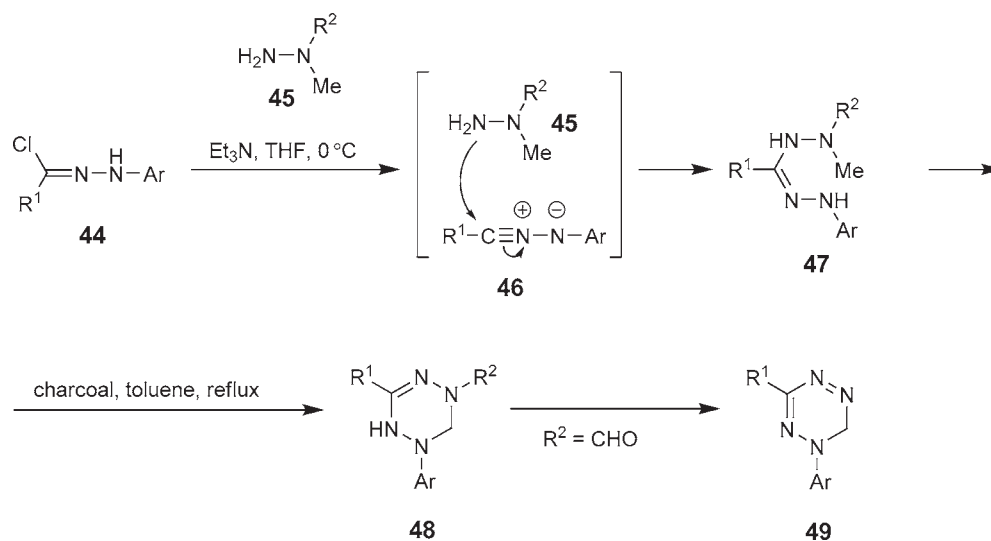
Scheme 10

Under the same conditions as described above, the phenylcarbamoylhydrazonoyl chloride **50** was transformed with *N*-methylhydrazones **51** into the 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **53** (Scheme 12) <2003HCO507, 2002ASJ1225>.

In contrast, reactions of *C*-acylnitrile imines **54** with *N*-unsubstituted and *N*-benzoylated hydrazones **55** gave only the acyclic adducts **56**, which did not cyclize upon heating in the presence of charcoal <2003HCO507, 2003SC243>. However, in the presence of Pd-C, these cyclizations took place at room temperature to give the corresponding 1,6-dihydropyridazines **58** (Scheme 13) <1996JCM174, 2002ASJ1235>.

Head-to-tail dimerization of nitrile imine **60**, formed in the reaction of *N'*-(4-nitrophenyl)furan-2-carbohydrazonoyl chloride **59** with triethylamine <2001JCCS693> or with diethyl phosphite in the presence of potassium carbonate <2006PS683>, afforded tetrazine **61** (Scheme 14).

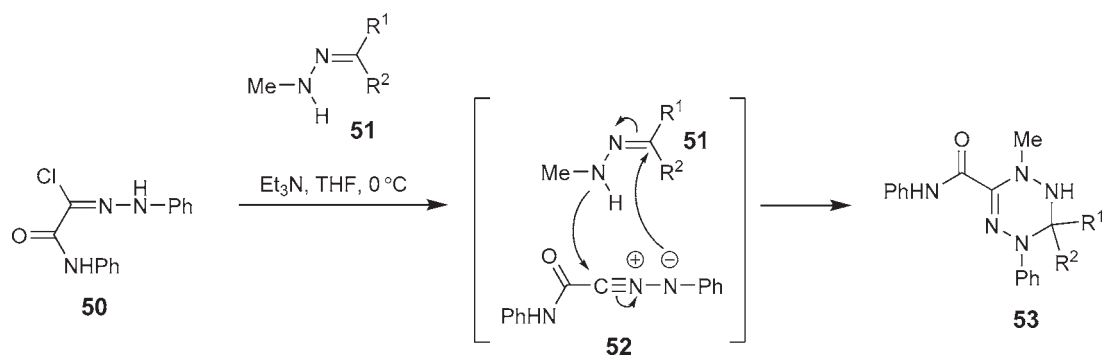
4-Chlorobenzenediazonium chloride underwent smooth coupling with *N*-(benzofuran-2-ylcarbonylmethyl)pyridinium bromide **62** to give the amidrazonium salt **63**. Heating of compound **63** with ammonium acetate in acetonitrile furnished the 1,4-dihydro-1,2,4,5-tetrazine derivative **64** in 60% yield (Scheme 15) <2006AP133>.



R ¹	R ²	Ar	Yield (%)		Reference
			47	48 or 49	
MeCO	COOEt	Ph	80	65	1998JPR623
MeCO	COOEt	4-Fluorophenyl	76	55	1998JPR623
MeCO	COOEt	4-Chlorophenyl	93	60	1998JPR623
MeCO	COOEt	4-Bromophenyl	90	57	1998JPR623
2-Furylcarbonyl	CHO	4-Chlorophenyl	67	34	2003HCO307
2-Thienylcarbonyl	CHO	4-Chlorophenyl	69	35	2003HCO307
2-Furylcarbonyl	COMe	4-Chlorophenyl	71	72	2003HCO307
2-Thienylcarbonyl	COMe	4-Chlorophenyl	72	74	2003HCO307
2-Furylcarbonyl	COOEt	4-Chlorophenyl	76	78	2003HCO307
2-Thienylcarbonyl	COOEt	4-Chlorophenyl	78	77	2003HCO307
PhCO	COOEt	4-Chlorophenyl	76	80	2002HCO369
2-Naphthoyl	COOEt	4-Chlorophenyl	78	85	2002HCO369
MeCO	CHO	4-Chlorophenyl	75	75	2003SC1245
PhCO	CHO	4-Chlorophenyl	70	70	2003SC1245
2-Naphthoyl	CHO	4-Chlorophenyl	75	75	2003SC1245
MeCO	MeCO	4-Chlorophenyl	80	70	2003SC1245
PhCO	MeCO	4-Chlorophenyl	72	75	2003SC1245
2-Naphthoyl	MeCO	4-Chlorophenyl	75	80	2003SC1245

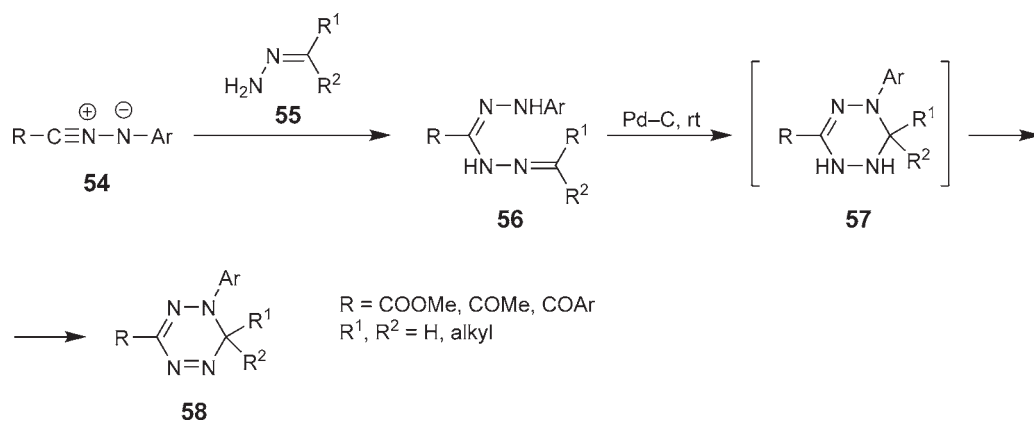
Scheme 11

Recently, Demirbaş reported preparation of 3,6-di[(4,5-dihydro-1,2,4-triazol-1-yl)methyl]-1,4-dihydro-1,2,4,5-tetrazines **2a–e** by heating of equimolar mixtures of ([1,2,4]triazol-1-yl)acetohydrazides **65a–e** and carboxylic acids **66** at 130–140 °C. Formation of 1,2,4,5-tetrazines **2a–e** was quite unexpected, since more stable 1,3,4-oxadiazoles or 1-amino-1,2,4-triazoles could also be formed. However, the hydrazides **65a–e** did not react with the carboxylic acid **66** and underwent cyclocondensation with another molecule of hydrazide **65a–e**, respectively, to furnish the corresponding tetrazines **2a–e** (Scheme 16) <2004MI311>.

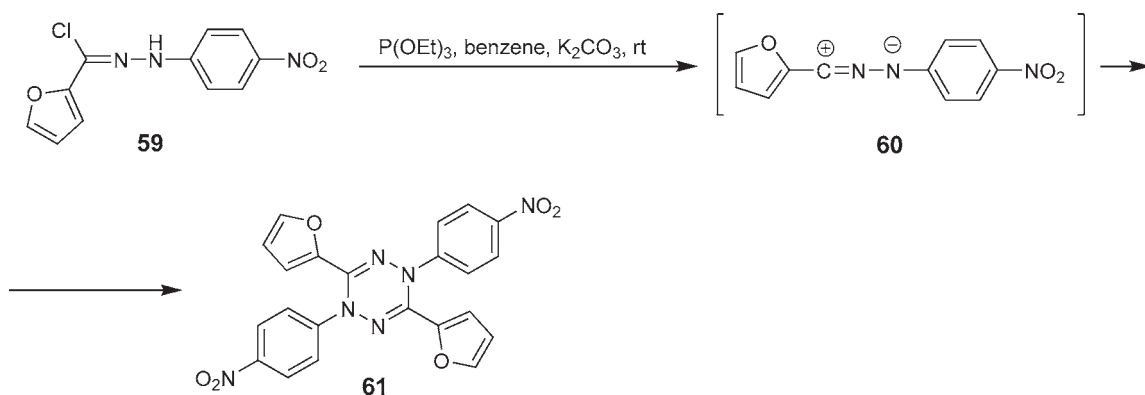


R^1, R^2	R^3	Yield (%)	Reference
Me, Me	PhNH	80	2003HCO507
$-(CH_2)_4-$	PhNH	76	2003HCO507
$-(CH_2)_5-$	PhNH	82	2003HCO507
$-(CH_2)_2CH(\text{Me})(CH_2)_2-$	PhNH	80	2003HCO507
$-(CH_2)_2CH(t\text{-Bu})(CH_2)_2-$	PhNH	79	2003HCO507
$-(CH_2)_6-$	PhNH	75	2003HCO507
$-(CH_2)_7-$	PhNH	73	2003HCO507
Me, Me	Ph	83	2002ASJ1225
$-(CH_2)_4-$	Ph	85	2002ASJ1225
$-(CH_2)_5-$	Ph	87	2002ASJ1225
$-(CH_2)_6-$	Ph	82	2002ASJ1225
$-(CH_2)_7-$	Ph	80	2002ASJ1225
Me, Me	2-Naphthyl	85	2002ASJ1225
$-(CH_2)_4-$	2-Naphthyl	88	2002ASJ1225
$-(CH_2)_5-$	2-Naphthyl	90	2002ASJ1225
$-(CH_2)_6-$	2-Naphthyl	83	2002ASJ1225
$-(CH_2)_7-$	2-Naphthyl	82	2002ASJ1225

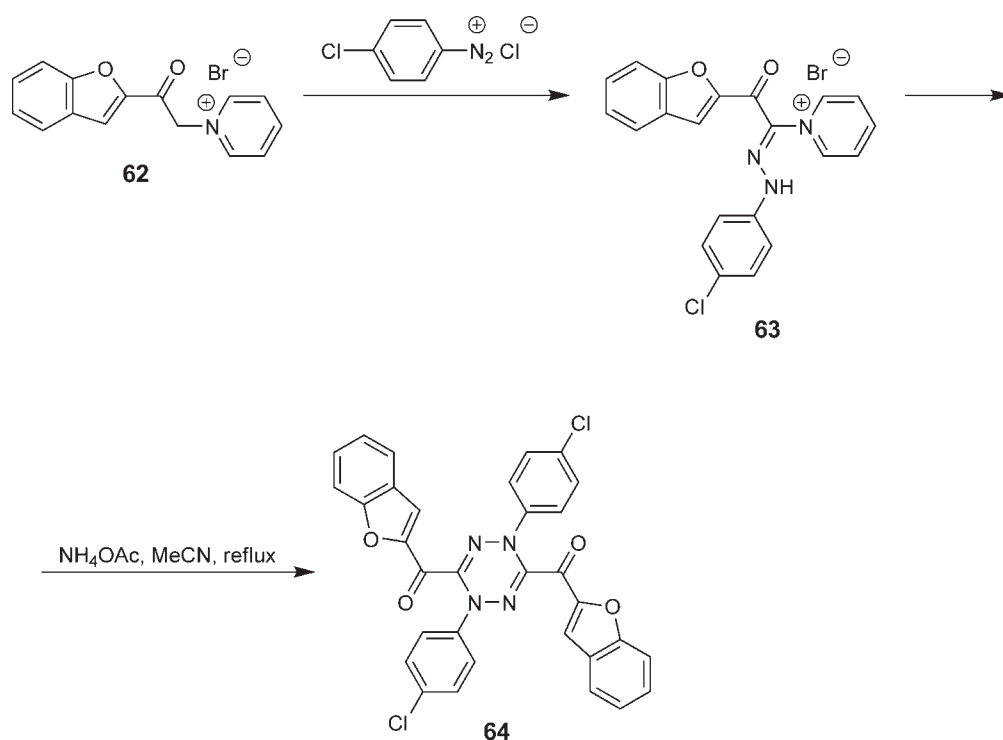
Scheme 12



Scheme 13



Scheme 14

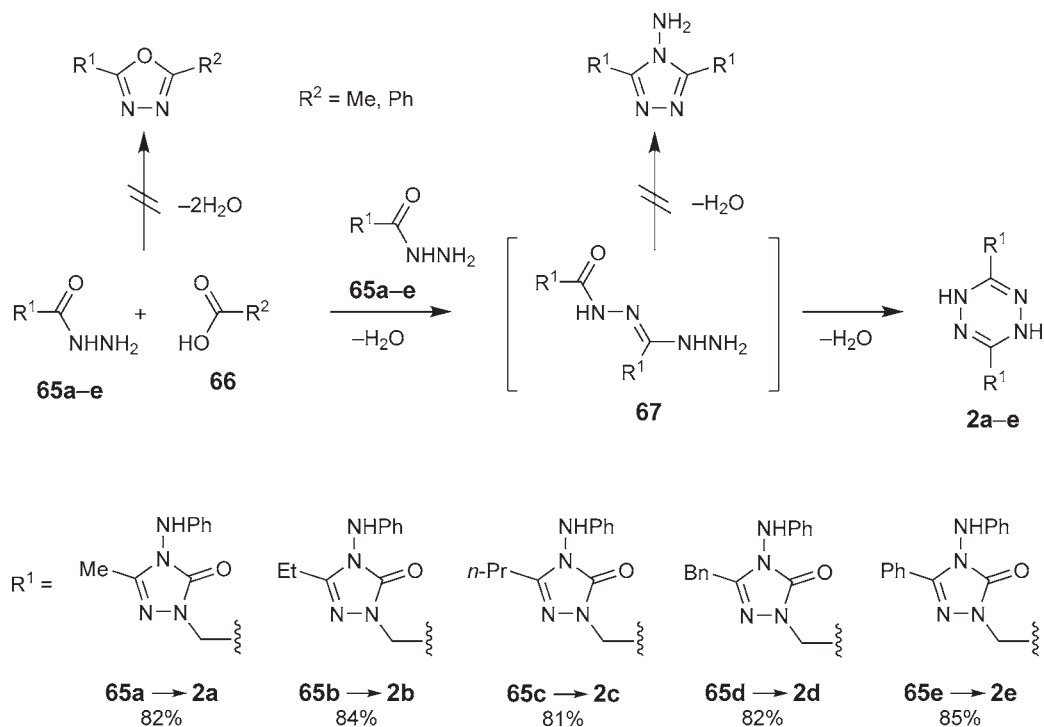


Scheme 15

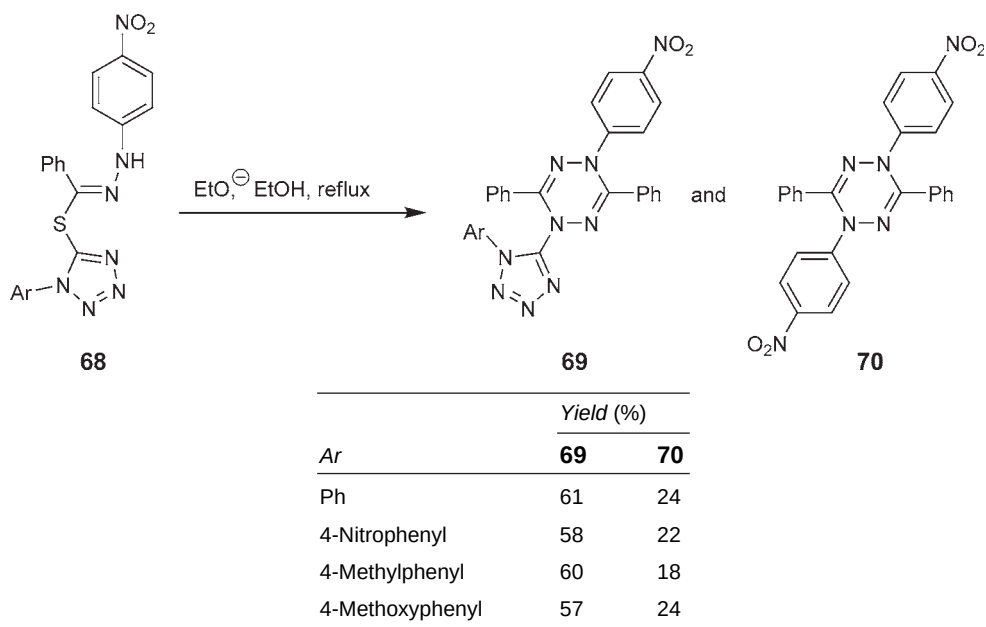
Unsymmetrically substituted 1,4-dihydropyridazines **69** and **70** were obtained as the major products in 18–61% yields upon treatment of benzothiohydrazonates **68** with sodium ethoxide in ethanol (Scheme 17) <1995JCM224>.

Oxidation of *N*-phenyl-2-(arylcabamothioyl)hydrazinecarboxamides **71** and benzyl *N*-aryl-2-(phenylcabamoyl)-hydrazinecarbimidothioates **73** with bromine in water-moistened chloroform resulted in the formation of 1-aryl-2-phenyl-6-thioxo-1,2,4,5-tetrazinan-3-ones **72** and 6-(benzylthio)-5-aryl-4-phenyl-4,5-dihydro-1,2,4,5-tetrazin-3(2*H*)-ones **74**, respectively (Scheme 18) <1998IJH173>.

Heating a mixture of 2-cyano-*N*-(4-ethoxyphenyl)-3,3-bis(methylthio)acrylamide **75** and thiocarbazate **76** at 100 °C furnished 2-cyano-*N*-(4-ethoxyphenyl)-2-[6-thioxo-1,2,4,5-tetrazin-3(6*H*)-ylidene]acetamide **77** in 70% yield (Scheme 19) <2005JCCS553>.

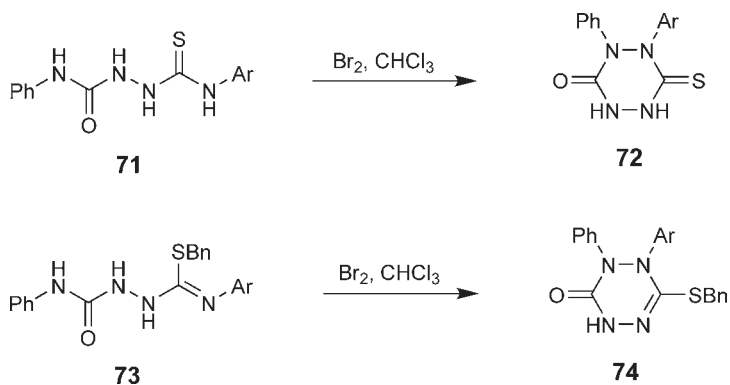


Scheme 16

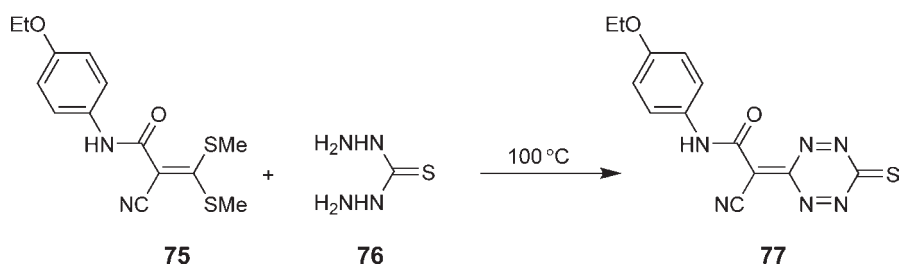


Scheme 17

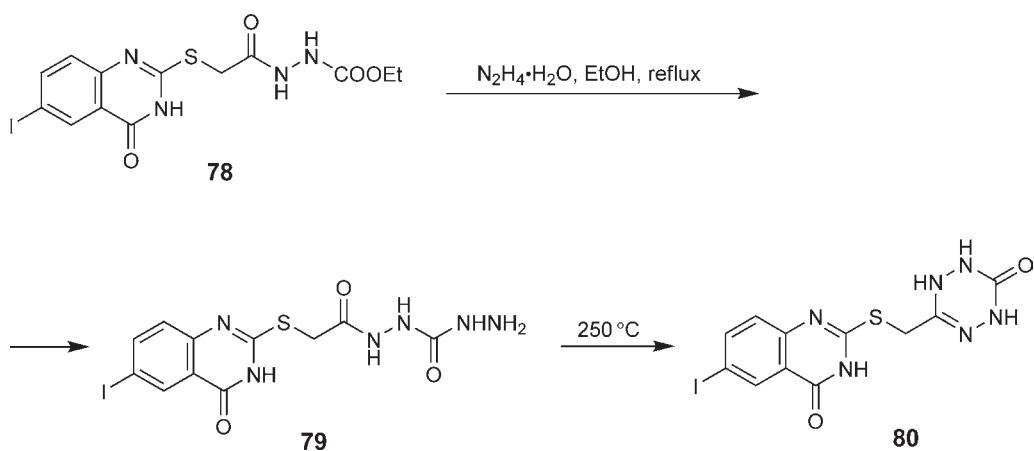
Treatment of ethyl 2-[2-(6-iodo-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetyl]hydrazine-carboxylate **78** with hydrazine hydrate in refluxing ethanol afforded the carbazate **79** in 70% yield. Further heating of **79** at 250 °C gave 6-iodo-2-((6-oxo-1,2,5,6-tetrahydro-1,2,4,5-tetrazin-3-yl)methylthio)quinazolin-4(3*H*)-one **80** in 68% yield (Scheme 20) <1998PS57>.



Scheme 18



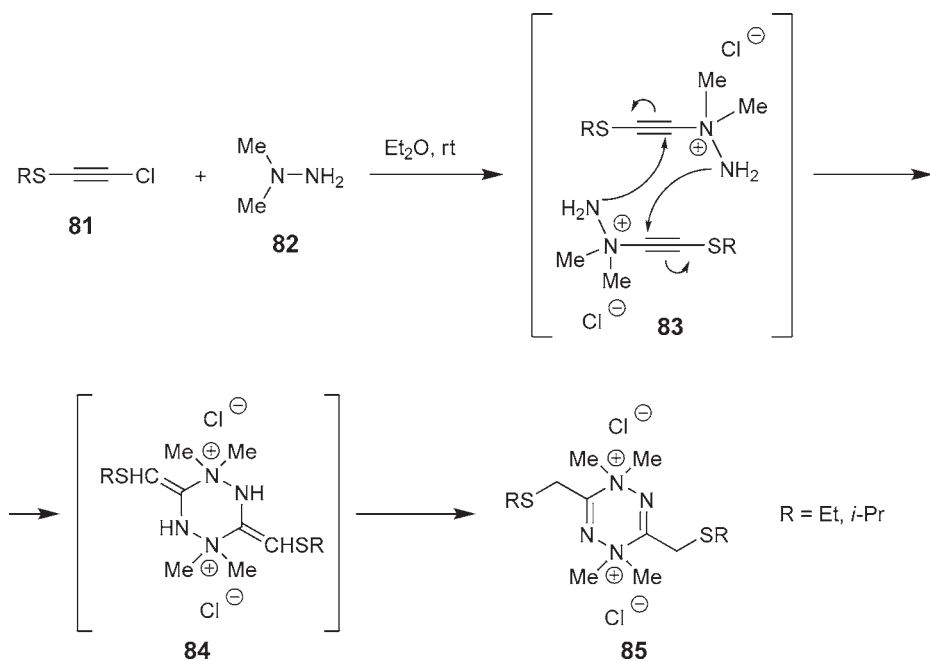
Scheme 19



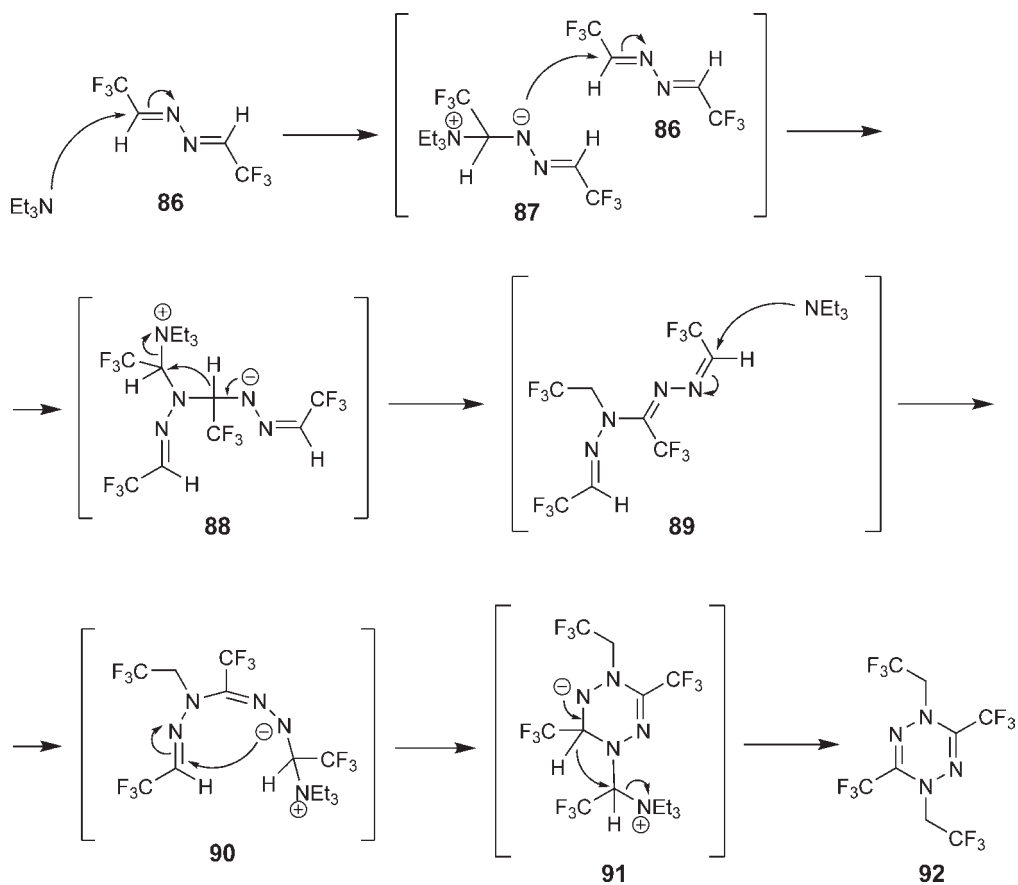
Scheme 20

Reaction of alkylsulfanylchloroacetylenes **81** with 1,1-dimethylhydrazine **82** at room temperature afforded the corresponding 2,5-bis(alkylthiomethyl)-1,1,4,4-tetramethyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dium chlorides **85** in 67% and 80% yield. The reaction pathway is explained by initial formation of hydrazinium salt **83**, which dimerizes into the tetrazinium salt **84**. Tautomerization of the salt **84** leads to the product **85** (Scheme 21) <2005RJO1458>.

Kamachi and co-workers reported a base-induced transformation of trifluoroacetaldehyde azine **86** into 1,4-bis(2,2,2-trifluoroethyl)-3,6-bis(trifluoromethyl)-1,4-dihydro-1,2,4,5-tetrazine **92**. The proposed reaction mechanism involves addition of triethylamine to the $\text{C}=\text{N}$ bond followed by addition of the adduct **87** to another molecule of **86** to give the zwitterion **88**. Intermediate **88** undergoes hydride shift and elimination to give the intermediate **90**. Repetition of the latter part of the reaction sequence then results in cyclization to give dihydrotetrazine **92** (Scheme 22) <1995BCJ2025>.



Scheme 21

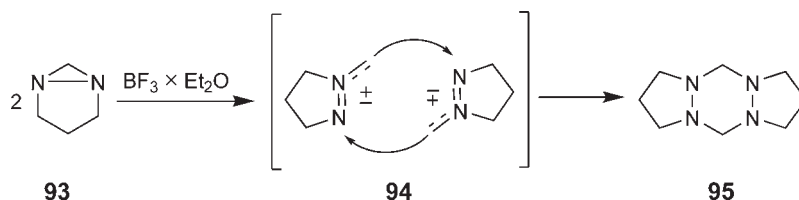


Scheme 22

Recently, a convenient modification of the classical 3,6-dialkyltetrazine synthesis from aldehydes and hydrazine has been reported. Expensive PtO_2 has been replaced by palladium on charcoal as the catalyst in the oxidation of the intermediate hexahydro-1,2,4,5-tetrazines with oxygen gas <2003SC2769>.

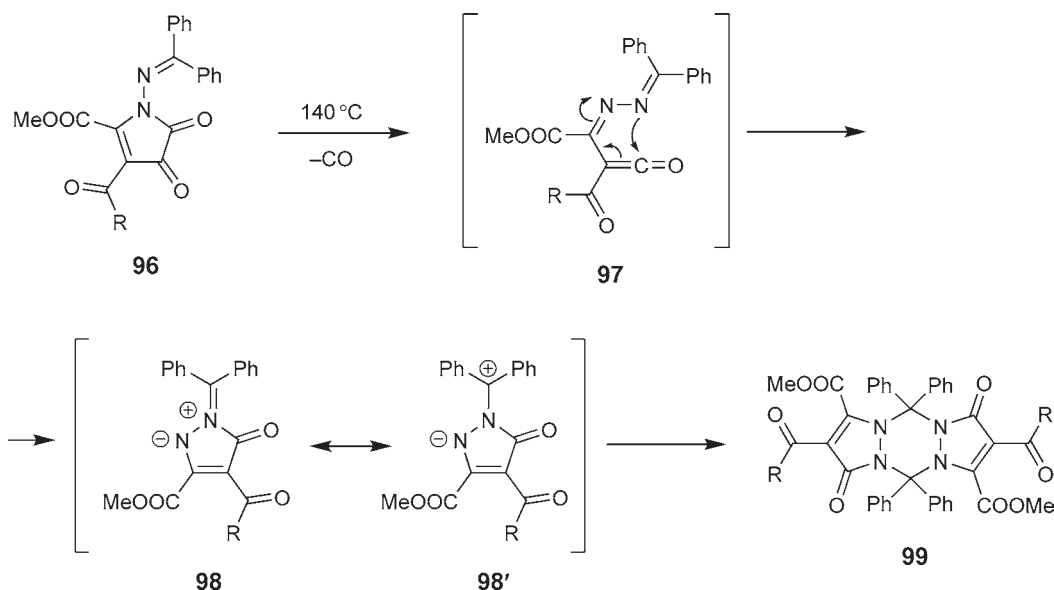
9.12.6.3 Synthesis of Annelated 1,2,4,5-Tetrazines

Treatment of 1,5-diazabicyclo[3.1.0]hexane **93** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in ether at 0°C gave dihyprazolotetrazine **95** in 62% yield. A plausible explanation for this rather unusual transformation is a Lewis acid-catalyzed ring opening of **93** to give the intermediate azomethine imine **94**, which then cyclizes into the bis-annulated tetrazine **95** (Scheme 23) <1999RJO144>.



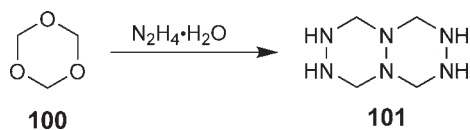
Scheme 23

Similarly, heating of methyl 3-acyl-1-(diphenylmethyleneamino)-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **96** gave the corresponding dimethyl 2,8-diacyl-3,9-dioxo-5,5,11,11-tetraphenyl-3,5,9,11-tetrahydrodipyrzolo[1,2-*a*:1',2'-*d'*][1,2,4,5]tetrazine-1,7-dicarboxylates **99** in good yields. The proposed mechanism involves thermal decarbonylation to give the ketene intermediate **97**, which cyclizes into the azomethine imine **98**, followed by dimerization (Scheme 24) <2004T5319>.

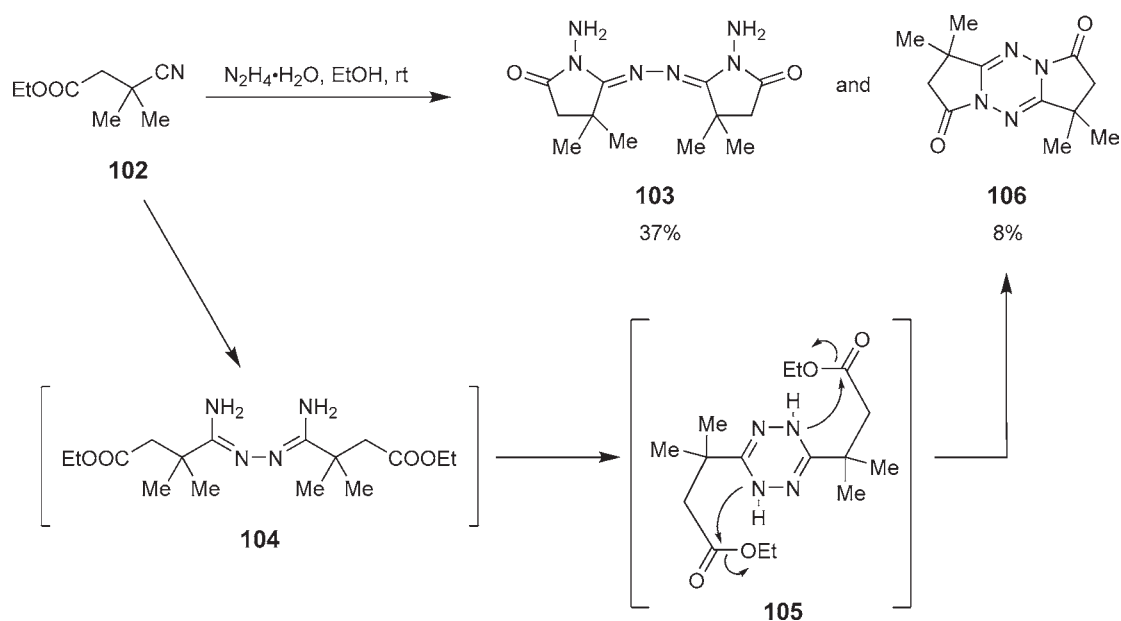


Scheme 24

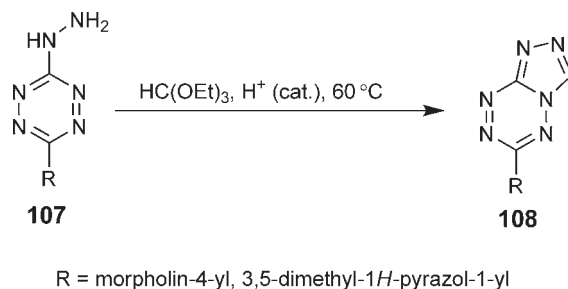
Recently, the structure of 1,2,3,4,5,6,7,8-octahydro-1,2,4,5-tetrazino[1,2-*a*][1,2,4,5]tetrazine **101**, prepared from paraformaldehyde **100** and hydrazine hydrate, was solved by simulated annealing from X-ray laboratory powder data and refined by Rietveld refinement without any restraints for non-H-atoms (Scheme 25) <2006AXEo1449>.

**Scheme 25**

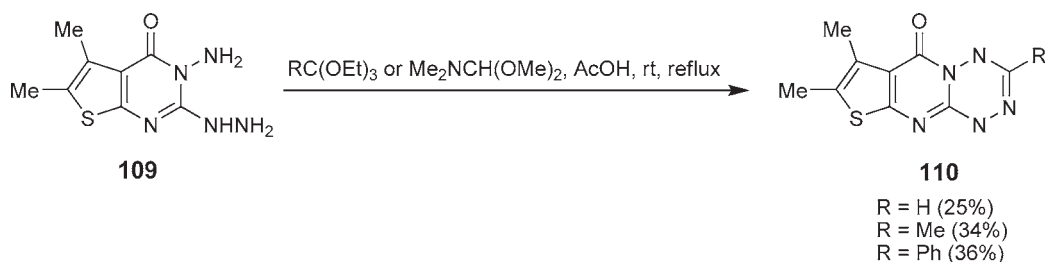
Upon treatment of ethyl 3-cyano-3-methylbutanoate **102** with 1.1 equiv of hydrazine hydrate in ethanol at room temperature for 37 days, 3,3,8,8-tetramethyl-2,3,7,8-tetrahydrodipyrrolo[1,2-*b*:1',2'-*c*][1,2,4,5]tetrazine-1,6-dione **106** was isolated as a side product in 8% yield. Most probably, compound **106** was formed via condensation of **102** with 0.5 equiv of hydrazine hydrate to give the intermediate dihydrotetrazine **105**, which undergoes cyclocondensation to both ester groups (Scheme 26) <2005JHC919>.

**Scheme 26**

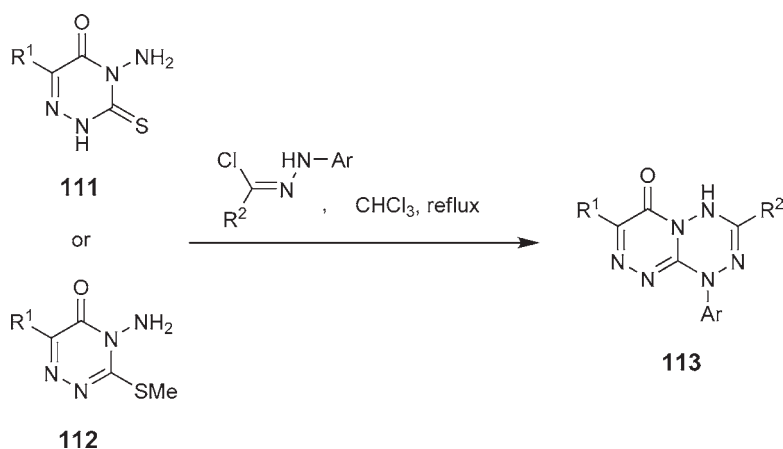
[1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazines **108** were prepared from the corresponding hydrazinotetrazines **107** by treatment with triethyl orthoformate (Scheme 27) <1998JHC1329, 2000ARK259>.

**Scheme 27**

Three novel 3-substituted 1,4-dihydro-7,8-dimethyl-9*H*-thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones **110** were prepared in moderate yields from 3-amino-2-hydrazinyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **109** upon treatment with orthoesters or *N,N*-dimethylformamide dimethyl acetal in acetic acid (Scheme 28) <2001JHC973>.

**Scheme 28**

A one-pot procedure for the synthesis of [1,2,4]triazino[4,3-*b*][1,2,4,5]tetrazines **113** from triazin-5(4*H*)-ones includes treatment of 4-amino-2,3-dihydro-3-thioxo-1,2,4-triazin-5(4*H*)-ones **111** or 4-amino-3-methylsulfanyl-1,2,4-triazin-5(4*H*)-ones **112** with hydrazonoyl chloride in the presence of triethylamine in refluxing chloroform (Scheme 29) <2000JPR96>.

**Scheme 29**

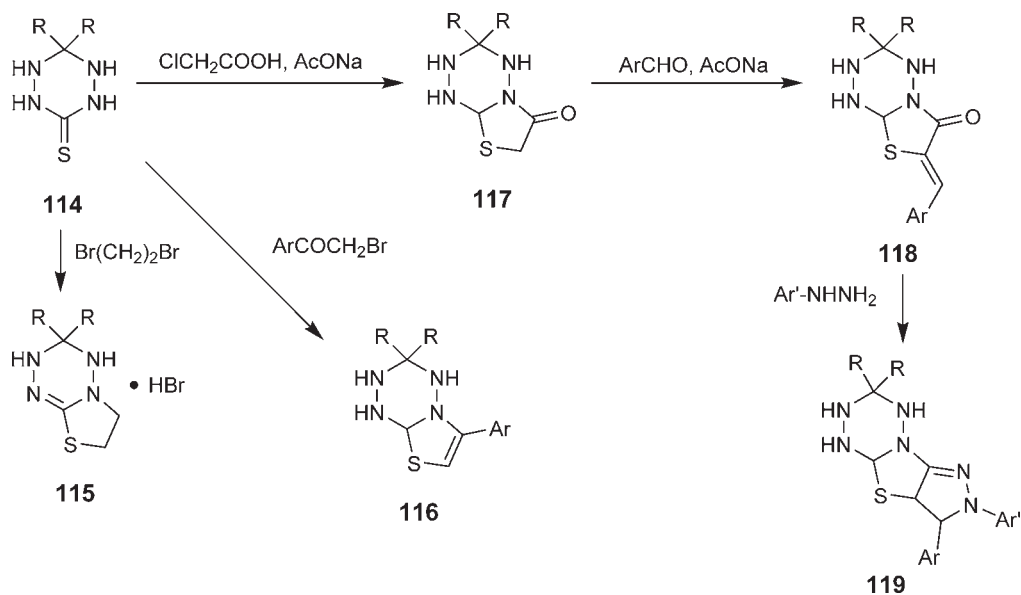
Mohan *et al.* <1995IJB1013, 1996IJB133, 1996IJB685, 1996IJH73, 1997IJB414, 1997IJH225, 1998IJH7, 1998IJH233, 2000IJH89, 2001IJB584, 2002IJH169, 2003IJB1176, 2003IJB1460, 2004IJH323, 2005IJH7> reported the synthesis of a series of thiazolo[3,2-*b*][1,2,4,5]tetrazines **115–119**, prepared from 6,6-disubstituted-1,2,4,5-tetrazinane-3-thiones **114** via cyclocondensation with 1,2-dielectrophiles to give thiazoozolo-fused tetrazines **115–117**. Condensation of **117** with aromatic aldehydes gave benzylidene derivatives **118**. Treatment of **118** with 2,4-dinitrophenylhydrazine furnished pyrazolo[3',4':4,5]thiazolo[3,2-*b*][1,2,4,5]tetrazines **119**. Similarly, some spiropiperidine derivatives in these series have been prepared by Venkataraman and Sithik Ali (Scheme 30) <2001IJH93, 2001IJH219>.

9.12.7 Transformations of Fully Conjugated Systems

9.12.7.1 Retention of the Ring System

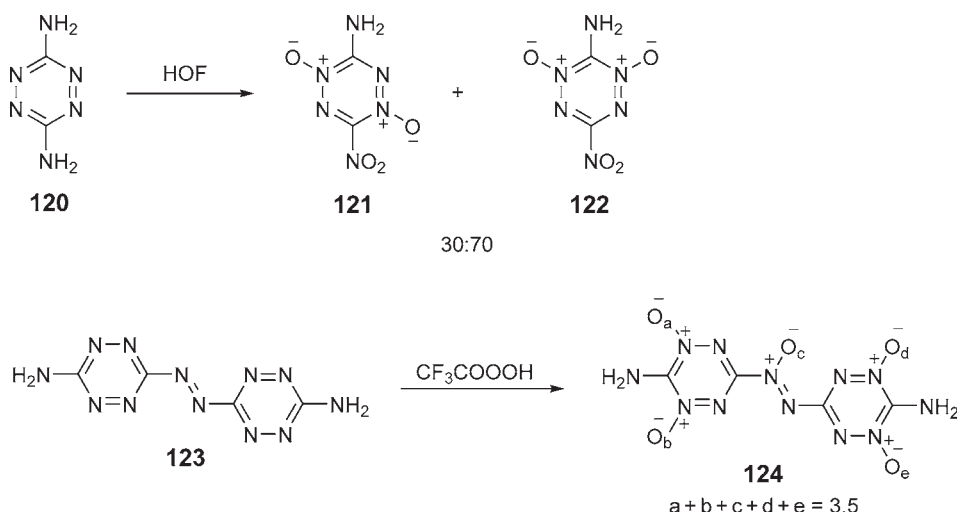
9.12.7.1.1 N-Oxidation and redox reactions

In their study of 1,2,4,5-tetrazine-based energetic materials, Chavez *et al.* prepared numerous 1,2,4,5-tetrazine di-*N*-oxide derivatives. As oxidizing agents, peroxymonosulfuric acid (Caro's acid), peroxytrifluoroacetic acid, and hypofluorous acid were used. Oxidation of 3,6-diamino-1,2,4,5-tetrazine **120** into bis-*N*-oxides **121** and **122** and oxidation of 3,3'-azobis(6-amino-1,2,4,5-tetrazine) **123** into *N*-oxide **124** are exemplified in Scheme 31. Denotation **124** represents a complex mixture of various *N*-oxides of **123**, whereby five of the most plausible sites of N-oxidation are given. By elemental analysis, the average oxygen content was calculated to be approximately 3.5 (a + b + c + d + e ~ 3.5) (Scheme 31) <2004MI209, 1999JEM357>.



R	Reference
Et	1996IJB(B)133
	1996IJH73, 1997IJB414
Et	2001IJB584, 1998IJH
	1995IJB1013, 2003IJB1176, 2002IJH169, 2004IJH323
	2003IJB1460
	2001IJH219, 2005IJH7
	2001IJH93
	2000IJH89
	1997IJH225
	1998IJH233
	1996IJB685

Scheme 30



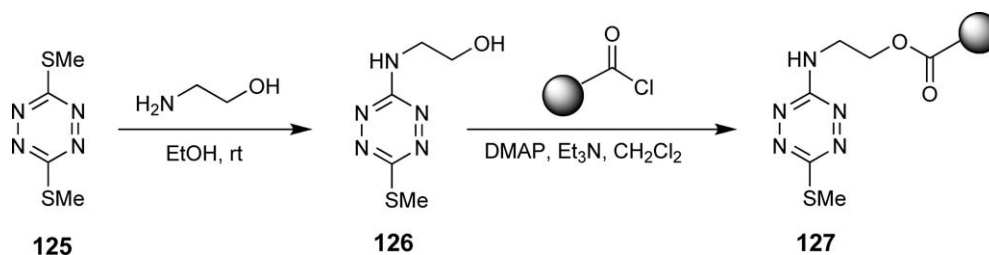
Scheme 31

Suenobu and co-workers studied scandium ion-promoted reduction of the heterocyclic N=N bond of 3,6-diphenyl-1,2,4,5-tetrazine with different hydride and/or electron-donor reagents [\[2002JA12566\]](#). The triplet excited state of 3,6-diphenyl-1,2,4,5-tetrazine ($^3\text{Ph}_2\text{Tz}^*$) is formed efficiently by photosensitization with $\text{Ru}(\text{bpy})_3^{2+}$. The lifetime ($\tau = 28.4 \mu\text{s}$) and oxidizing ability ($E_{\text{red}} = 1.09 \text{ V}$ vs. saturated calomel electrode (SCE)) of $^3\text{Ph}_2\text{Tz}^*$ make it a promising new strong oxidant in photoinduced electron-transfer reactions [\[2006CC561\]](#).

9.12.7.1.2 Nucleophilic substitution

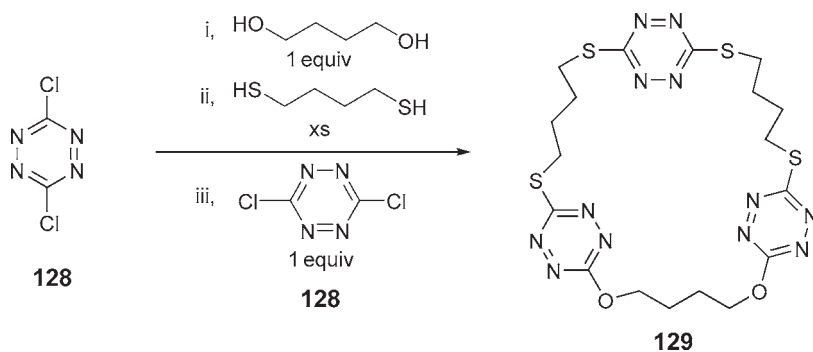
Substituents in the 3- and/or 6-position in 1,2,4,5-tetrazines, which are good leaving groups, such as halogens, SMe, SOMe, SO_2Me , and azolyl groups, are substituted readily by reactive C-, N-, O-, and S-nucleophiles in nucleophilic aromatic substitution reactions. These reactions, with the subsequent modifications of the newly introduced groups, enable easy access to a large number of symmetrically and nonsymmetrically substituted 1,2,4,5-tetrazines.

Boger *et al.* replaced one SMe group of 3,6-bis(methylthio)-1,2,4,5-tetrazine **125** with different N-nucleophiles and assessed the reactivity and selectivity of the newly synthesized nonsymmetrical 1,2,4,5-tetrazines in cycloaddition reactions [\[1998JOC6329\]](#). Similarly, substitution of an SMe group of **125** with N-nucleophiles bearing appropriately tethered alkenes or alkynes, followed by intramolecular [4+2] cycloadditions, gave interesting bicyclic and polycyclic pyridazine heterocycles [\[2000JOC9120, 2000T1165, 1998JOC6329\]](#). Selective mono- or bis-substitution of SMe groups in **125** with sodium methoxide has been described [\[1997TL3805\]](#). Replacement of one thiomethyl group of **125** with aminoethanol afforded a nonsymmetrical 1,2,4,5-tetrazine **126**, suitable for immobilization to carboxylated polystyrene (**Scheme 32**) [\[1996TL8151\]](#).



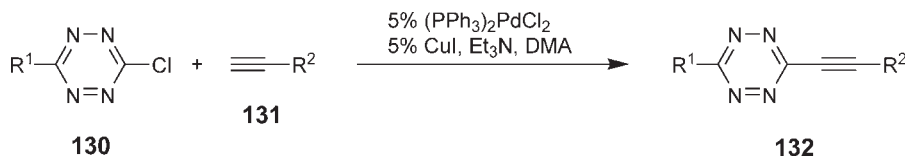
Scheme 32

Halogens are good leaving groups and substitutions with various C-, N-, O-, and S-nucleophiles have been described [\[2005CEJ5667, 2003H\(60\)2653, 2000T1165, 1999JEM357, 1996RFP117\]](#). The first tetrazine-based cyclophane **129**, designed for recognition of electron-donating entities, was prepared in three nucleophilic aromatic substitution steps starting from dichloro-*s*-tetrazine **128** (**Scheme 33**) [\[2006JEC147\]](#).



Scheme 33

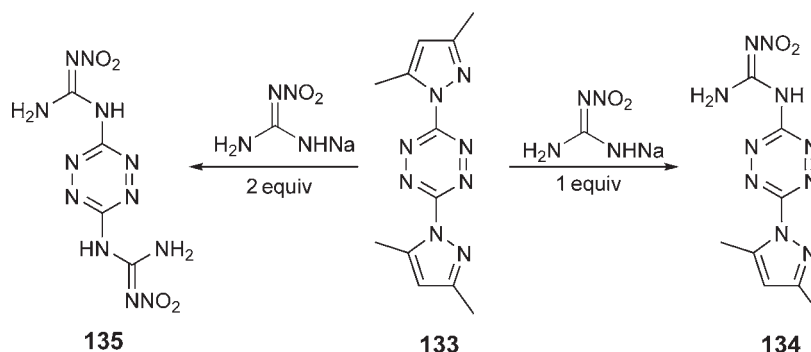
Recently, the first cross-coupling reactions on 3-substituted-6-chloro-1,2,4,5-tetrazines **130** have been reported by Novák and Kotschy. A series of chlorotetrazines **130** were reacted with different terminal alkynes **131** under Sonogashira and Negishi coupling conditions to furnish alkynyl-tetrazines **132** in good to moderate yields. The electron-donating properties of the substituent on the tetrazine core were found to have a significant influence on the reaction (Scheme 34) <2003OL3495>.



R^1	R^2	Yield (%)
Morpholinyl	$\text{C}(\text{CH}_3)_2\text{OH}$	57
Morpholinyl	Ph	56
Morpholinyl	<i>n</i> -Bu	29
Morpholinyl	SiMe_3	Dec.
Pyrrolidinyl	$\text{C}(\text{CH}_3)_2\text{OH}$	52
Pyrrolidinyl	Ph	23
Pyrrolidinyl	<i>n</i> -Bu	56
Et_2N	$\text{C}(\text{CH}_3)_2\text{OH}$	30
Et_2N	Ph	48
Et_2N	<i>n</i> -Bu	65
<i>n</i> -BuNH	<i>n</i> -Bu	Traces
NH_2	$\text{C}(\text{CH}_3)_2\text{OH}$	0
NH_2	Ph	0
NH_2	<i>n</i> -Bu	0
Dimethylpyrazolyl	$\text{C}(\text{CH}_3)_2\text{OH}$	Dec.
Dimethylpyrazolyl	Ph	Dec.
Dimethylpyrazolyl	<i>n</i> -Bu	Dec.
OMe	$\text{C}(\text{CH}_3)_2\text{OH}$	Dec.
Cl	$\text{C}(\text{CH}_3)_2\text{OH}$	Dec.

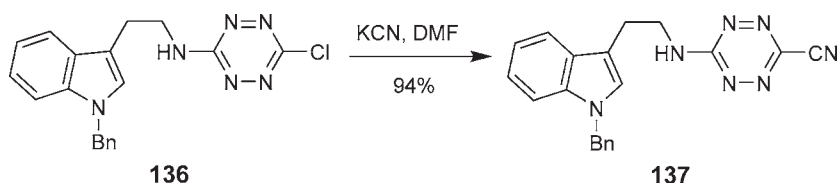
Scheme 34

Azoles (imidazoles, benzotriazole, and 3,5-dimethylpyrazoles) are very good nucleofuges. C-Nucleophilic substitution of one of the two dimethylpyrazolyl, benzotriazolyl, or imidazolyl moieties with 1-methylquinaldinium and 1,6-dimethylquinaldinium anhydro bases proceeds easily in acetonitrile <2006HCO99>. Novák *et al.* studied selective nucleophilic substitutions of 3,6-dichloro-1,2,4,5-tetrazine **128**, 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **133**, and its 4-bromo-3,5-dimethylpyrazol-1-yl derivative with a series of different nucleophiles. The origin of the observed regioselectivity was rationalized using quantum-chemical calculations <2003H(60)2653>. Latosh *et al.* prepared a large number of monosubstitution products via reactions of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **133** and its 4-bromo- and 4-chloro-3,5-dimethylpyrazol-1-yl derivatives with primary and secondary aliphatic, alicyclic, and aromatic amines, hydrazines, and carbohydrazides <1999RJO1363>. Similar substitutions of 3,5-dimethylpyrazol-1-yl groups with methyl esters of several amino acids <2005PCJ8> and other mono- and diamines, amino alcohols, and hydrazine have been reported <2005AGE3889, 2005JA12537, 2004MI11, 2004MI209, 2000AGE1791, 1999JEM357, 1998MI11-1, 1997J(P2)1167>. Selective mono- and bis-substitution is exemplified nicely by the reaction of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **133** with 1 or 2 equiv of the sodium salt of nitroguanidine giving mono- or bis-substitution products **134** and **135**, respectively (Scheme 35) <2004OL2889>. The latter is a new energetic material with high nitrogen content <2005MI412, 2004OL2889>.



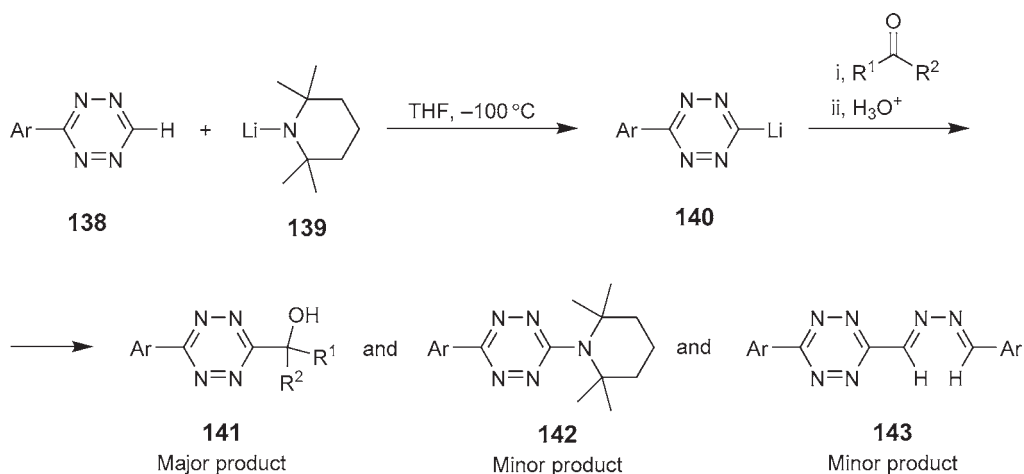
Scheme 35

Work by Kotschy and co-workers showed that reactions of different symmetrical 1,2,4,5-tetrazines with a variety of organometallic reagents furnished, depending upon the combination of reactants, azaphilic addition, reduction or complexation products and not the nucleophilic aromatic substitution products <2004T1991>. On the other hand, Benson *et al.* reported a smooth displacement of one chlorine substituent in chlorotetrazine **136** using cyanide anion as a soft C-nucleophile (Scheme 36) <2000T1165>.



Scheme 36

Lithiation of 3-aryl-1,2,4,5-tetrazines **138** with lithium 2,2,6,6-tetramethylpiperidide **139** afforded the corresponding lithiated tetrazines **140**, which were trapped with aldehydes or benzophenone to give 3-aryl-6-(α -hydroxymethyl)-1,2,4,5-tetrazines **141** as the major products, as well as 3-aryl-6-(2,2,6,6-tetramethylpiperidinyl)-1,2,4,5-tetrazines **142** and 1-aryl-4-(6-aryl-1,2,4,5-tetrazin-3-yl)-2,3-diazabutadienes **143** (Scheme 37) <1998HCO301>.



Ar	R ¹	R ²	Yield (%)		
			141	142	143
Ph	Ph	H	26	5	3
4-Cl-C ₆ H ₄	Ph	H	20	4	0
4-MeO-C ₆ H ₄	Ph	H	19	3	6
4-Me-C ₆ H ₄	Ph	H	15	4	8
Ph	4-Br-C ₆ H ₄	H	30	2	7
Ph	4-Me-C ₆ H ₄	H	25	2	10
Ph	Me	H	9	11	1
Ph	Ph	Ph	10	17	5

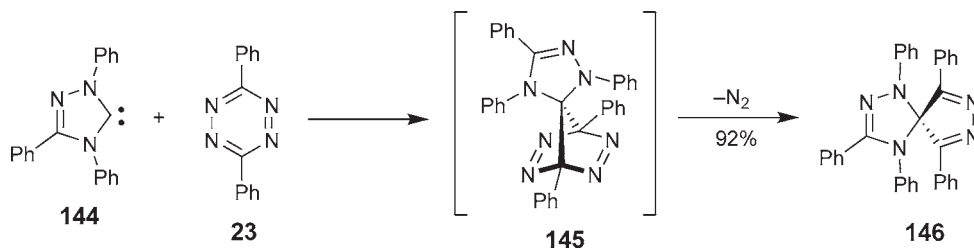
Scheme 37

9.12.7.2 Transformation of the Ring System

9.12.7.2.1 [4+1] Cycloaddition reactions

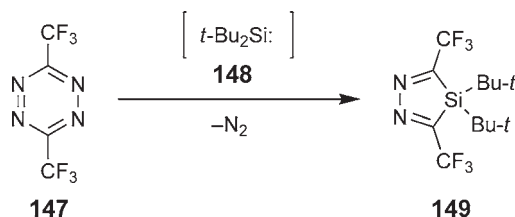
Various donor-substituted carbenes can be trapped with electron-deficient 1,2,4,5-tetrazines in electronically reversed [4+1] cycloaddition reactions [<1996CHEC-II\(6\)901>](#).

In a reactivity study of a stable triazolyldiene **144** by Enders *et al.*, a [4+1] cycloaddition of **144** to 3,6-diphenyl-1,2,4,5-tetrazine **23** is described. The initially formed cycloadduct intermediate **145** extrudes a molecule of nitrogen in a cycloelimination step, thus giving the final stable spiro product **146** (Scheme 38) [<1996LA2019>](#).



Scheme 38

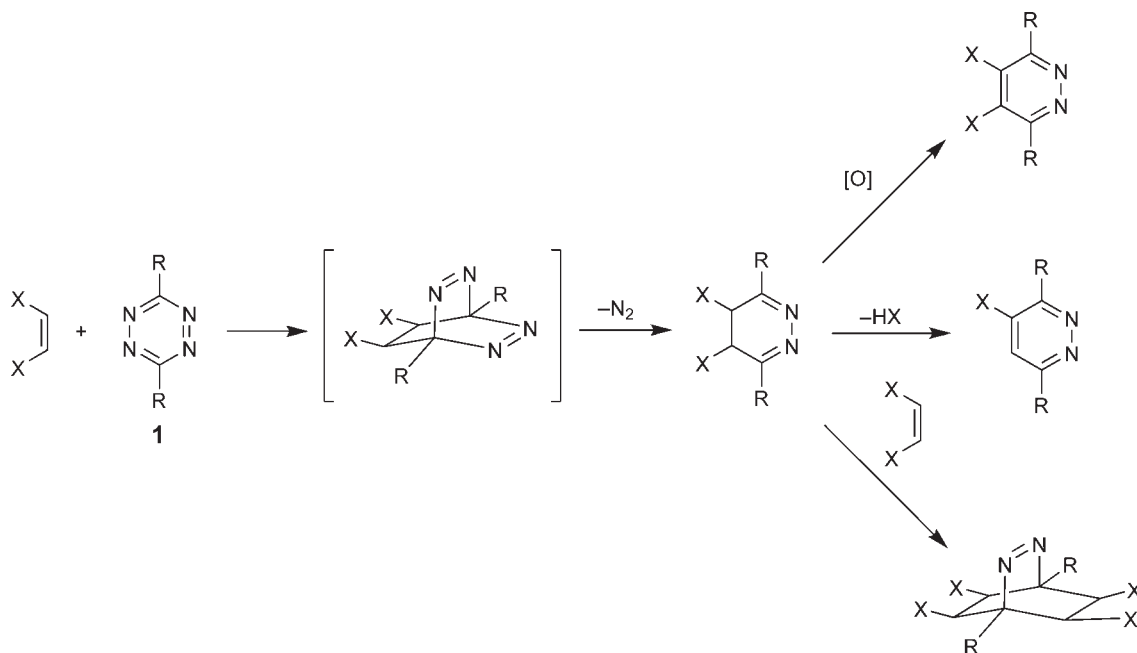
Reaction of di-*tert*-butylsilylene **148**, formed *in situ* by photolysis of the corresponding cyclotrisilane, with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** formed 2,5-bis(trifluoromethyl)-1-*tert*-butyl-1,2,4-diazasilole **149** via a [4+1] cycloaddition reaction (Scheme 39) <1996JOM(521)355>.



Scheme 39

9.12.7.2.2 [4+2] Cycloaddition reactions

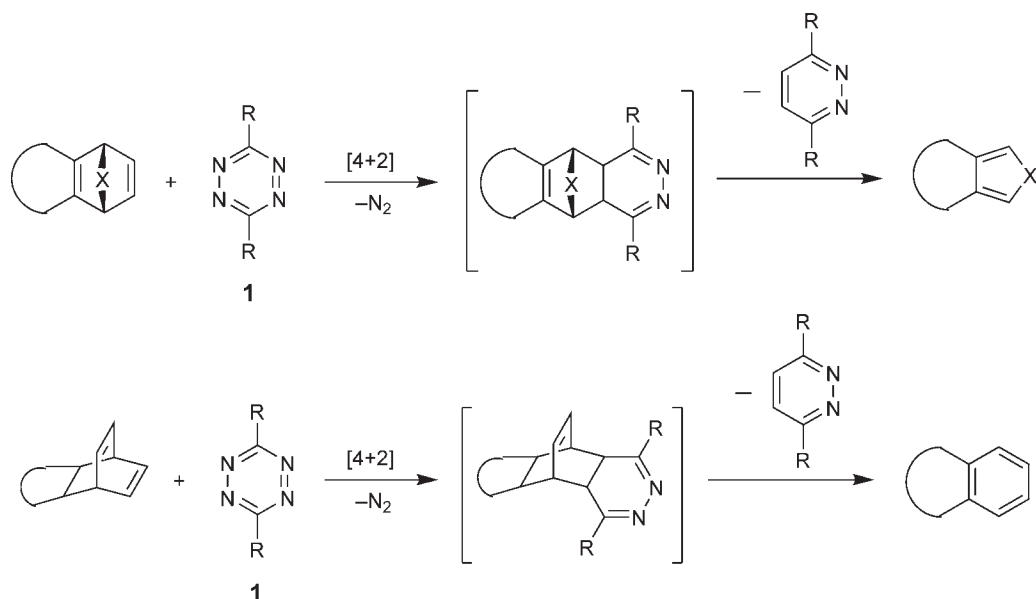
1,2,4,5-Tetrazines **1** undergo [4+2] cycloadditions with a variety of electron-rich as well as electron-deficient alkenes, according to the 'normal electron demand' and 'inverse electron demand' protocols. The initially formed dihydropyridazine derivatives are unstable and, thus, rarely isolated. Usually, they are transformed into the corresponding pyridazines by oxidation or elimination. In the case of extremely reactive dienophiles, the intermediate dihydropyridazines may undergo a second Diels–Alder reaction giving polycyclic products (Scheme 40) <1984CHEC(3)531, 1996CHEC-II(6)901>.



Scheme 40

In the reactions with cyclic alkenes, such as benzo-fused 2,5-dihydrothiophenes, 2,5-dihydrofurans, 2,5-dihydropyrroles, and bicyclo[2.2.2]octa-2,5-diene, the initially formed fused dihydropyridazines may be unstable and undergo cycloreversion reaction via elimination of the pyridazine derivative to give the corresponding thiophenes, furans, pyrroles, fulvalenes, and benzenes (Scheme 41) <1984CHEC(3)531, 1996CHEC-II(6)901>.

The examples depicted in this chapter complement and extend Sauer's report in CHEC-II(1996) <1996CHEC-II(6)901> and Neunhoeffer's report in CHEC(1984) <1984CHEC(3)531>.



Scheme 41

9.12.7.2.2(i) Alkenes as dienophiles

Pericyclic domino reactions of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** with dienes offer convenient entries into azo cage compounds **156–160** under mild conditions (Scheme 42) <1997JPR623>.

Sauer *et al.* reported a one-pot synthesis of a series of semibullvalenes **164** starting from 3,6-disubstituted-1,2,4,5-tetrazines **1** and 1,1'-dimethyl-1,1'-bi(cycloprop-2-ene) **161**. A plausible mechanistic explanation for the overall reaction consists of [4+2] cycloaddition to give the *anti*-isomer of diazanorcaradiene **162**. Upon *anti-syn*-isomerization, another [4+2] cycloaddition leads to the final product **164**. In the case of aryl substituents, which weaken the tendency for *anti-syn*-isomerization, the corresponding 2,5-diaryldiazanorcaradienes **163** were isolated as the early intermediates in this reaction sequence (Scheme 43) <2002EJO791>.

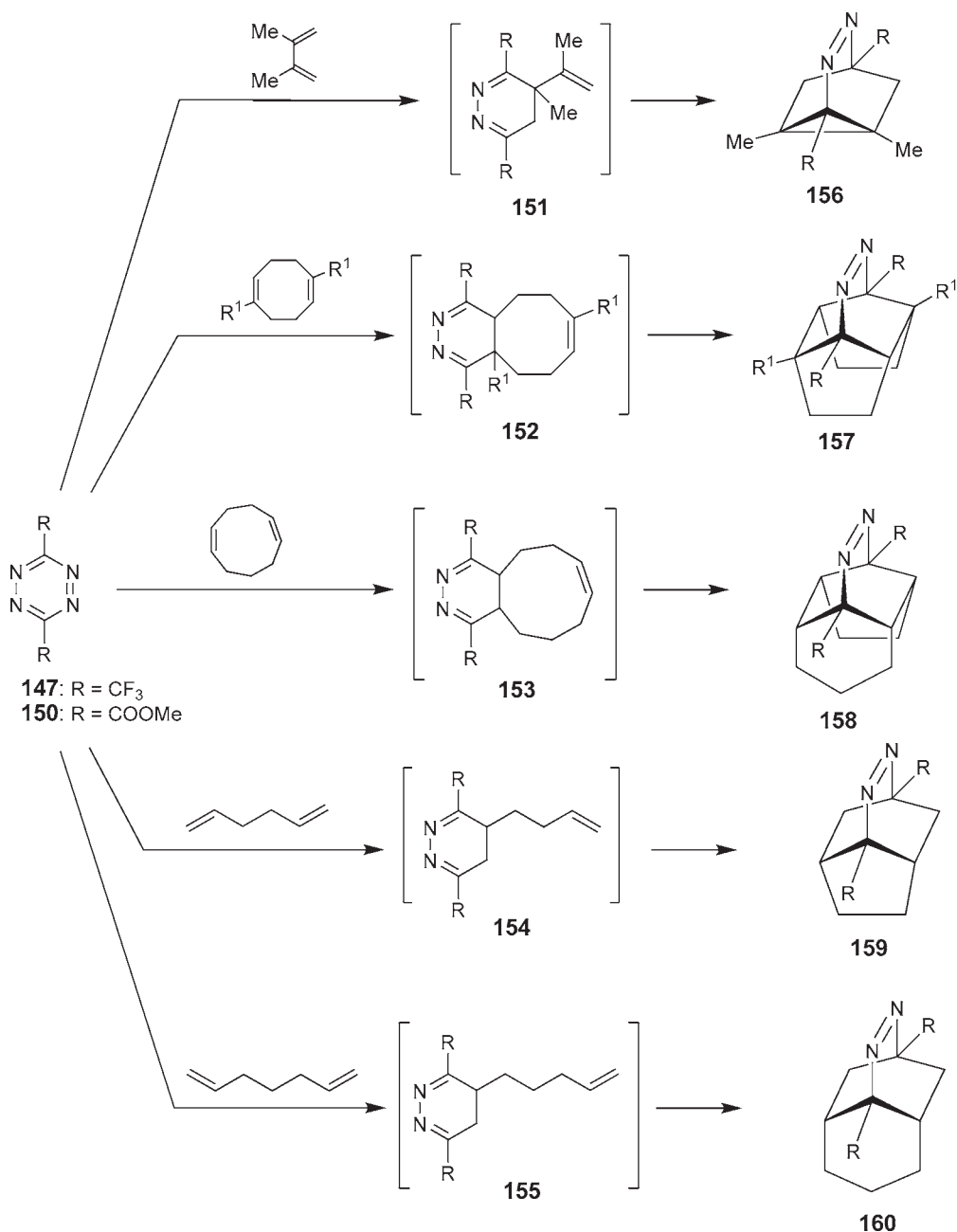
In the reaction of tetrazines **1** with cyclopropene (**165**: R² = H) and 2,2-dimethylcyclopropene (**165**: R² = Me) in dichloromethane at 0 °C, a series of diazanorcaradienes **166** were obtained. In the case of electron-withdrawing substituents at the tetrazine ring, the so-formed diazanorcaradienes **166** reacted further with another equivalent of cyclopropene to give 9,10-diazatetracyclo[3.3.2.0^{2,4}.0^{6,8}]dec-9-enes **167** (Scheme 44) <2001EJO2629>.

[4+2] Cycloadditions of 1,2,4,5-tetrazines **1** to tetrahydrodianthracene **168** have also been reported. Under mild conditions, 1:1 adducts **169** were obtained in high yields. Further treatment of **169** with another molecule of tetrazine **1**, usually under more drastic conditions, gave 1:2 adducts **170** in excellent yields (Scheme 45) <1997LA1473>.

In contrast to reactions with tetrahydrodianthracene **168**, cycloadditions of electron-poor tetrazines to *p*-cyclophene **171** proceeded smoothly at 20 °C/1bar. On the other hand, with the unsubstituted 1,2,4,5-tetrazine (**1**: R = H), more drastic conditions were required to produce the oxidized product **173** in 36% yield (Scheme 46) <1997LA1473>.

Warrener and coworkers utilized cycloaddition of 3,6-di-(pyridin-2-yl)-1,2,4,5-tetrazine **174** to norbornene, 7-azanorbornene, and 7-oxanorbornene units as the key step in the construction of rigid polycyclic scaffolds as molecular blocks of different shape, size, and functionality (Scheme 47) <1999OL199, 1999NN2631, 1998SL566, 1998SL585, 1998SL590, 1998SL593, 1998TL4721, 1997SL47, 2006OL273, 2003AJC811, 2000AJC959, 1996AGE2485, 1996TL2825, 1998TL5277, 2001STC291, 2001MOL353, 2002T3445, 1995CC1417>.

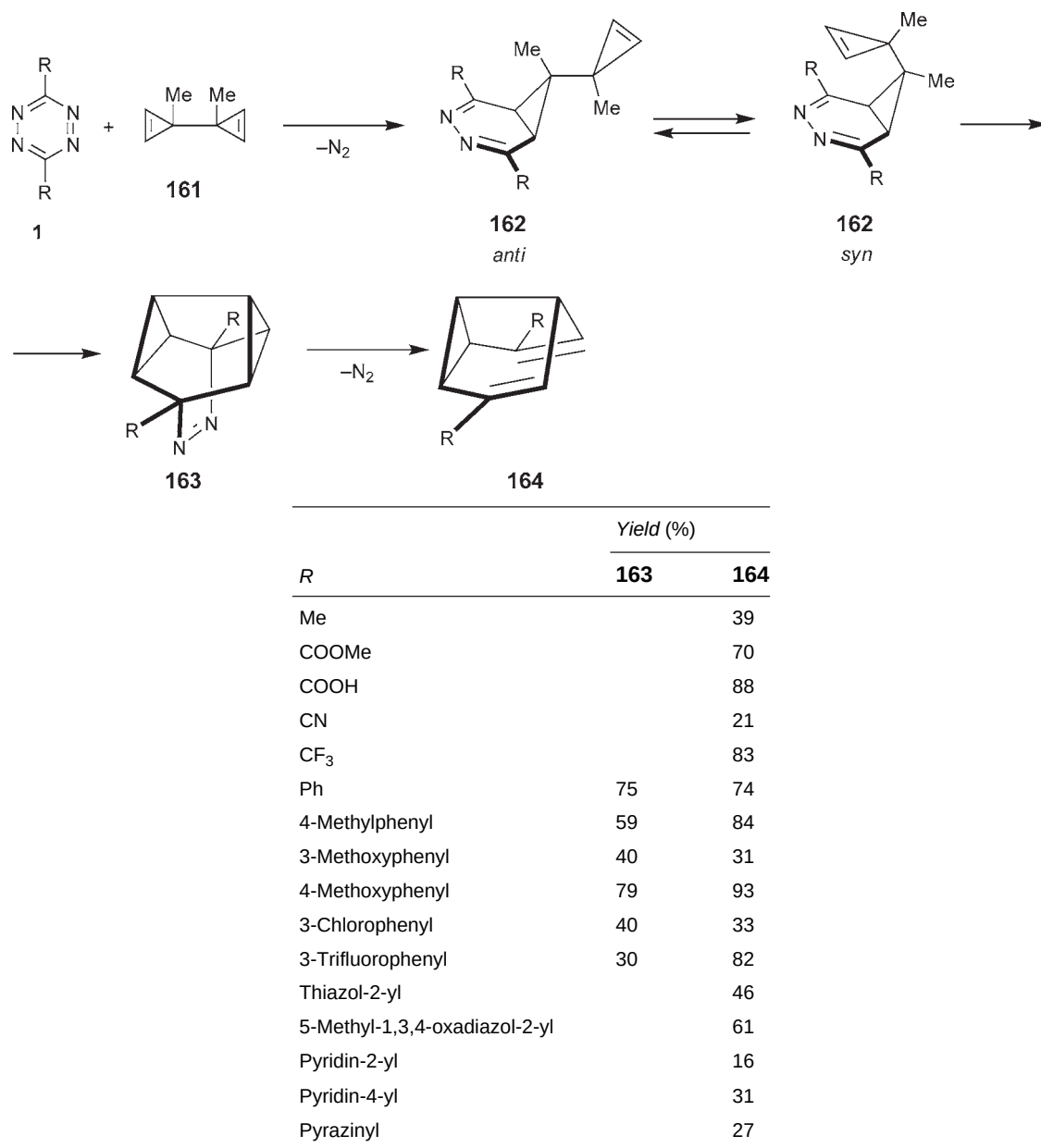
Another synthetic application of 3,6-di-(pyridin-2-yl)-1,2,4,5-tetrazine **174** is cycloaddition to [60]fullerene **175** (Scheme 48) <2000OL3091, 2001CC1758, 2000MI20, 2003BCJ1669>.



Scheme 42

Cycloadditions of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** to benzocyclopropene **177** <1996ZNB348>, bicyclo[2.1.1]hex-2-ene **178** <2003EJO901>, and secododecahedradiene dicarboxylate **179** <2001HCA1518> gave polycyclic pyridazine derivatives **181–183**. Reaction with cyclooctatetraene **180** in refluxing dichloromethane afforded 1:1 and 1:2 cycloadducts **184** and **185** (Scheme 49) <1995LA661>.

An intriguing reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** with tricyclic sulfone **188**, leading to the fused 5,6-dihydro-1,2-diazocine **190**, was reported recently by Paquette *et al.* Presumably, compound **190** was formed by retrograde elimination of the nitrogen in the initially formed [4+2] cycloadduct **189** via cleavage of the cyclobutane ring (Scheme 50) <2004OL1313>.



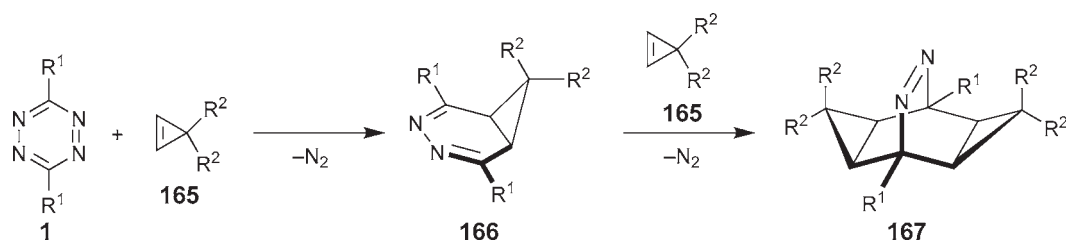
Scheme 43

Pyridazino annelated biyclic endoperoxides **197–202** were prepared by cycloadditions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** to unsaturated endoperoxides **191–196** in dichloromethane (Scheme 51) <1996TL921, 2000H(53)761, 2003JHC529, 2003JOC7009>.

Possibly carcinogenic dihydrodiols and a diol epoxide of phthalazine, viz. **207** and **208**, were obtained by cycloadditions of the corresponding aromatic dihydro diols **203** and tetrahydro diol epoxide **204** to dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** (Scheme 52) <2005T1545>.

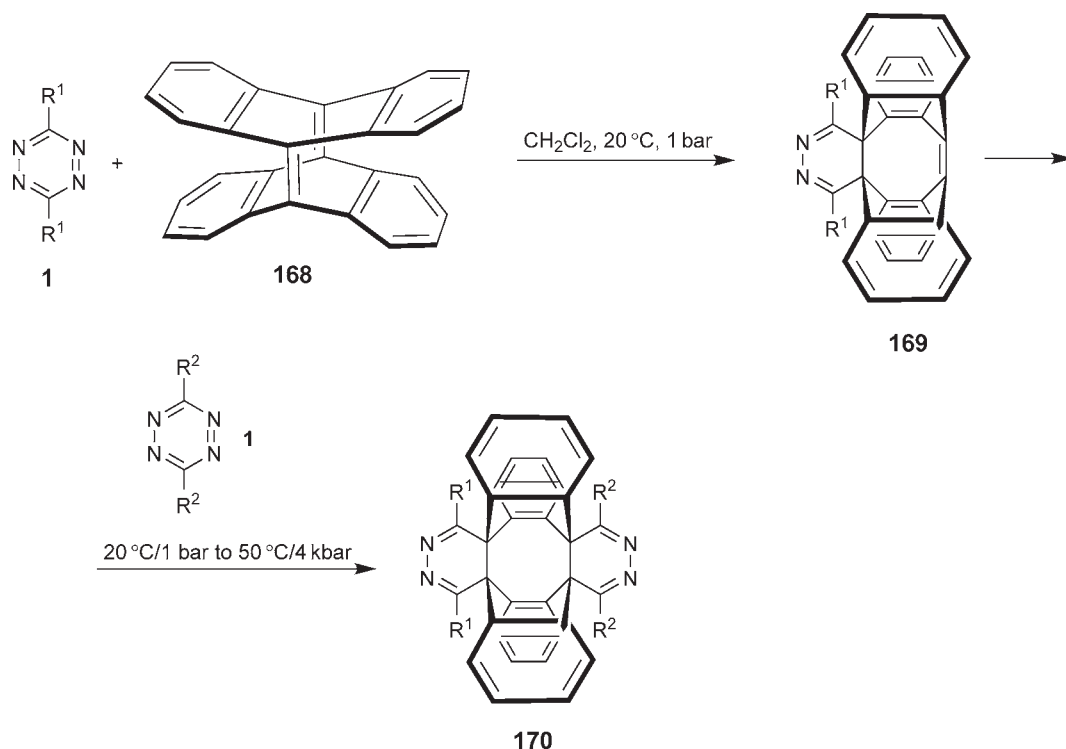
Cycloadditions of tetrazines **1** to acenaphthylenes **209** have also been reported (Scheme 53) <2003RCB218>.

Long reaction times, which are usually required in [4+2] cycloadditions of 1,2,4,5-tetrazines to various alkenes under classical heating, were shortened drastically by microwave-assisted reactions supported on graphite. In contrast to conventional conditions, microwave-assisted cycloadditions of 3,6-diphenyl-1,2,4,5-tetrazine **23** furnished fully conjugated pyridazines **212** (Scheme 54) <1996LA739>.



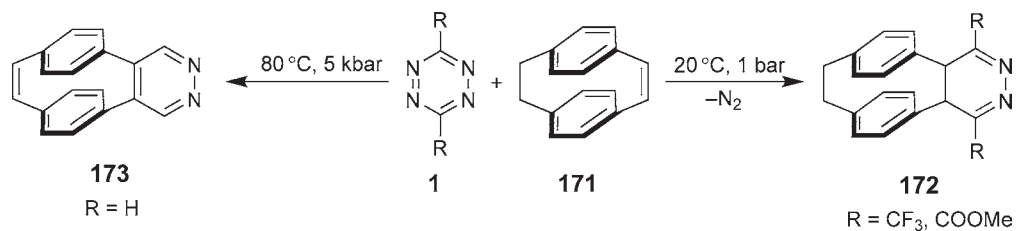
<i>R</i> ¹	<i>R</i> ²	Yield (%)	
		166	167
COOMe	Me		63
CF ₃	Me	95	54
CF ₃	H		47
Ph	H	84	25
Ph	Me	86	
3-Methylphenyl	H	61	
4-Methylphenyl	H	58	
4-Methylphenyl	Me	83	
3-Methoxyphenyl	H	83	
4-Methoxyphenyl	H	97	
4-Methoxyphenyl	Me	53	
3-Chlorophenyl	H	49	
4-Chlorophenyl	H	95	
4-Chlorophenyl	Me	75	
4-Fluorophenyl	H	65	
4-Fluorophenyl	Me	89	
1-Methylpyrrol-5-yl	Me	74	
2-Thienyl	H	74	
2-Thienyl	Me	67	
Thiazol-2-yl	H	81	35
Thiazol-2-yl	Me	59	74
2-Furanyl	Me	80	
5-Methyl-1,3,4-oxadiazol-2-yl	H	75	90
5-Methyl-1,3,4-oxadiazol-2-yl	Me	97	88
Pyridin-2-yl	H	78	89
Pyridin-2-yl	Me	59	74
Pyridin-3-yl	H	59	23
Pyridin-3-yl	Me	66	
Pyridin-4-yl	H	71	74
Pyridin-4-yl	Me	72	
Pyrazinyl	H	79	
Pyrazinyl	Me	97	
SMe	H	58	
SMe	Me	56	
OMe	H	88	
OMe	Me	66	

Scheme 44



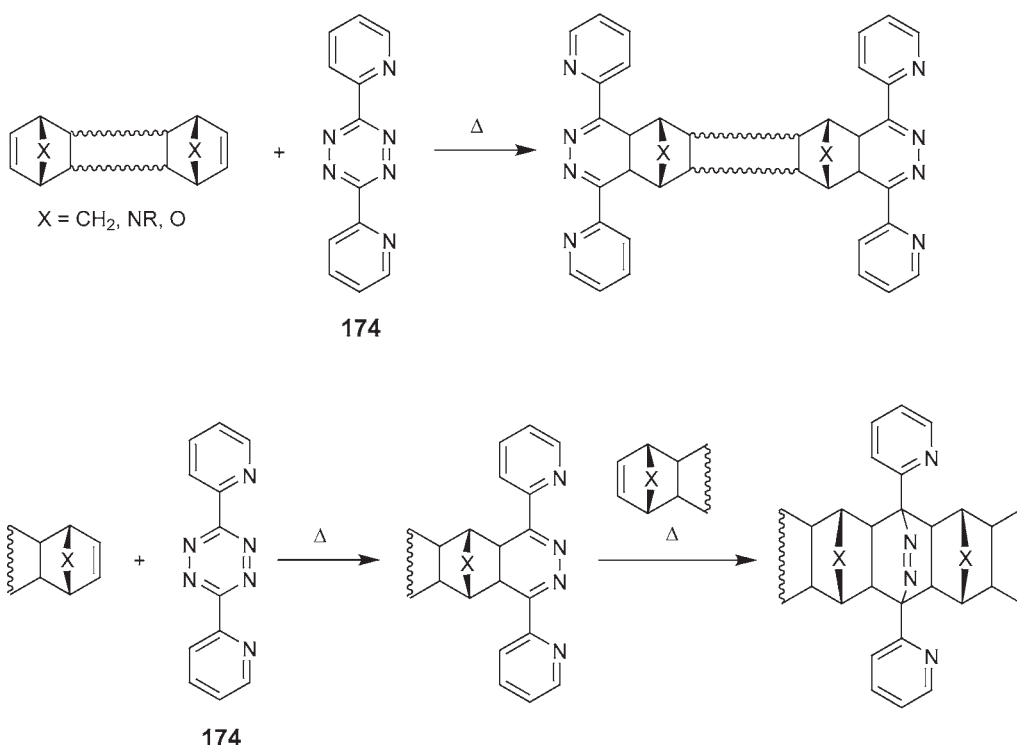
R^1	R^2	Yield (%)	
		169	170
H	H	98	90
Me	H	77	92
COOMe	H	54	88
COOMe	Me		96
COOMe	COOMe		66
CF_3	H	100	99

Scheme 45

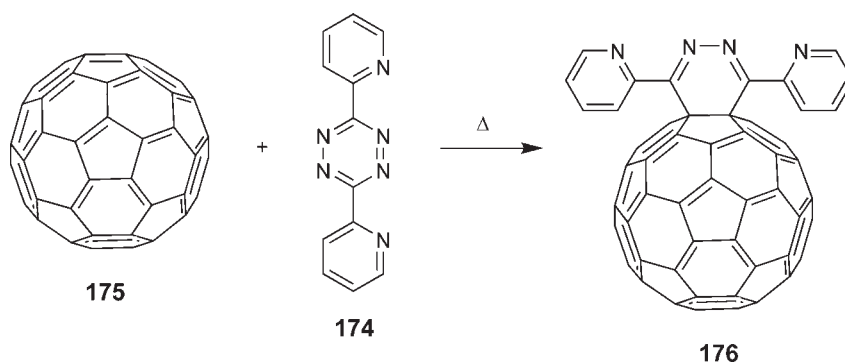


Scheme 46

Tetrazines are utilized as the key reagents (dipolarophiles) in synthetically useful cycloaddition–cycloreversion reactions. In such cases, the tetrazine first undergoes a [4+2] cycloaddition to the isolated double bond of a suitable Diels–Alder adduct. The so-formed dihydropyridazine intermediate undergoes aromatization via elimination of the pyridazine system. An example of a tetrazine-based cycloaddition–cycloreversion reaction cascade is the application



Scheme 47



Scheme 48

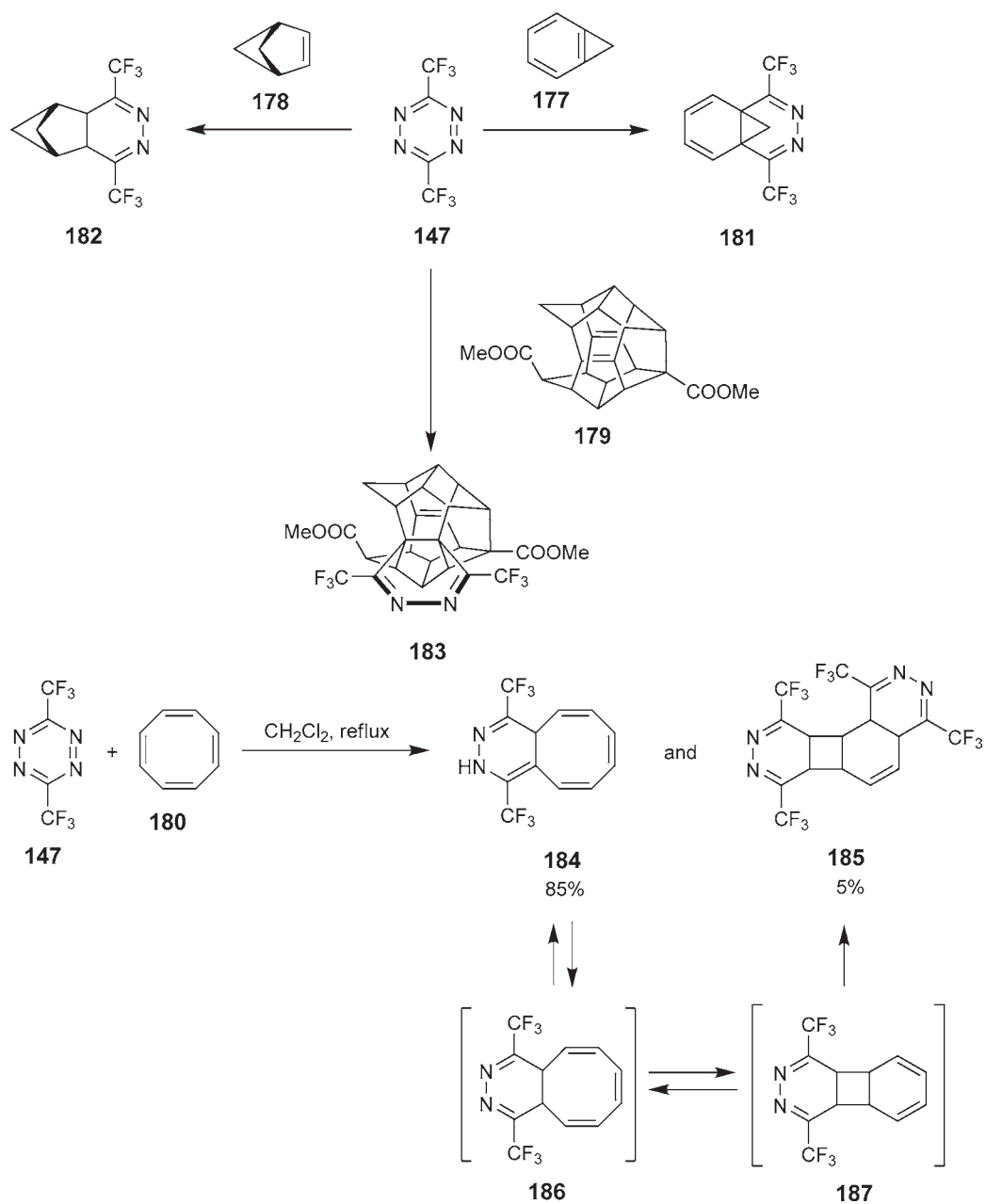
of 3,6-bis(pyridin-2-yl)-1,2,4,5-tetrazine **174** in transformations of monoiodinated octafluoro[2.2]paracyclophane **213** into naphthaleno- and anthraceno-octafluoro[2.2]paracyclophanes **218** and **219** as precursors of paralene-type polymers (Scheme 55) <2004S2747>.

Another general application of tetrazines **1** in cycloaddition–cycloreversion transformations is the synthesis of isobenzofurans **223** <1996AJC1263, 1998AJC409, 2001H(54)249, 2002T9413, 2003OBC2383, isobenzothiophenes **224** <1996AJC1263>, and isoindoles **225** (Scheme 56) <2006OL273, 2003CEJ2758, 2001STC291>.

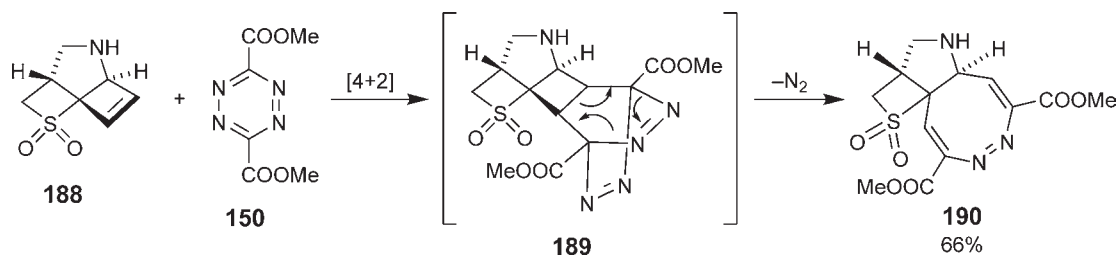
9.12.7.2.2(ii) Alkynes as dienophiles

Reactions of 1,2,4,5-tetrazines **1** with alkynes **226** proceed via initially formed 2,3,5,6-tetraazabicyclo[2.2.2]octa-2,5,7-trienes **227**, which decompose immediately with extrusion of nitrogen to form pyridazine derivatives **228**. Generally, reactions with alkynes require higher temperatures and more prolonged reaction times than with alkenes (Scheme 57).

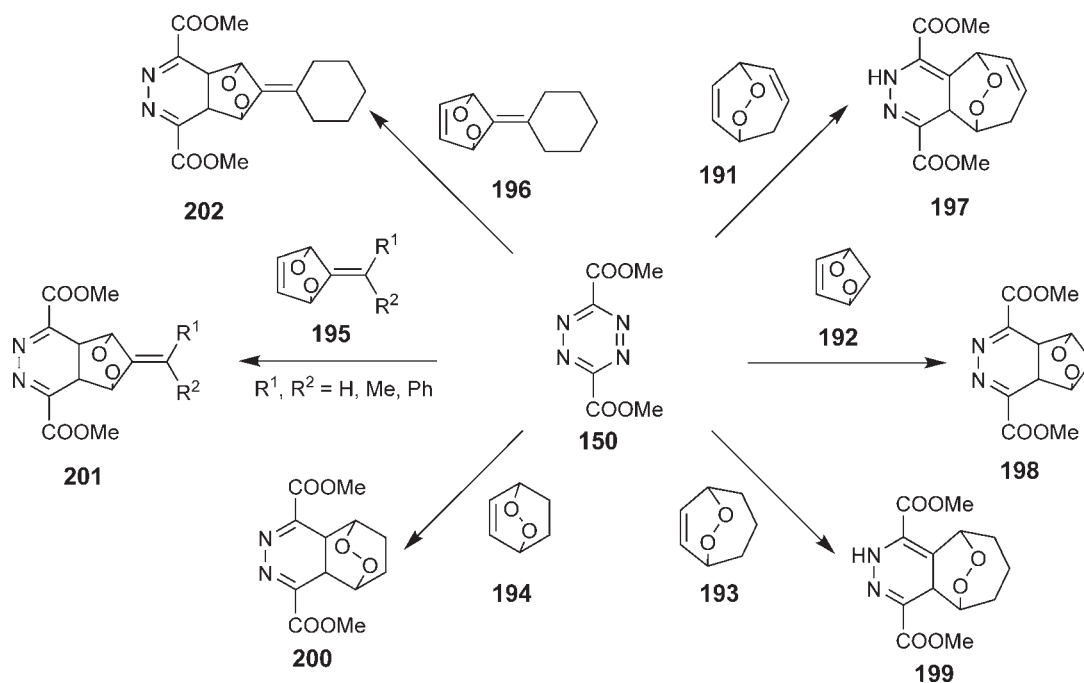
Diyne **229** have been used as dienophiles in the reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** to yield dipyridazines **230** (Scheme 58) <1996JCM448>.



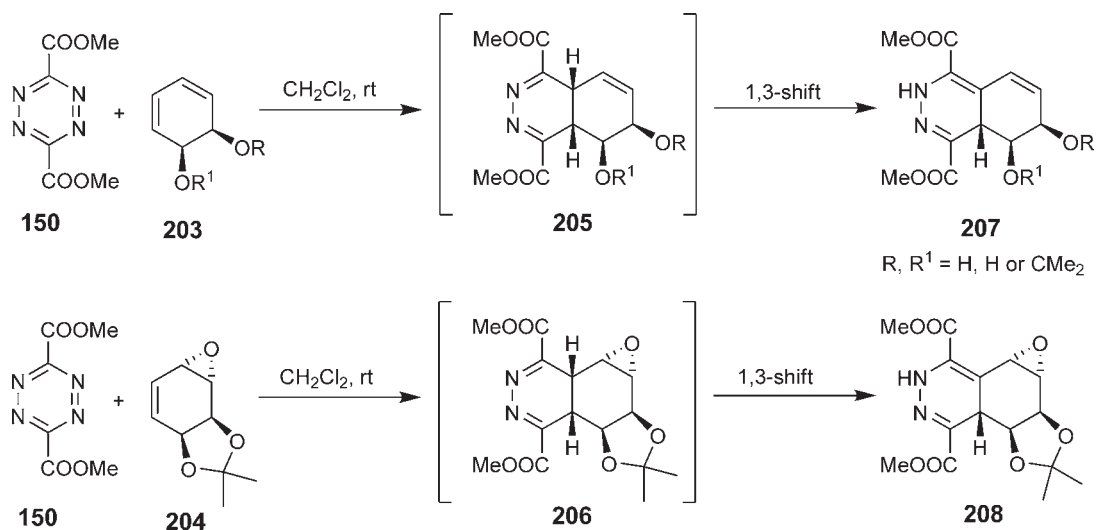
Scheme 49



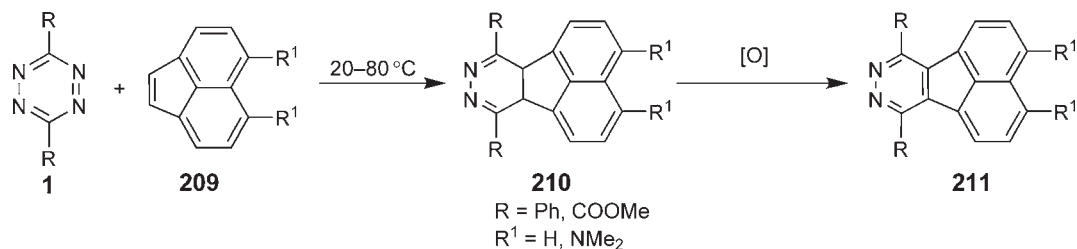
Scheme 50



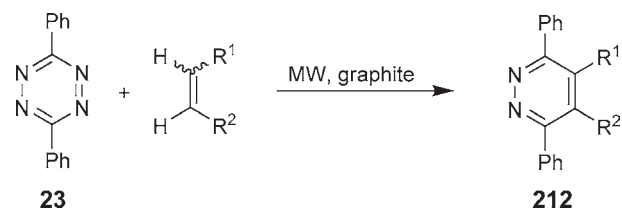
Scheme 51



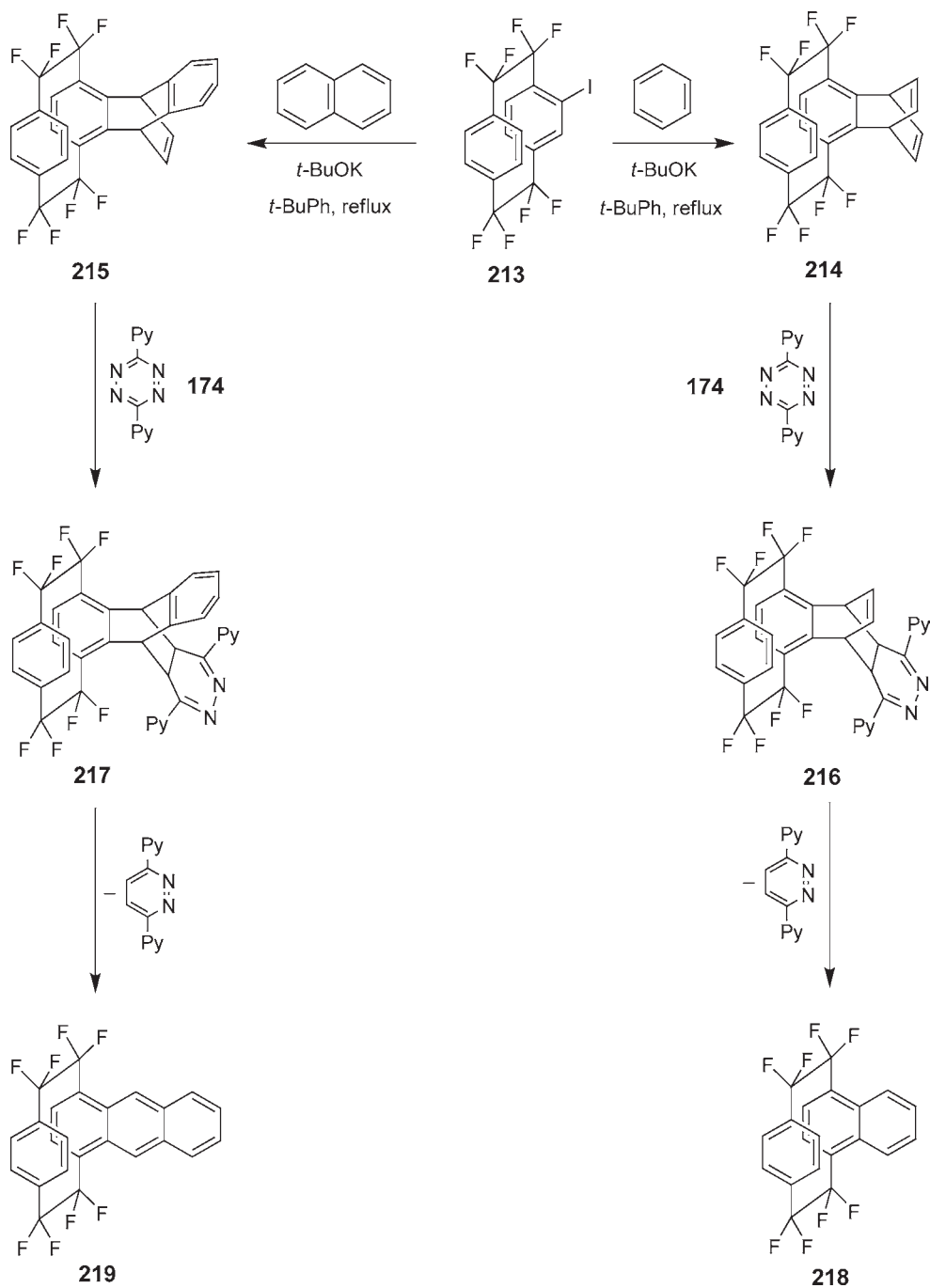
Scheme 52



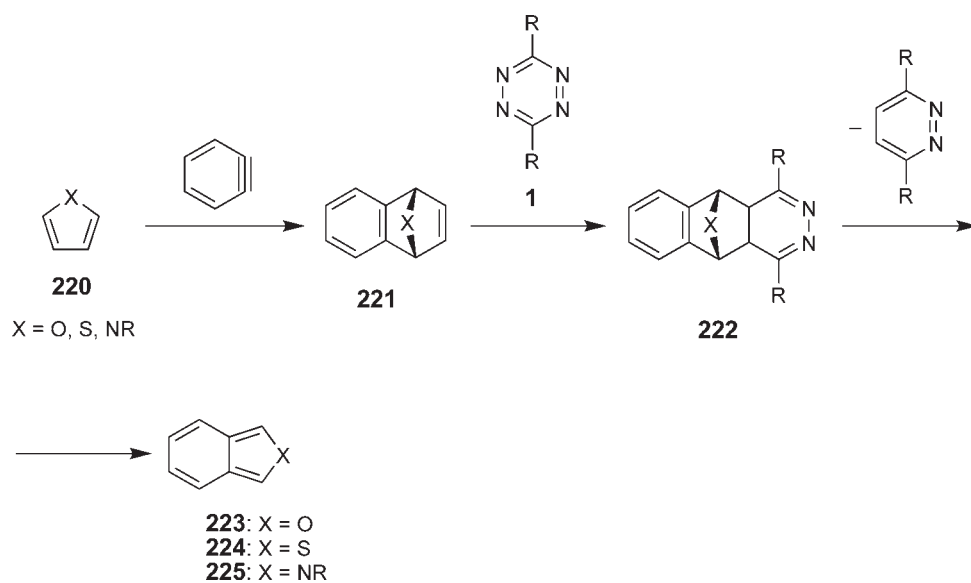
Scheme 53



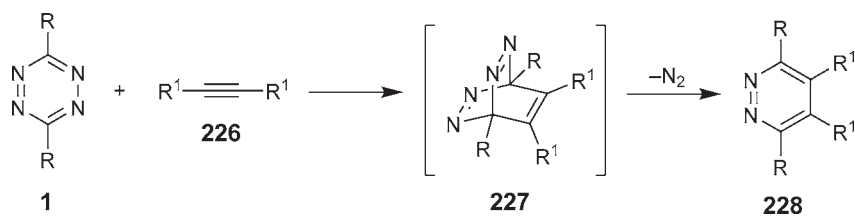
Scheme 54



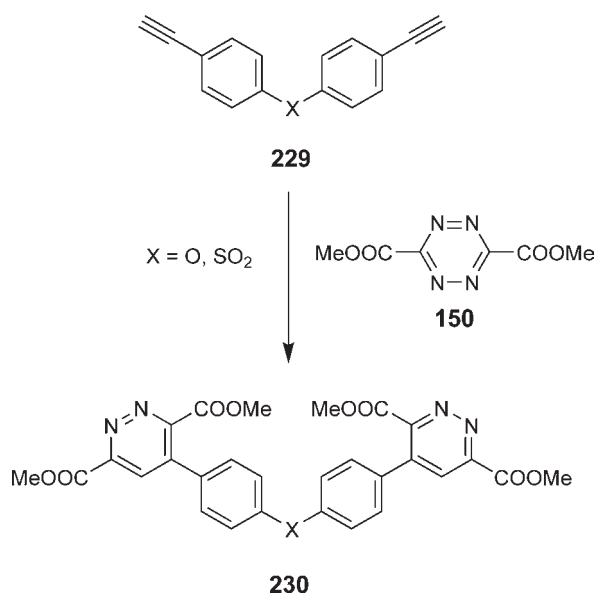
Scheme 55



Scheme 56

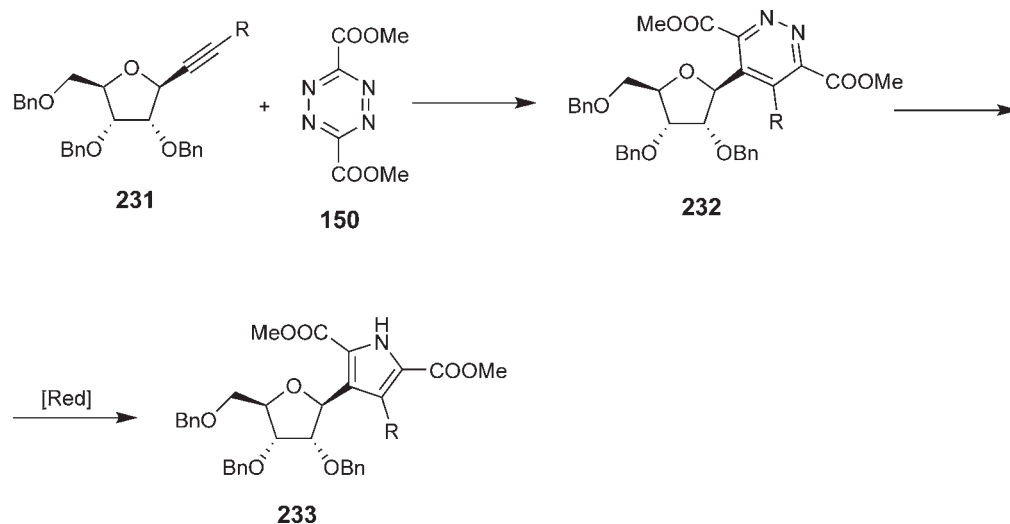


Scheme 57



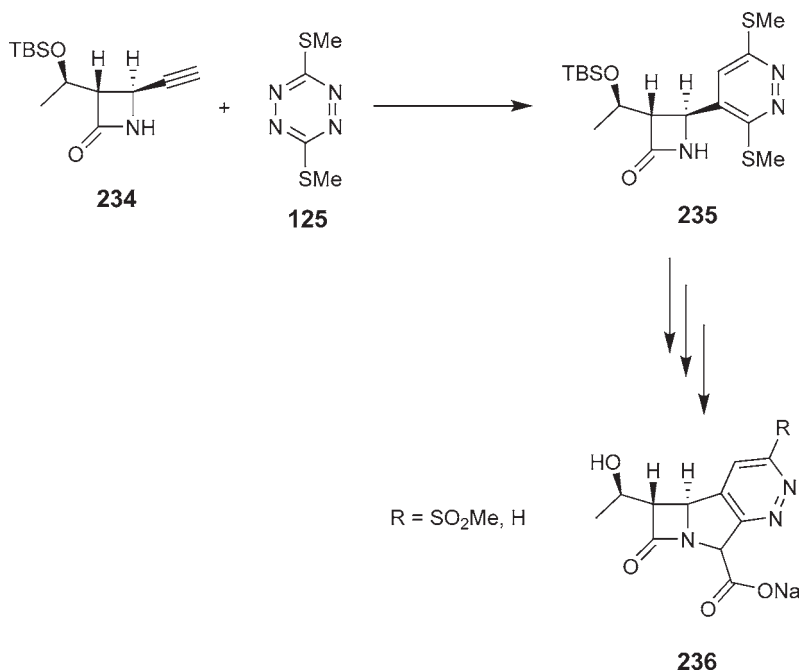
Scheme 58

Novel pyrrole C-nucleosides **233** were synthesized in two steps by cycloaddition of alkynyl C-nucleosides **231** to dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** <1994AP365>, followed by extrusion of nitrogen from the resultant pyridazine C-nucleosides **232** using electrochemical and/or chemical reduction (Scheme 59) <2004TL1031>.



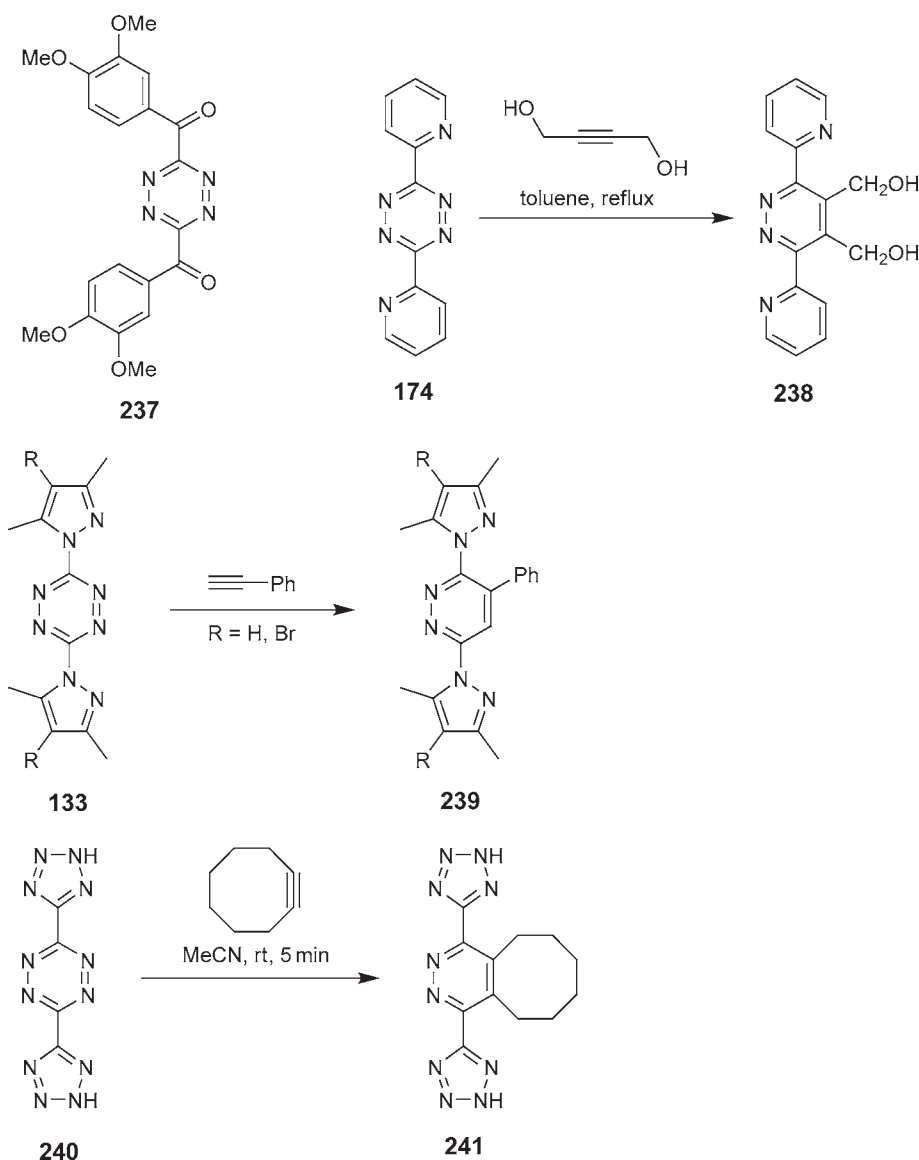
Scheme 59

Sakya *et al.* reported the preparation of novel tricyclic diazo carbapenem derivatives **236**, where one of the key steps in their synthesis involved cycloaddition of 3,6-bis(methylthio)-1,2,4,5-tetrazine **125** to alkynyl azetidinone **234**, which gave the corresponding pyridazine **235**. Attempted preparation of analogs of **235** via reaction of **125** with vinyl azetidinone analogs of **234** resulted in the formation of undesired rearrangement products (Scheme 60) <1997TL5913>.



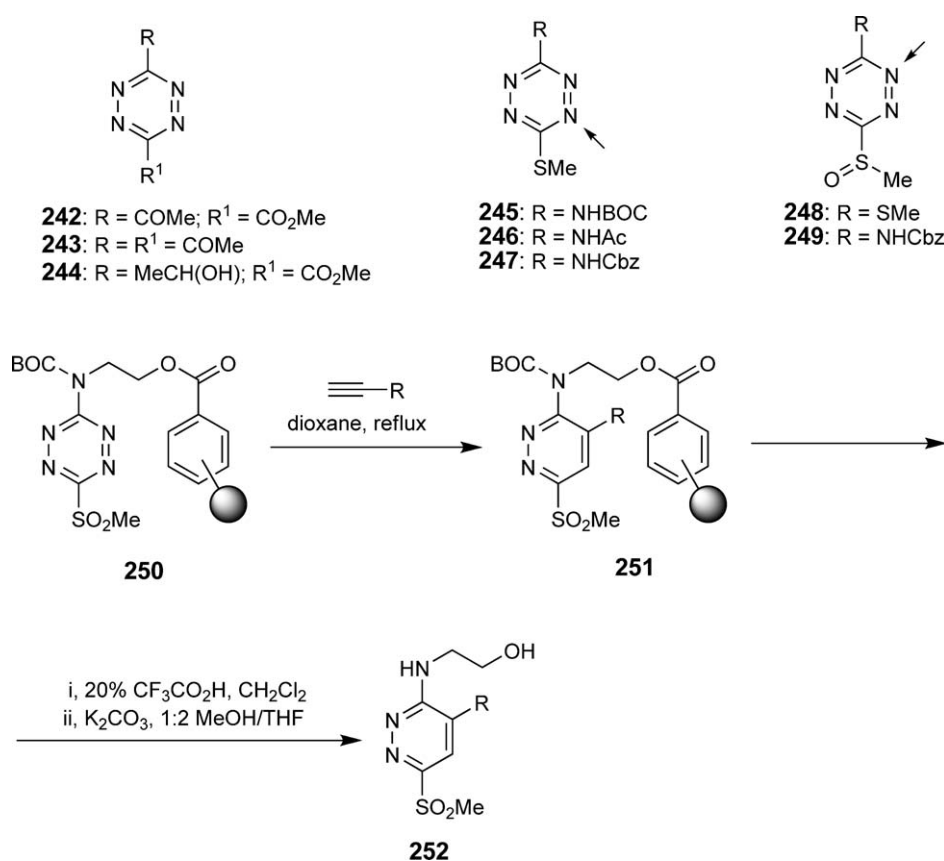
Scheme 60

A number of symmetric 1,2,4,5-tetrazine derivatives **1** were prepared and reacted with different alkynes and alkenes. Boger and co-workers prepared a new 3,6-bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine derivative **237** in five steps and 28% overall yield starting from commercially available 3,4-dimethoxybenzaldehyde. Tetrazine **237** was shown to undergo [4+2] cycloadditions readily with electron-rich, neutral, and even electron-poor alkynes <2003JOC3593>. Hoogenboom *et al.* reacted 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **174** with various alkynes including hydroxyl-functionalized alkynes under thermal <2003EJO4887> and microwave-assisted conditions <2006JOC4903> in the preparation of new pyridazine derivatives. Thus-formed 4,5-bis(hydroxymethyl)-3,6-di(2-pyridyl)pyridazine **238** and other hydroxyalkylpyridazines, together with their polymer bound derivatives, were studied in self-assembly reactions with copper(i) and silver(i) ions <2005MI873, 2004MI3131, 2004PP335, 2003EJO4887, 2003MM4743>. Reactions of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**133**: R = H) and its 4-bromo-3,5-dimethylpyrazol-1-yl derivative (**133**: R = Br) with phenylacetylene afforded the corresponding pyridazine products **239** <2000RCB355>. Cycloaddition of a highly explosive 3,6-bis(2*H*-tetrazol-5-yl)-1,2,4,5-tetrazine **240** to highly reactive cyclooctyne gave, after 5 min at room temperature, the desired hexahydrocycloocta[*d*]pyridazine **241** (Scheme 61) <2001EJO697>. Other examples of cycloadditions of various 3,6-diaryl-1,2,4,5-tetrazines **1** (R = Ar) to cyclooctyne have also been reported <1999HCO53>.



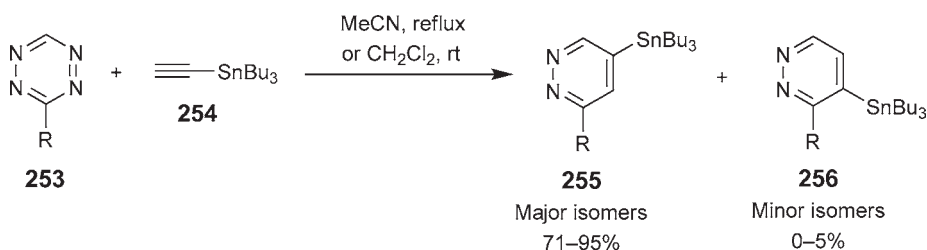
Scheme 61

An increasing number of papers report on the preparation of unsymmetrical 1,2,4,5-tetrazines and their regioselectivity in cycloaddition reactions with different alkenes and alkynes. Reaction of 3-methoxy-6-methylthio-1,2,4,5-tetrazine with phenylacetylene and hex-5-ynenitrile provided both regioisomeric pyridazines as a 1:1 mixture <1997TL3805>. Snyder and co-workers prepared three 1,2,4,5-tetrazine derivatives **242**–**244**. Reactions of **242** and **243** with benzyne gave the corresponding pyridazines in moderate (39%) and good (84%) yield, respectively. In contrast, reactions of **242** and **244** with ethoxyacetylene furnished the corresponding pyridazines, in the former case with no regioselectivity and, in the latter case, with excellent regioselectivity (ethoxy group positioned *ortho* to the CO₂Me group in the major isomer) <1998JOC10063>. Boger and co-workers prepared a number of novel unsymmetrical 1,2,4,5-tetrazines **245**–**249** and evaluated their reactivity and regioselectivity in reactions with various alkenes and alkynes. The positions of the major regioisomers in the reactions with unsymmetrical alkynes are indicated with arrows on the starting 1,2,4,5-tetrazines. The regioselectivities of cycloadditions to **245**–**247** and **248**, **249** complement each other and seem to be dictated by the oxidation state of the sulfur atom <2006JOC185, 1998JOC6329>. Unsymmetrical 1,2,4,5-tetrazines immobilized on polystyrene **250** were prepared and reacted with a wide range of dienophiles. Reactions with terminal alkynes gave pyridazines **252** with excellent regioselectivity (Scheme 62) <1996TL8151>.



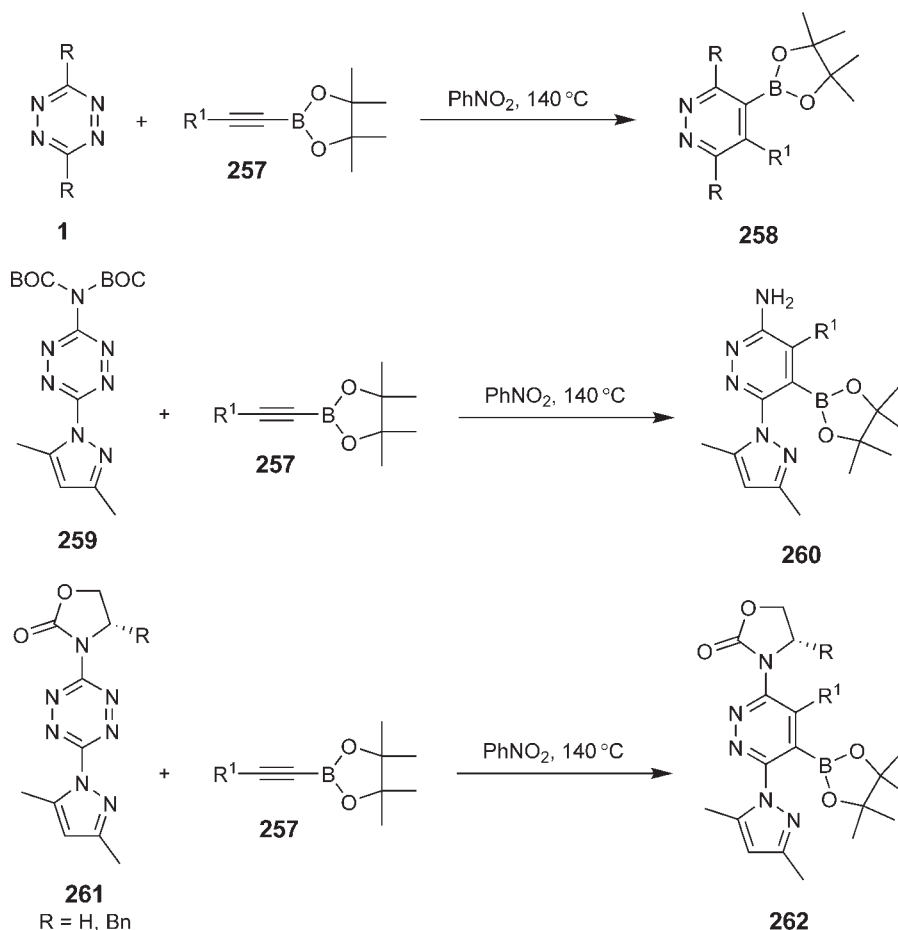
Scheme 62

Stannylated pyridazines are attractive compounds because of the possibility of their further elaboration in palladium-catalyzed cross-coupling reactions, transmetalation reactions, and other transformations. Sauer *et al.* reported extensively on the cycloaddition reactions of the parent 1,2,4,5-tetrazine (**1**: R = H) with a large number of alkynes, including mono- and disubstituted silyl, germanyl, and stannyl alkynes. Rate constants of these reactions were measured <1998EJO2885, 1997TL5791>. They also demonstrated that reactions of 3-aryl-1,2,4,5-tetrazines **253** with ethynyltributyltin led regioselectively to the formation of 3,5-disubstituted pyridazines **255** (Scheme 63) <1998T4297>. 3,6-Dichloro-1,2,4,5-tetrazine **128** undergoes Diels–Alder reaction with a range of alkenes and alkynes, including stannyl alkynes <1998TL5873>.



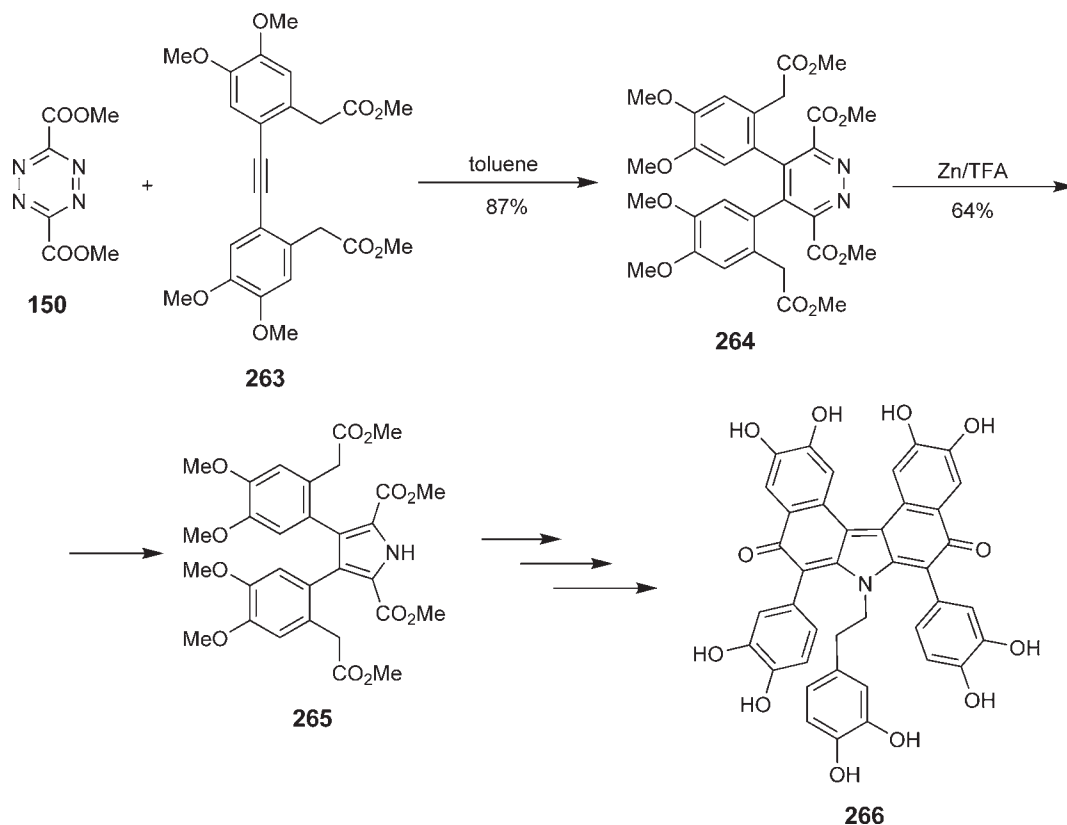
Scheme 63

Pyridazine boronic esters are substrates in Suzuki cross-coupling reactions. [4+2] Cycloaddition reactions of 1,2,4,5-tetrazine derivatives **1** with alkynyl boronic esters **257** provide easy access to functionalized pyridazine boronic esters **258**. New unsymmetrical 1,2,4,5-tetrazines **259** and **261** have been prepared and tested in reactions with alkynyl boronic esters **257**, providing the corresponding pyridazines **260** and **262** as single regioisomers (Scheme 64) <2005AGE3889>.



Scheme 64

Boger and co-workers were highly successful in employing cycloaddition reactions of 1,2,4,5-tetrazine derivatives with appropriately substituted alkynes as one of the key steps in the total synthesis of a number of natural products and their derivatives <2005JA10767, 2000JOC2479, 2000JOC9120, 1999JA54>. An example is the total synthesis of ningalin D **266**, which was based on a key cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** to alkyne **263**, thus affording pyridazine **264**, followed by reductive ring contraction of **264** to provide the tetrasubstituted pyrrole **265** (Scheme 65) <2005JA10767>.



Scheme 65

9.12.7.2.2(iii) Enolates as dienophiles

Inverse demand Diels-Alder reactions of tetrazines **1** to psoralenes **267** were reported to furnish tetracyclic pyridazine dicarboxylates **268**, which were used as the key intermediates in the synthesis of nitrogenated isosteres of potent DNA inhibitors <2003T8171>. In some cases, cycloaddition was followed by opening of the furan ring to give pyridazinyl-substituted coumarins **271** (Scheme 66) <2000JHC907, 2003SL2225>.

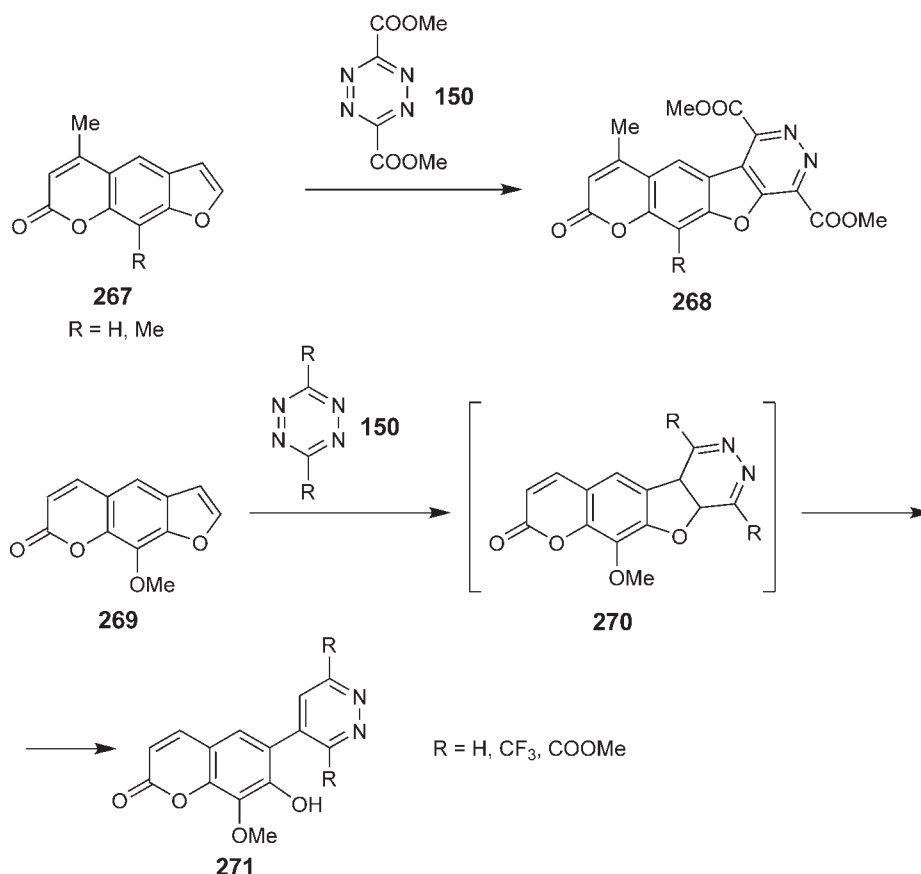
Pyridazino-fused coumarins **275** were obtained in the reactions of tetrahydrobenzodifuran **272** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150**. The reactions proceeded via [4+2] cycloaddition to give **273**, followed by a 'ring switching' reaction to give **274**, then **275** (Scheme 67) <2005T4805>.

The reactions of coumaran-3-ones **276** and **278** with tetrazines **1** were used for the preparation of the pyridazino-fused analogs **277** and **279** (Scheme 68) <2002SL2095, 2002S43>.

Cycloaddition of 3,6-diphenyl-1,2,4,5-tetrazine **23** to the enolate of **281** produced molecular clefts **283** (Scheme 69) <1996T13531>.

Cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** to (*R*)-1-benzyloxy-2-isopropyl-4-methoxybut-3-ene **284** to form **285** was also used as the first step in the total synthesis of *ent*-(-)-roscophilin <2001JA8515>. Reaction with 1,1-dimethoxyethene **286** provided the pyridazine derivative **287** in 84% yield. Compound **287** was used then for further transformations in the synthesis of isochrysohermidin-distamycin hybrids (Scheme 70) <2003JOC5249>.

Bioisostere **289** of (±)-pyrido[3,4-*b*]homotropine, as a novel nicotinic acetylcholine receptor (nAChR) ligand, was prepared by treatment of silylenol ether **288** with 1,2,4,5-tetrazine **1** <2002BMC1>. Cycloaddition of 1,2,4,5-tetrazine **1** to the enol ether **290** was used in the last step of the preparation of ferrugininoid **291** <2004PHA427>. (±)-Epibatidine analogs **294** were prepared by cycloaddition of tetrazines **1** to the enol ether **293** <2002T1343, 2001JME47>. Similarly, anabasine analogs **297** were prepared by treatment of enol ether **296** with tetrazines **1** <2002T1343>. 3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine **174** was used in the key step of the synthesis of pyridazinomorphinan **299** (Scheme 71) <1997AP163>.



Scheme 66

9.12.7.2.2(iv) Enamines as dienophiles

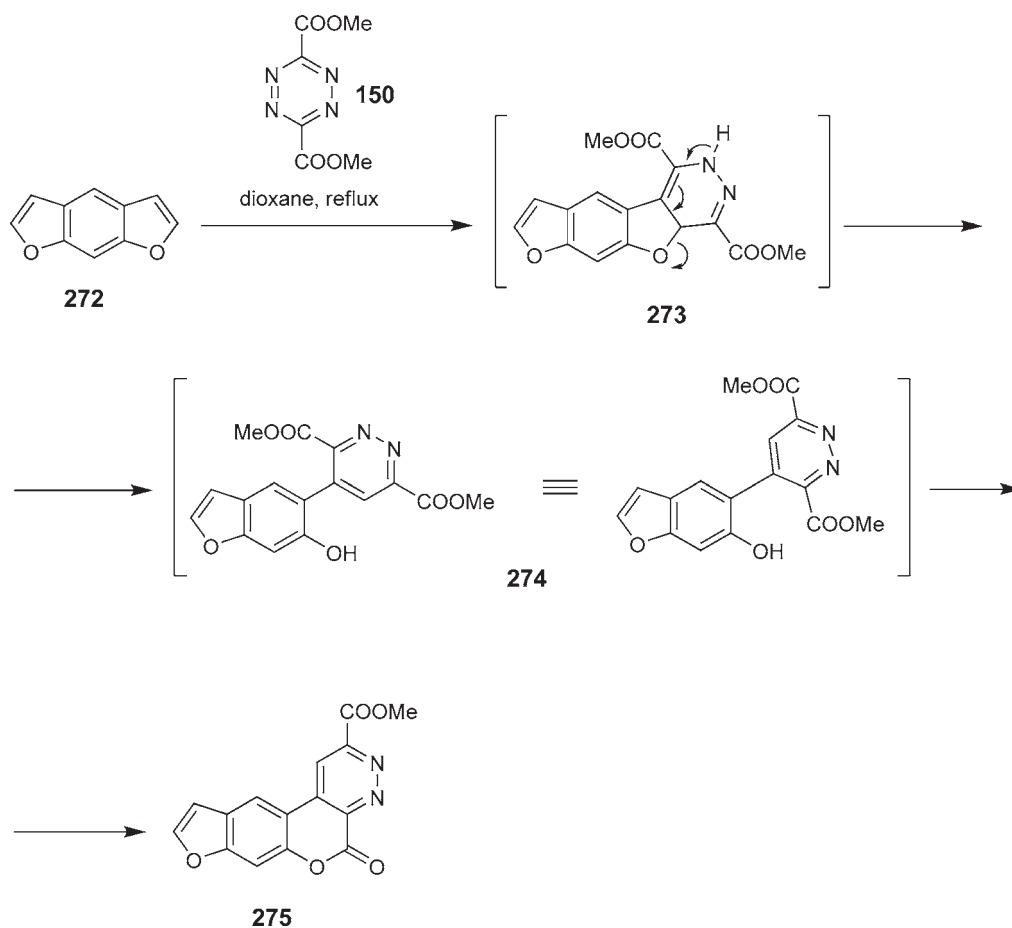
Since cycloadditions of tetrazines follow the 'inverse electron demand' in Diels–Alder reactions, cycloadditions to electron-rich enamines usually proceed easily and under mild conditions. In general, elimination of amine takes place from the initially formed dihydropyridazine to give the fully conjugated pyridazines as products.

4-Heteroaryldienamines **300a–c** and **301a–c** were reported to react with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** selectively at the enamine C=C bond to give 4-(2-heteroarylvinyl)pyridazines **302a–c** and **303a–c** in 32–52% yields. 4-[(1*E*,3*E*)-4-Heteroarylbuta-1,3-dienyl]morpholines **300** afforded the (*E*)-4-(2-heteroarylvinyl)pyridazines **302**, while 4-[(1*E*,3*EZ*)-4-heteroarylbuta-1,3-dienyl]-2-methylaziridines **301** gave the (*Z*)-isomers **303** (Scheme 72) <1995JOC4919, 1996JOC4423>.

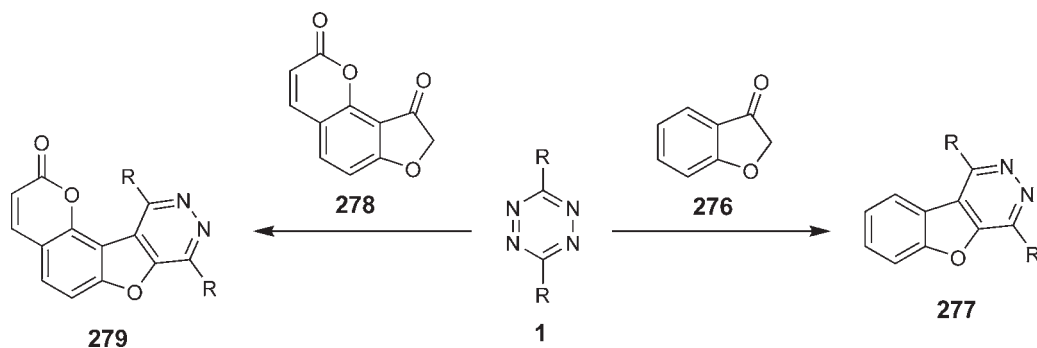
On the other hand, reactions of 4-heteroaryl-2-methyldienamines **304** with tetrazines **1** furnished 4-heteroarylpyridazines **307** and dihydropyridazines **308** in 38–92% yields. Presumably, these two products are formed by initial double cycloaddition of the tetrazine **1** to both C=C bonds to give the intermediate **306**, which disproportionates into **307** and **308** (Scheme 73) <1999TL6313>.

Smith and co-workers reported a tandem 'inverse electron demand' Diels–Alder reaction of acyclic dienamines **309** with 1,2,4,5-tetrazine **150**, which produced 8,9-diazatricyclo[2.2.2.0^{2,6}]oct-8-ene derivatives **312** under mild reaction conditions. A plausible mechanistic rationalization involves cycloaddition of the tetrazine **150** to the less-hindered 3,4-double bond of the dienamine **309** followed by intramolecular addition of the enamine moiety to the azadiene system. On the other hand, cyclopentadipyridazine **314** was obtained upon reaction of tetrazine **150** with the analogous cyclic dienamine **313** (Scheme 74) <1998TL1045>.

meta-Phenylene- and *para*-phenylene-bis(dienamines) **315** and **316** were transformed with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** into the corresponding phenylene-bis(triazolylvinylpyridazines) **317** and **318** in 59–90% yields. Cycloadditions took place selectively at the enamine C=C bond (Scheme 75) <2004T3421>.



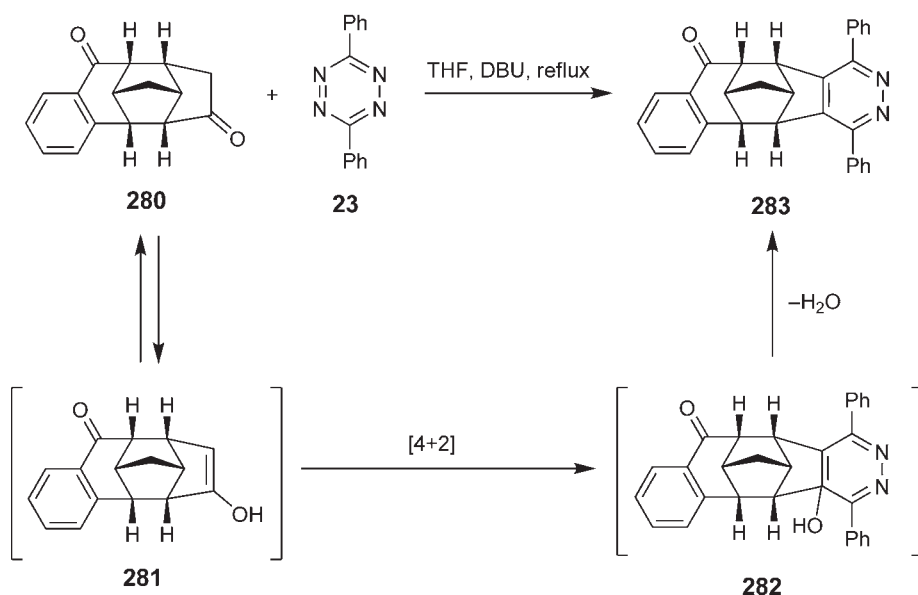
Scheme 67



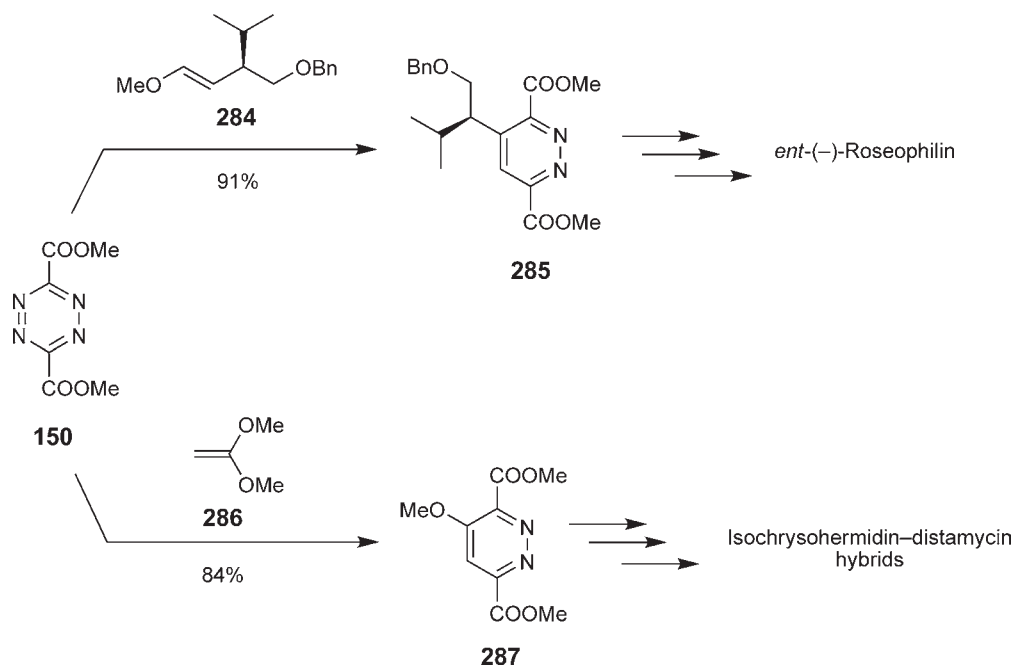
Scheme 68

Recently, Rusinov *et al.* reported unexpected formation of cyclopenta[4,5]imidazo[1,2-*b*]-1,2,4,5-tetrazines **321** in the reactions of *s*-tetrazine hydrazones **319** with enamines **320** in methanol. When carried out in acetonitrile, these reactions produced the expected cyclopenta[4,5]pyridazines **322** (Scheme 76) <2003HCO39>.

4-Methylpyrrolo[2,3-*h*]coumarin **323** was treated with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** to give 8,11-disubstituted-9,10-diaza-4-methylbenzopyrrolo[2,3-*h*]coumarins **324** (Scheme 77) <2002S475>.

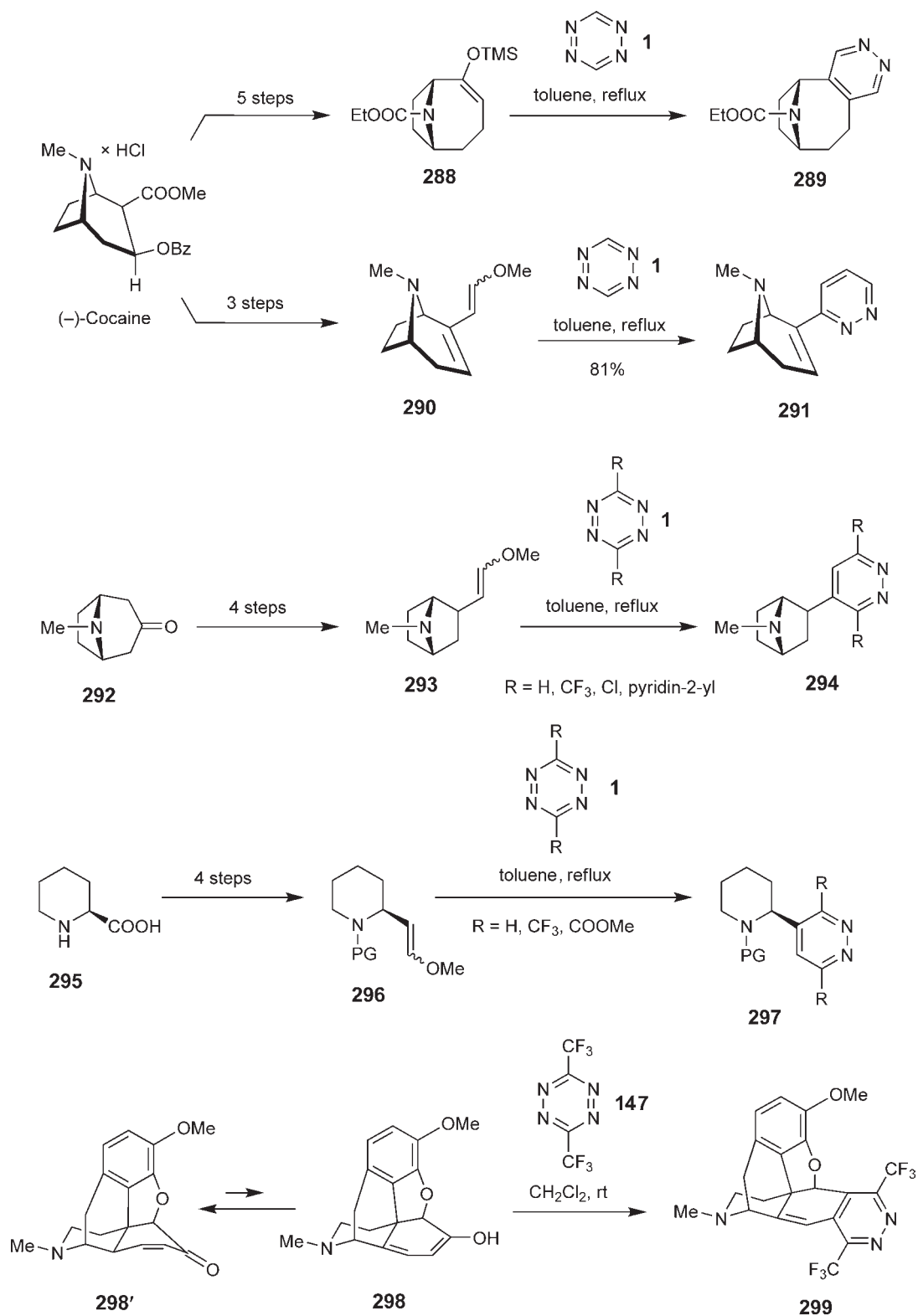


Scheme 69

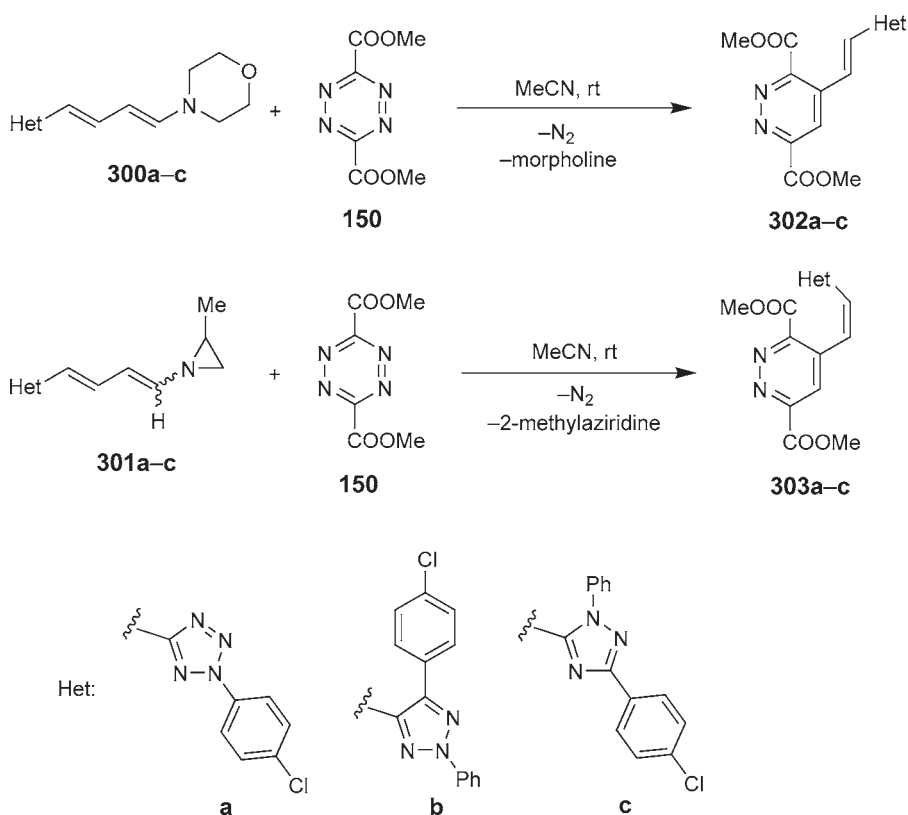


Scheme 70

Snyder and co-workers tried to utilize cycloadditions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** to N-substituted indoles **325** as the key step in the attempted preparation of carbazoles [<1997TL8611>](#). However, unlike previous examples reported by Haider and Wanko with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** [<1994ACO205, 1994H\(38\)1805>](#), the initially formed dimethyl 5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylates **326** did not react further with any dienophile. On the other hand, they underwent reductive ring contraction readily with zinc in acetic acid to furnish dimethyl 5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylates **327** (Scheme 78) [<1997TL8611>](#).



Scheme 71



Scheme 72

2-Substituted imidazoles **328** were reported also as dienophiles in inverse demand Diels–Alder reactions leading to purine analogs **329** (Scheme 79) <2001T5497>.

Bioisosteres **332** of ($\pm$)-pyrido[3,4-*b*]tropane, as nAChR ligands, were prepared by treatment of enamine **331** with 1,2,4,5-tetrazines **1** (Scheme 80) <2002BMC1>.

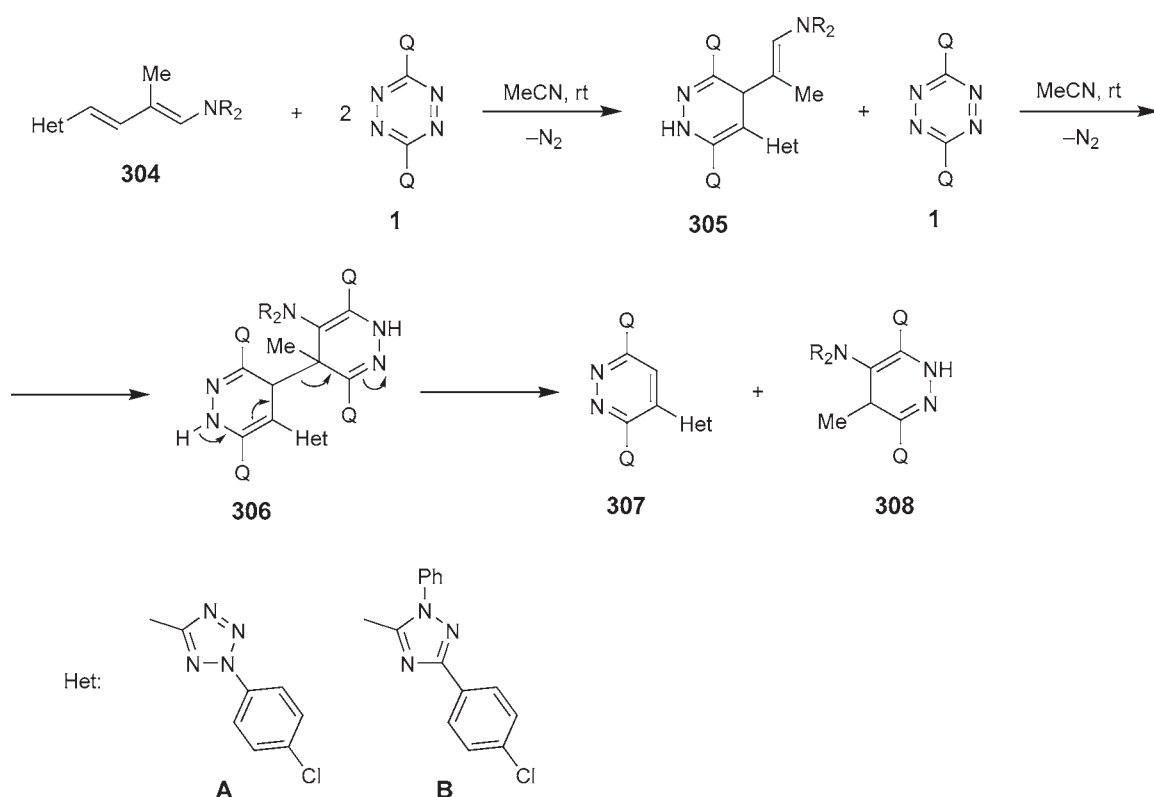
Tetrazines **1** were used in the key step for the synthesis of pyridazinomorphinans **334** (Scheme 81) <1997AP163>.

9.12.7.2.2(v) Iminoethers and amidines as dienophiles

For a cycloaddition reaction of a 1,2,4,5-tetrazine **1** with a heterodienophile to proceed successfully, the latter must be activated with an electron-donating group. In this sense, thioimides, imidates, and amidines **335** proved to be reactive heterodienophiles in the inverse Diels–Alder reactions with 1,2,4,5-tetrazines **1**. The reaction proceeds via the initial formation of the bicyclic adduct **336**, followed by the loss of a nitrogen molecule to form the dihydro cycloadduct **337**, and final aromatization by the loss of a thioalkoxy, alkoxy, or amino group to form the final 1,2,4-triazines **338** (Scheme 82).

Other reactive heterodienophiles include electron-rich hydrazones and cyanamides, oxazolines, thiazolines, pyrazolines, donor-substituted benzonitriles, thioketones and aldehydes, thioformic acid derivatives, and thionylimines <1996CHEC-II(6)901>.

Seitz *et al.* prepared various 1,2,4-triazine-*C*-nucleosides **340** via cycloaddition of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** to monosaccharide-derived imido esters **339** as intermediates in their quest for new pyridine *C*-nucleosides <1999ZNB549, 1997ZNB851, 1995AP175>. Similarly, the same group reported the preparation of novel 2-(2'-pyrrolidinyl)pyridines from (*S*)- and (*R*)-proline via cycloaddition of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **147** to heterodienophilic imidates or hydrazones derived from (*S*)- and (*R*)-proline <1999TA573>. Reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **150** with either *O*-methylisourea or cyanamide gave 4-amino-1,2,4-triazine **341**. Further, reductive ring contraction of 1,2,4-triazine **341** gave the corresponding imidazole **342** (Scheme 83) <2006S1513>.



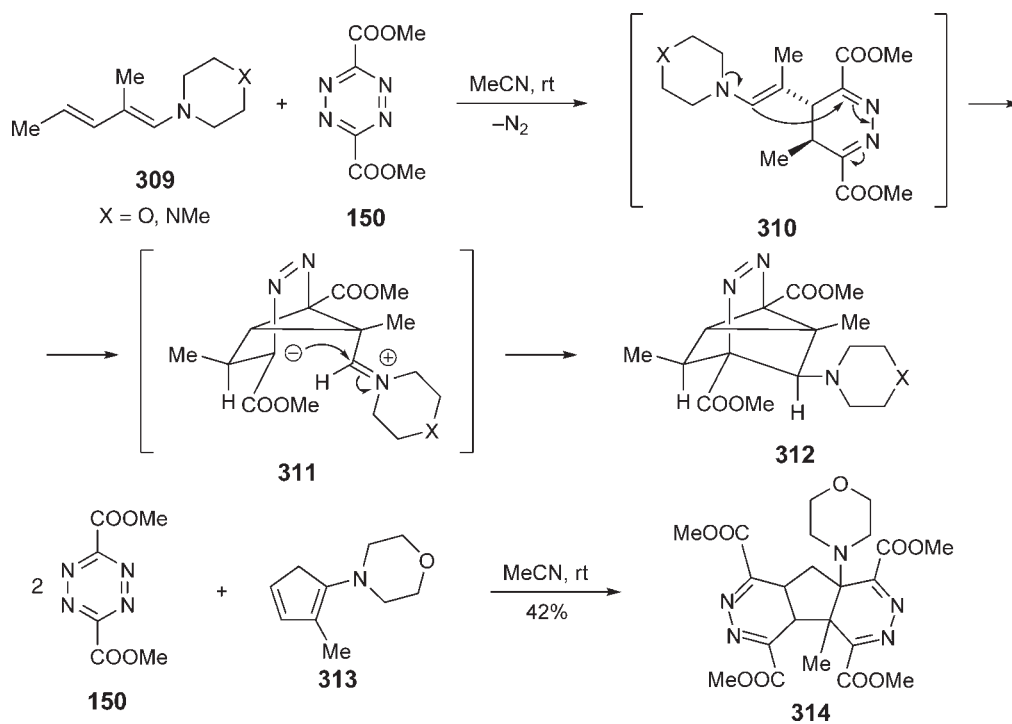
<i>NR</i> ₂	<i>Het</i>	<i>Q</i>	Yield ^a (%)	
			307	308
Morpholin-4-yl	A	COOMe	68	71
Pyrrolidin-1-yl	A	COOMe	92	94
Pyrrolidin-1-yl	B	COOMe	47	53
Pyrrolidin-1-yl	A	CF ₃	38	44
Morpholin-4-yl	A	Pyridin-2-yl	39	42
Pyrrolidin-1-yl	A	Pyridin-2-yl	45	56
Pyrrolidin-1-yl	B	Pyridin-2-yl	42	37

^aYields of analytically pure products based on starting dienamine.

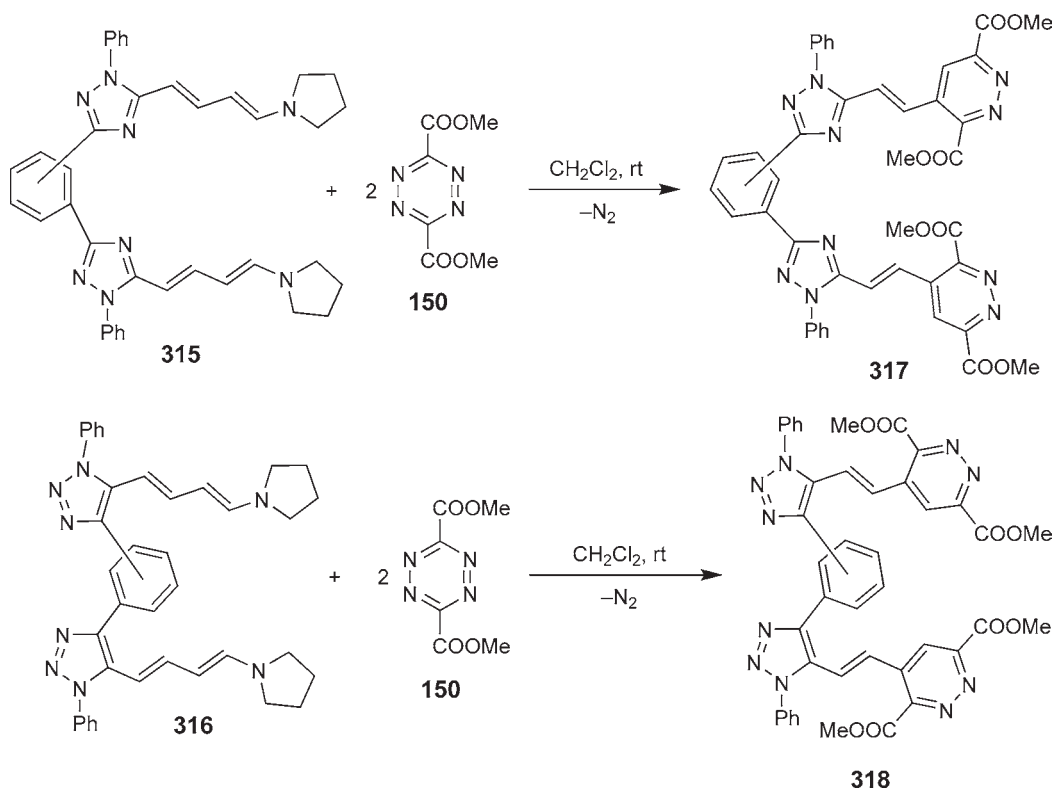
Scheme 73

When tetrazine **150** was treated with ketene *N,O*-acetals **343** in dichloromethane at 25 °C, pyridazine-3,6-dicarboxylates **344** were obtained in 21–98% yields. In the case of the carboxamido electron-withdrawing group, further cyclization between the amide nitrogen and the ester group afforded pyrrolopyridazine **345** (Scheme 84) <2006S1513>.

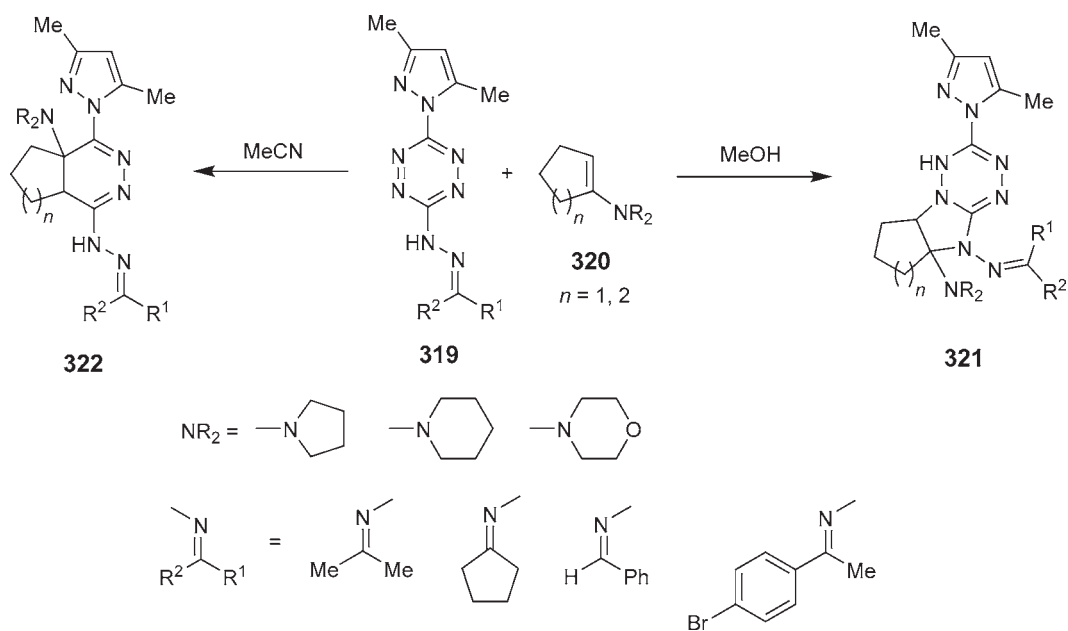
An interesting phenomenon was observed by Hartmann and Heuschmann in their study on the regioselectivity of cycloadditions of unsymmetrically substituted 3,6-diaryl-1,2,4,5-tetrazines **346a** and **346b** to 2-cyclopropylidene-1,3-dimethylimidazolidine **347**. On addition of **347** to a solution of tetrazine **346a** in tetrahydrofuran below –10 °C, a mixture of the intermediate zwitterions **348a** and **349a** was formed in a ratio of 67:33. Slow heating of this mixture above 0 °C resulted in evolution of nitrogen and produced the dihydropyridazine **351a**, exclusively. In contrast,



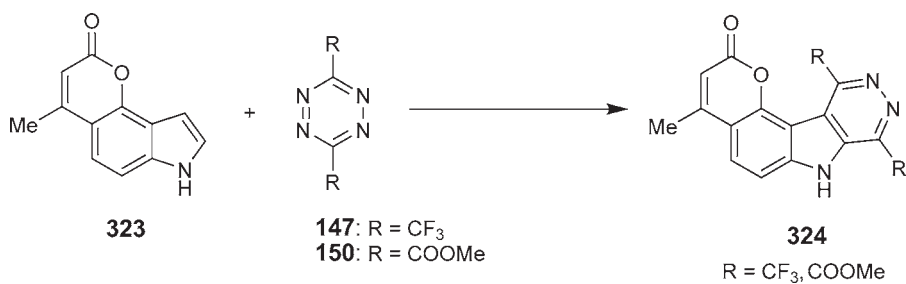
Scheme 74



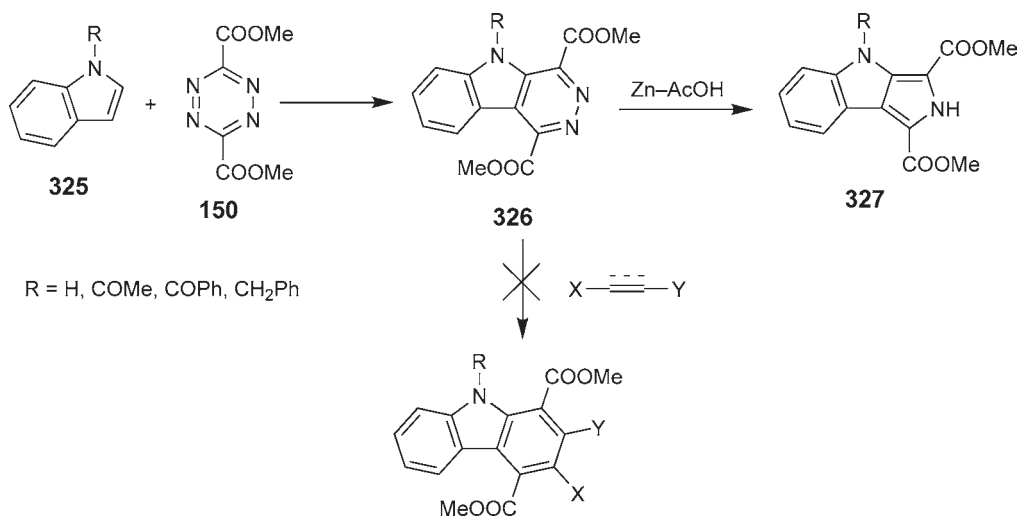
Scheme 75



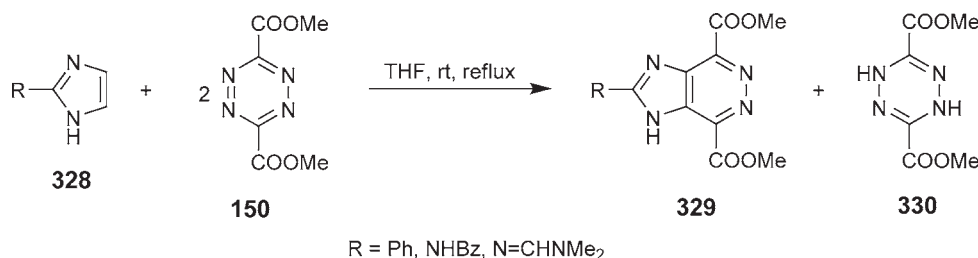
Scheme 76



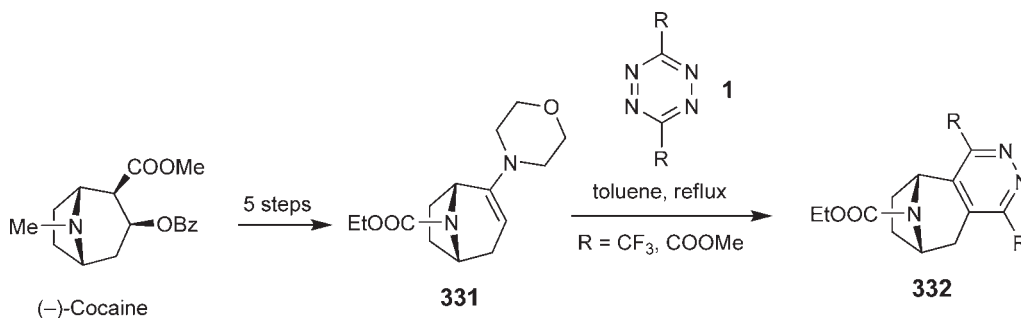
Scheme 77



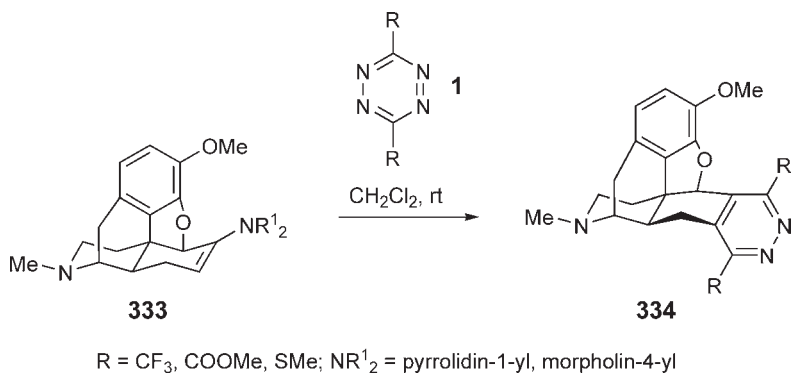
Scheme 78



Scheme 79



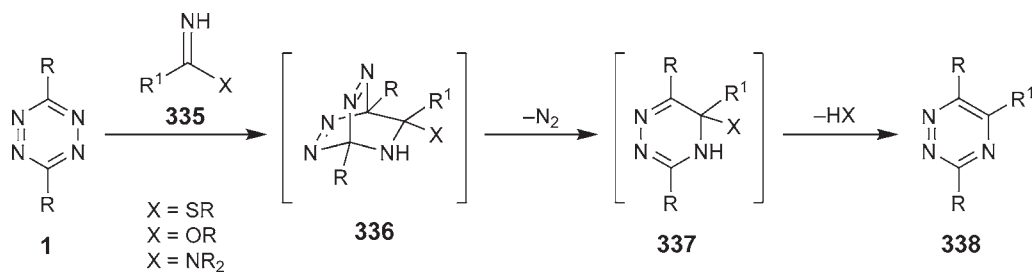
Scheme 80



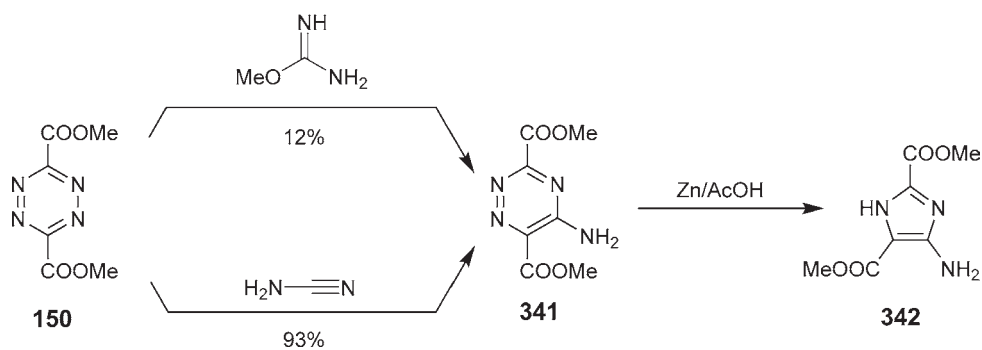
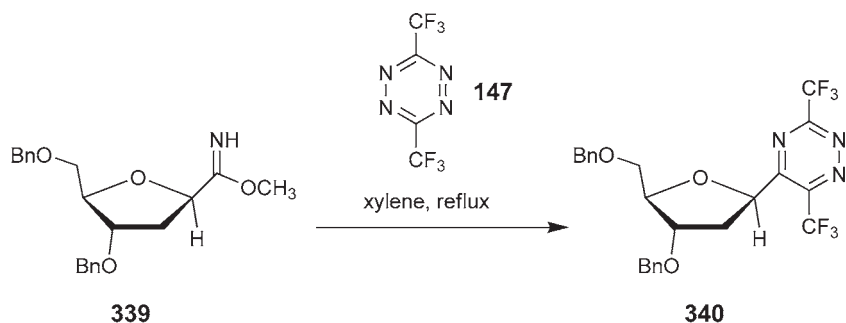
Scheme 81

tetrazine **346b** gave only the zwitterion **348b** on reaction with 2-cyclopropylidene-1,3-dimethylimidazolidine **347**. Warming of **348b** to room temperature did not lead to gas evolution and no traces of [4+2] cycloadduct could be identified. After prolonged heating, the zwitterion **348b** decomposed to the starting tetrazine **346b**. The only reasonable explanation demands that the zwitterion **348a** split up into the starting materials, which recombine again into a mixture of **348a** and **349a**. While **348a** is caught in a dead-end equilibrium, **349a** is gradually converted to the [4+2] cycloadduct **351a**. The reason for this behavior again must be a steric effect. In order to achieve ring closure, the imidazolium ring and the aryl ring must be nearly coplanar. This is easily achieved with the phenyl ring in **349a**, while the *ortho*-methyl group in **348a** disfavors this conformation. The reactivity of **348b** is consistent with this picture. The mesityl group prevents the ring closure to **350b** (Scheme 85) <2000T4213>.

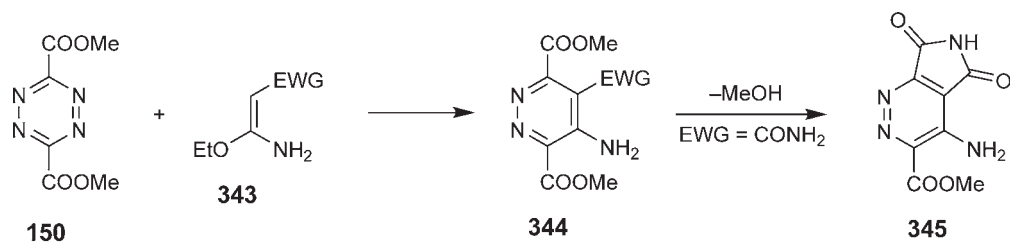
Bicyclic ketene-*S,N*-acetals **352** were reacted with tetrazines **1** in toluene at 100 °C to afford a series of condensed pyridazines **354**. In some cases, the intermediate dihydropyridazines **353** were isolated (Scheme 86) <1996H(43)1967>.



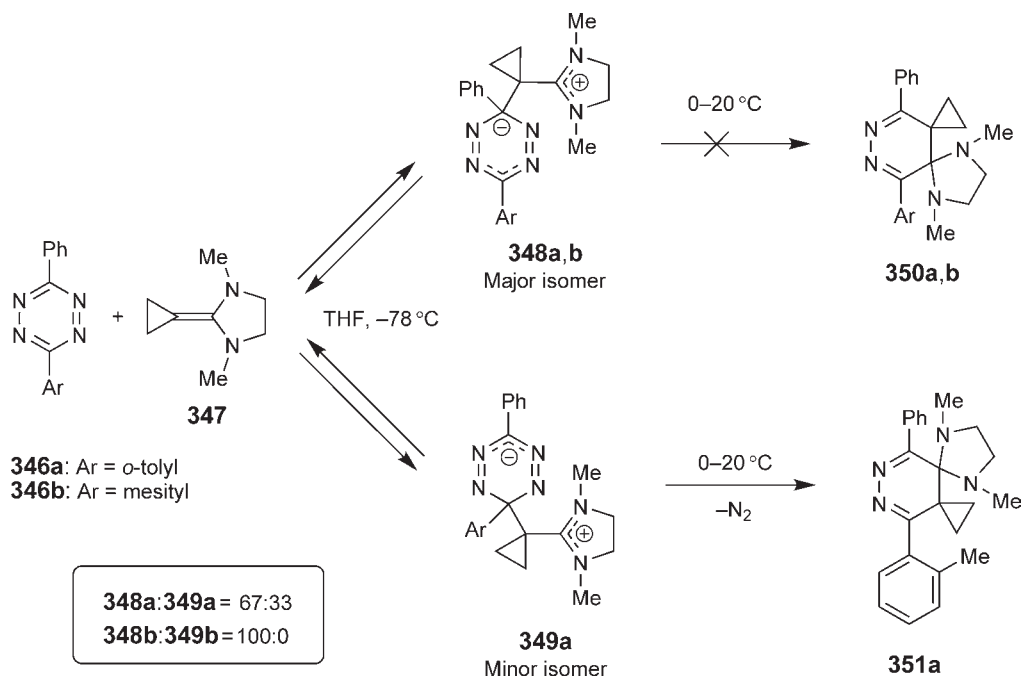
Scheme 82



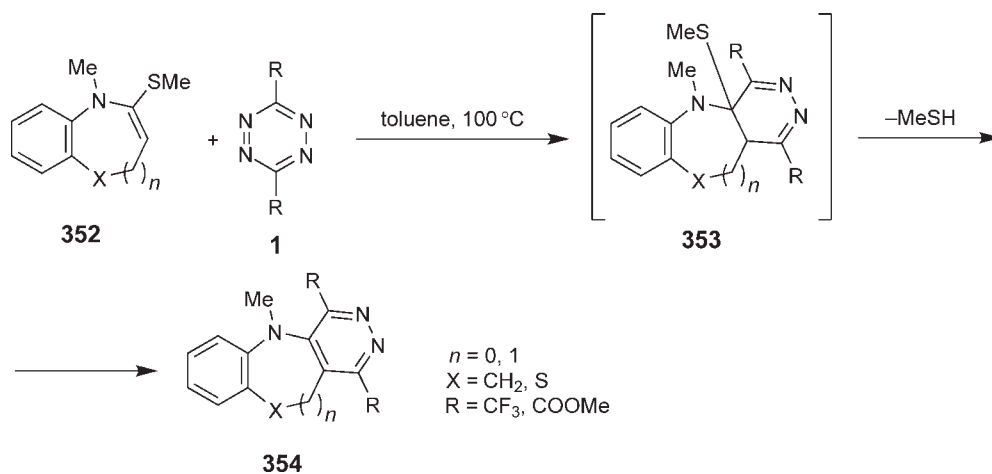
Scheme 83

EWG = $COOMe$, $COOEt$, $COMe$, $COPh$, $COCF_3$, $CONH_2$

Scheme 84



Scheme 85

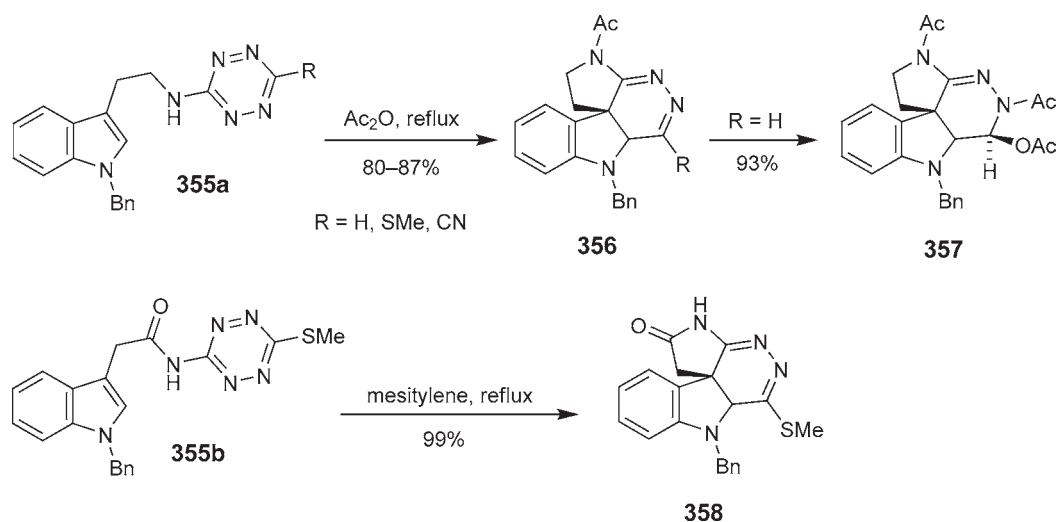


Scheme 86

Other isolated examples of cycloaddition reactions of different 1,2,4,5-tetrazines **1** with activated thioimides, imidates, and amidines can be found in [<2003JOC3593>](#) and [<1998JOC6329>](#).

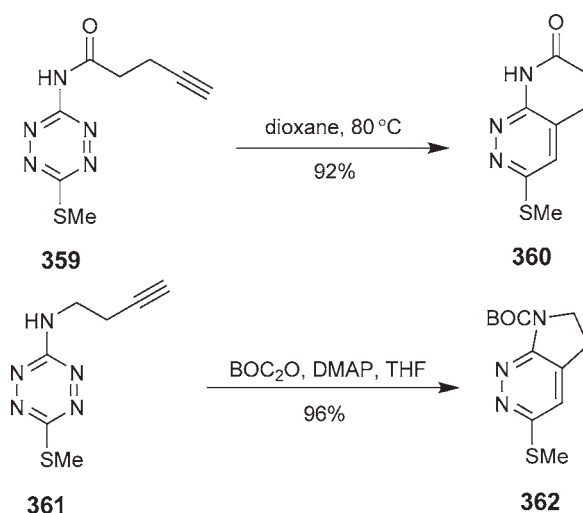
9.12.7.2.2(vi) Intramolecular cycloaddition reactions

Intramolecular cyclizations of 1,2,4,5-tetrazines **355**, tethered at position 3 of the indole ring, were used to produce the skeleton **356–358** of the [AbazaCE]-Aspidosperma alkaloids in good to excellent yields ([Scheme 87](#)) [<1996TL5061, 2000T1165>](#).



Scheme 87

Interestingly, Boger *et al.* found that intramolecular cycloadditions of tethered alkynes **359** and **361** proceeded under milder conditions than their intermolecular analogs, giving the expected fused pyridazines **360** and **362**, respectively (Scheme 88) <1998JOC6329>.



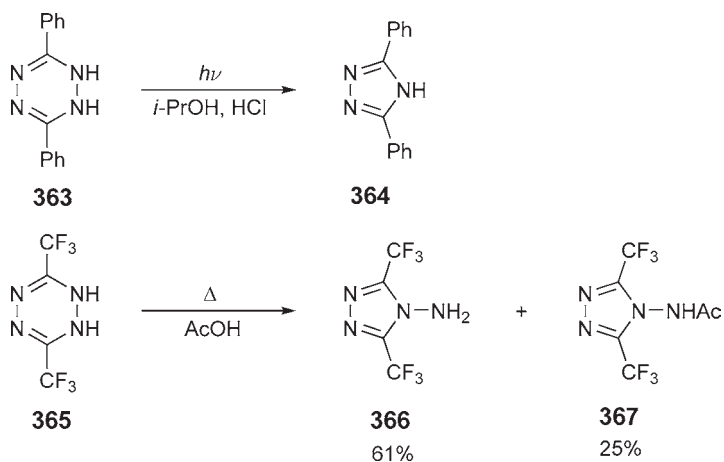
Scheme 88

9.12.7.2.3 Ring contractions

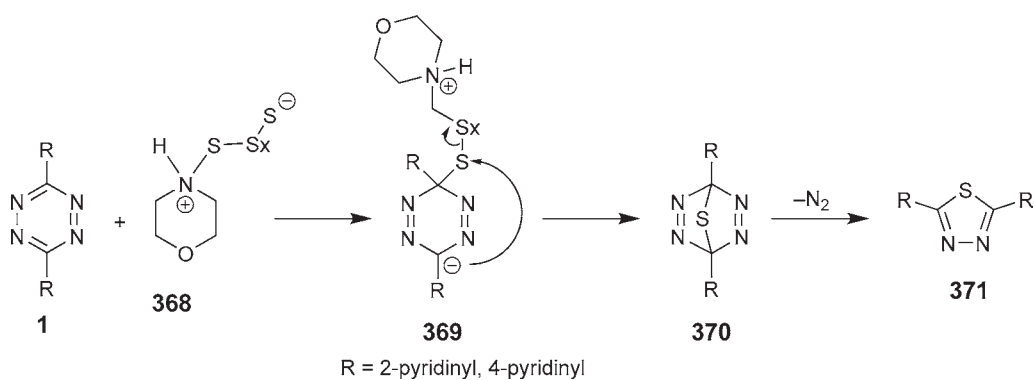
Reports describing 1,2,4,5-tetrazine ring contractions are scarce. However, photochemically induced ring contraction of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine **363** into triazole **364** has been reported in the presence of hydrochloric acid <2000JPR281>. Similarly, thermal rearrangement of 3,6-bis(trifluoromethyl)-1,2-dihydro-1,2,4,5-tetrazine **365** in acetic acid afforded 1,2,4-triazoles **366** and **367** (Scheme 89) <1995JFC(72)95>.

A new ring transformation of 1,2,4,5-tetrazines **1** into 1,3,4-triazoles **371** using elemental sulfur and morpholine has been reported and a possible mechanistic explanation is shown in Scheme 90 <1997HCO521>.

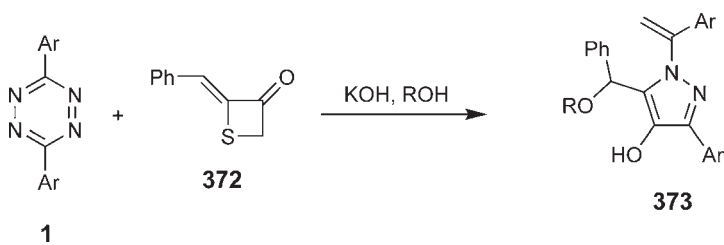
Interesting and unexpected ring contractions of 3,6-diaryl-1,2,4,5-tetrazines **1** into pyrazol-4-ols **373** were observed when the tetrazines **1** were treated with 2-benzylidenethietan-3-one **372** in the presence of a base (Scheme 91) <2005JOC8468>.



Scheme 89



Scheme 90



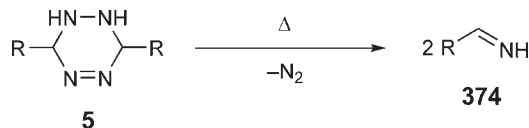
Ar	R	Yield (%)
Ph	Me	56
Ph	Et	45
4-Br-C ₆ H ₄	Me	48
4-Br-C ₆ H ₄	CH ₂ CH ₂ OH	35
Pyridin-2-yl	Me	15
Pyridin-2-yl	CH ₂ CH ₂ OH	9

Scheme 91

9.12.7.2.4 Thermal and photochemical unimolecular reactions

Thermal and photochemical decomposition of parent *s*-tetrazine and its 3,6-substituted derivatives have been of interest to both the experimental and theoretical communities. Thermal decomposition of 1,2,4,5-tetrazines results in complete loss of *s*-tetrazine ring structure. As in photodissociation, the principal products are nitrogen gas and substituted nitriles. Extensive studies of thermal properties, mass spectral fragmentations, thermal decomposition pathways, and kinetics of different nitrogen-rich tetrazines have been carried out <2005MI412, 2004MI111, 2003MI453, 2002MI91, 2002MI111, 2000PCA6764>. The thermal decomposition of 23 tetrazine derivatives was studied by Löbbecke *et al.* by thermo-analytical methods. Decomposition mechanisms initiated by ring opening could be established, and substituent effects on the exothermic decomposition characteristics were demonstrated <1999MI168>.

Pyrolyses of 3,6-disubstituted-1,2,3,6-tetrahydro-1,2,4,5-tetrazines **5** yielded the corresponding N-unsubstituted imines **374**. Calculations for the extrusion of nitrogen from tetrahydrotetrazines **5** resulted in a transition state for a [2+2+2] cycloreversion that leads to imines **374** as products (Scheme 92) <1998JST(471)189>.



Scheme 92

Papers dealing with photochemical decomposition of 1,2,4,5-tetrazines continue to resolve and clarify dilemmas outlined previously in CHEC-II(1996) <1996CHEC-II(6)901>. They cover experimental <1995JPC1733> and/or theoretical <2002PCP2554, 1997MI1> aspects of photochemical decomposition of 1,2,4,5-tetrazines.

9.12.8 Metal Complexes – Charge-Transfer Complexes

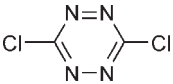
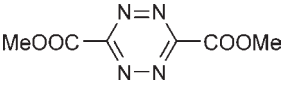
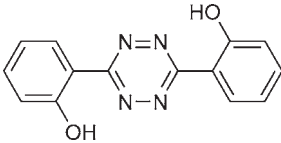
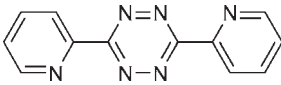
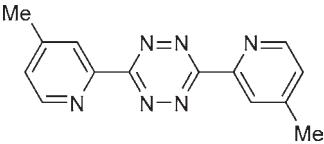
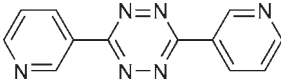
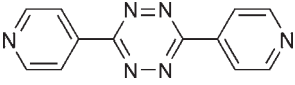
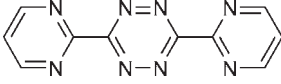
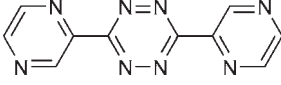
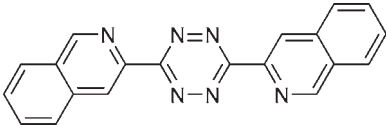
The special electronic situation of 1,2,4,5-tetrazine **1** and its 3,6-disubstituted derivatives characterized by the very low-lying π^* -molecular orbital and the presence of at least four nitrogen donor atoms provides them with a unique and diverse coordination chemistry, featured by electron- and charge-transfer phenomena. The facile electron uptake by tetrazine ligands has been responsible also for their occurrence as radical anions or 1,4-dihydro forms in well-characterized complexes. Coordination chemistry of 1,2,4,5-tetrazines is presented nicely in Wolfgang Kaim's report <2002CCR127>. The coordination chemistry of 1,2,4,5-tetrazines and the properties of the resulting products will not be discussed in detail in this report. Only a short review of the literature will be given based on the structure of the tetrazine ligand used (Table 1).

Table 1 1,2,4,5-Tetrazines used as ligands and corresponding references

Tetrazine ligand ^a	References
	2006JCR1311, 2005CEJ969, 2004IC1379, 2002ICA(336)55, 2002JMT(579)169, 2001EJI679, 2001IC2256, 1999AGE3072, 1998IC2655, 1998MI13, 1996AOM649, 1995MI13, 1995SM(71)2275
	1996JMC957
	2003JOM(688)112

(Continued)

Table 1 (Continued)

<i>Tetrazine ligand^a</i>	<i>References</i>
	1996JMC957
	1995IC1924
	2006CEJ489
	2006IC821, 2006ICA(356)659, 2006JA5895, 2006PCA4021, 2005CC46, 2005ICA(358)1317, 2005JA12909, 2004JCD3370, 2004JCD3727, 2004MI101, 2004MRC781, 2004ZFA1883, 2003JCD808, 2003ICC1196, 2002CR425, 2002EJI554, 2002IC2250, 2002ICA(336)55, 2002JCM247, 2002JOM(648)39, 2002JOM(642)48, 2002L7964, 2002MI199, 2002PNA4905, 2001CC2134, 2001CIL122, 2001IC3177, 2001JA773, 2001OM1437, 2000CC971, 1999AGE3477, 1999IC2242, 1999IC3270, 1999JCD3855, 1999JOM(582)153, 1998CC1429, 1998CJC1800, 1998JCF2979, 1998OM3532, 1997AGE2493, 1997JCD3765
	2004JCD3727, 2003IC6172
	2005CEO363, 1999IC2259, 1999MI123
	2005CEO363, 2004JA12989, 2004PCP3551, 2001PCB2792, 2001PCB8829, 2000JA4044, 1997AGE2327, 1995IC663
	2006PCA4021, 2004ICA(357)3657, 2004JCD3727, 2002ICA(336)55, 2001IC2263, 2001ZFA1441, 1999ICA(291)66, 1998CC1701, 1995ZNB123
	2006PCA4021, 2005CEO284, 2004JCD3727, 2003JCD3838, 2003ZFA1353
	2004JCD3727

(Continued)

Table 1 (Continued)

<i>Tetrazine ligand^a</i>	<i>References</i>
	2004JCD3727, 2003IC6172
	2005JCD1188, 2005POL333
	2005ICC524, 2003JST(656)207
	2005MI628, 2004IC6108, 2003JST(656)207, 2002JCD2097, 2002IAS443
	2002ICA(334)334
Verdazil radicals	2000IC562

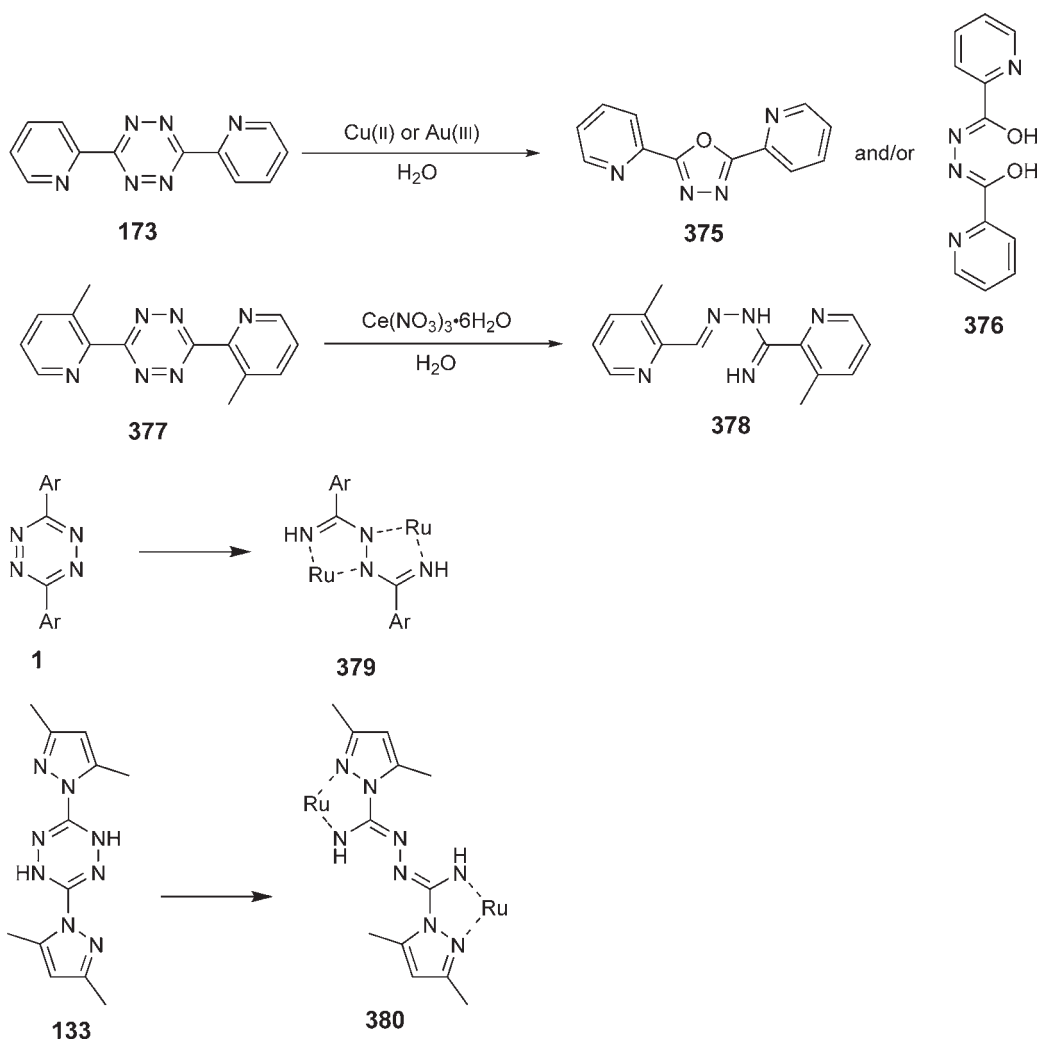
^aIncluding their dihydro and tetrahydro analogs.

During the preparation of metal complexes using 1,2,4,5-tetrazines and/or their 1,4-dihydro analogs as ligands, metal-assisted ring opening of the ligands occurs sometimes. The so-formed decomposition products of 1,2,4,5-tetrazines and/or their 1,4-dihydro analogs function as new ligands in the formation of complexes. Metal-assisted (Cu(II), Au(III)) hydrolysis of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **173** generated two new ligands, 2,5-di(pyridin-2-yl)-1,3,4-oxadiazole **375** and/or *N'*-[hydroxy(pyridin-2-yl)methylene]picolinohydrazonic acid **376** <2004MI141, 2004ICC220, 2002IC1855>. Similarly, the reaction of Ce(NO₃)₃·6H₂O with 3,6-bis(3-methylpyridin-2-yl)-1,2,4,5-tetrazine **377** generates a new polydentate ligand **378** <2004MI251>. Lahiri and co-workers reported ruthenium-assisted reductive ring opening of 3,6-diaryl-1,2,4,5-tetrazines **1** <2006IC1316> and 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,4-dihydro-1,2,4,5-tetrazine **133** <2003IC4707>, resulting in complexes of the type **379** and **380**, respectively (Scheme 93).

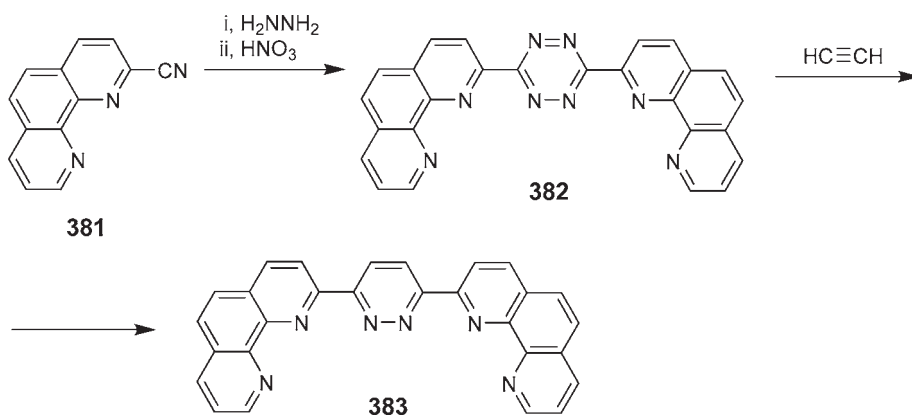
9.12.9 Applications and Important Compounds

3,6-Di-[1,10]-phenanthrolyl-1,2,4,5-tetrazine **382** has been prepared from nitrile **381** and used as the key intermediate in the synthesis of 3,6-di-[1,10]-phenanthrolylpyridazine **383** as a member of a new family of bis-tridentate chelators (Scheme 94) <2002OL1253>.

N,N'-Bis(aryl)-3,6-dialkyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxamides **384** <2005JCM91> and complexes of 3,6-di(2-hydroxy-5-chlorophenyl)-1,2,4,5-tetrazine **385** <2005MI1> with transition metals exhibit antitumor activity. Due to the efficacy of the cytotoxic tetrazine-based drugs temozolomide and mitozolomide in treatment of gliomas and melanoma <1995MI431, 2003MI435, 2003MI922>, some novel analogs of type **386** have also been synthesized <1995AXC937, 2000J(P1)4432>. Recently, Rao and Hu reported the synthesis, X-ray crystallographic analysis, and antitumor activity of 1-acyl-3,6-diaryl-1,4-dihydro-1,2,4,5-tetrazines **387** (Figure 2) <2005BML3174>.



Scheme 93



Scheme 94

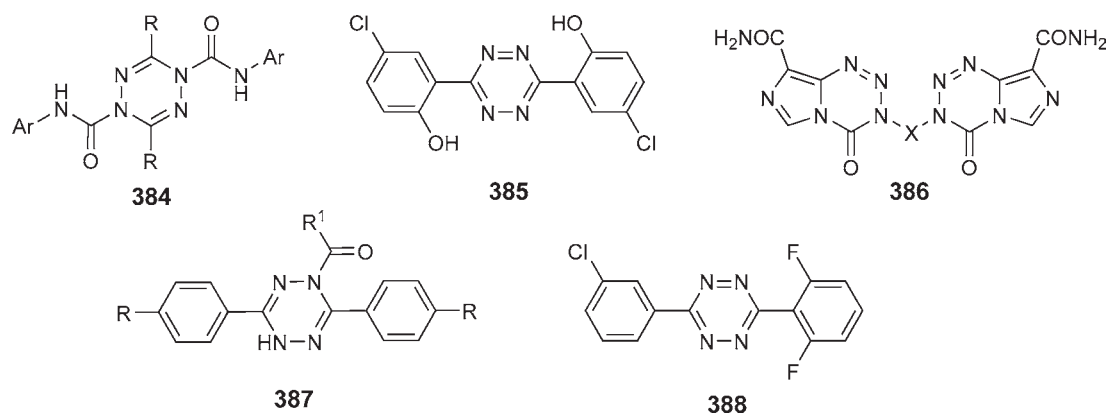


Figure 2

3-(2-Chlorophenyl)-6-(2,6-difluorophenyl)-1,2,4,5-tetrazine **388** was proposed as a tetrazine-type acaricide, which is very active against phytophagous mites and which possesses good toxicological and environmental properties (Figure 2) <1996JSH515, 1996JSH521>.

Tetrazine derivatives **389** were prepared and their mesomorphic, solubility, and absorption properties have been studied. The compounds containing the cyano group on the tetrazine ring showed smectic A phases, while nematic phases were observed in some of the alkoxy tetrazines (Figure 3) <1995LC871>.

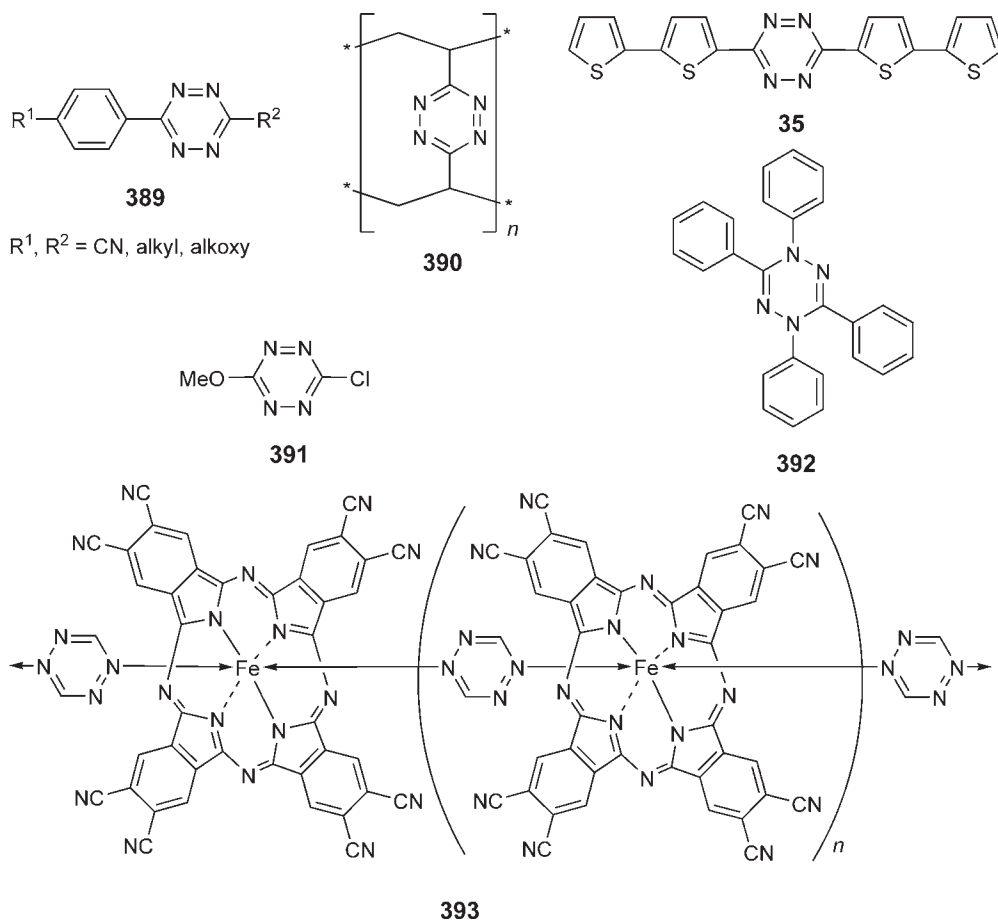


Figure 3

Hydrazidation of acrylonitrile and its copolymers leads to polymers **390** with 1,2,4,5-tetrazines as the main cross-linking units <1995RJA269>. Such polymer-bound 1,2,4,5-tetrazines **390** were used as resins for regeneration of rinse water containing copper and ammonia <1997MI43>. Similarly, application of the tetrazine-modified acrylonitrile fibers **390** for preconcentration of trace heavy metal ions has been reported <1999JAP2631>. 1,2,4,5-Tetrazine was used in the preparation of bridged complexes of polymerized acrylates as new adsorption polymers for advanced adsorption cycles (Figure 3) <1998MI11-2>.

Bis[5-(2,2'-bithienyl)]-1,2,4,5-tetrazine **35** has been synthesized and polymerized electrochemically as the first electroactive polymer containing a tetrazine moiety. Reduction of the tetrazine ring has been shown to be possible in films <2004MI144>. In addition, application of electroactive 3-chloro-6-methoxytetrazine **391** in new tetrazine-based electrofluorescent switches has been reported recently (Figure 3) <2006CC3612>.

1,4-Dihydro-1,3,4,6-tetraphenyl-1,3,4,5-tetrazine **392** was employed as a mediator for amperometric glucose sensing (Figure 3) <1998ALE569>.

1,2,4,5-Tetrazine **1** was used as the bidentate axial bridging ligand in the preparation of coordination polymer **393** based on octacyanophthalocyaninatoiron (FePcOC). The polymer **393** was used as cathode material for a rechargeable lithium battery (Figure 3) <2001JES305, 2001MI397>.

High-nitrogen compounds form a unique class of energetic materials deriving most of their energy from their very high heats of formation rather than from oxidation of the carbon backbone, as with traditional carbocyclic analogs. Moreover, good oxygen balance and high densities can be achieved due to the high nitrogen content of such energetic materials. High-nitrogen materials can show remarkable insensitivity to electrostatic discharge, friction, and impact. They are also more ecofriendly than the traditional energetic materials. Therefore, heterocyclic compounds based on the tetrazine framework are of particular interest. A large number of scientific reports describe the synthesis, properties, theoretical calculations, thermal decompositions, applications (including potential applications) of tetrazine-based energetic materials <2005JA12537, 2005MI264, 2005MI351, 2005MI412, 2004MI11, 2004MI120, 2004MI187, 2004MI209, 2004OL2889, 2003MI453, 2002MI11, 2002MI111, 2002MI187, 2000AGE1791, 2000MI919, 1999JEM357, 1999MI17, 1998MI11-1>. Some of the 1,2,4,5-tetrazine-derived energetic materials with their abbreviations are depicted in Figure 4.

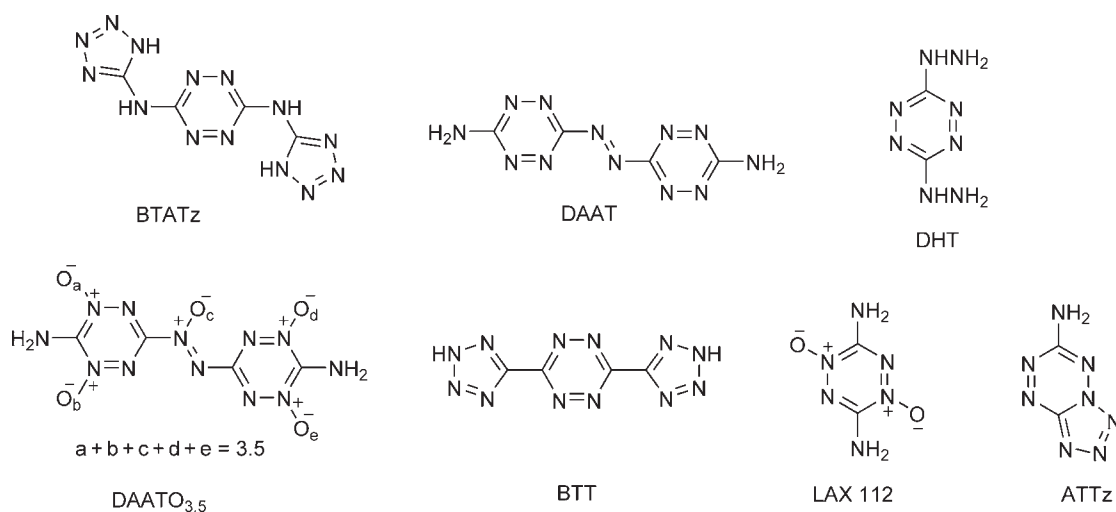


Figure 4

Similarly, some tetrazine-based salts **394–398** were prepared as highly energetic materials, possessing interesting explosive performance and extraordinary combustion properties (Figure 5) <2002MI91, 2004MI209, 2004OL2889, 2006AGE3584>.

Fine-particle zirconium titanates <1997MI83> and lead-based ferroelectric niobates <1998MI380> have been prepared by the solution combustion process using corresponding metal nitrates/oxalate and tetraformaltrisazine (octahydro-[1,2,4,5]tetrazino[1,2-*a*][1,2,4,5]tetrazine) <1966BCJ504>.

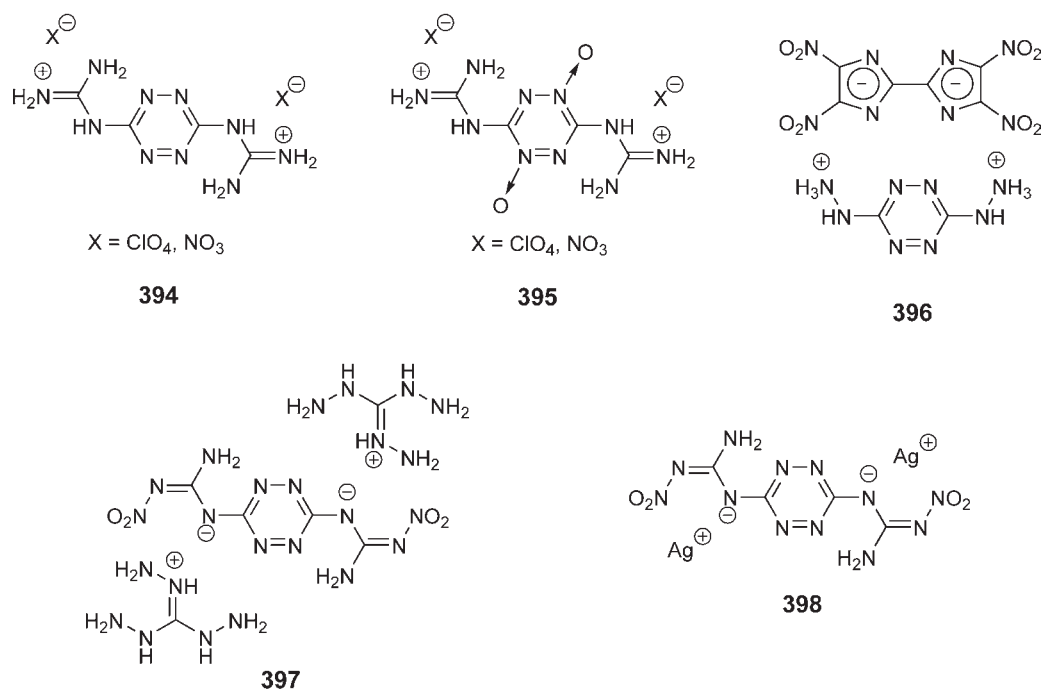


Figure 5

The 1,3,5-triphenylverdazyl coupling product with the 2-cyano-2-propyl radical was examined as a unimolecular initiator of the 'living' free radical polymerization of styrene <1998PB539>.

3,6-Di(azido)-1,2,4,5-tetrazine **399** was used as a precursor for the preparation of carbon nanospheres and nitrogen-rich carbon nitrides (Figure 6) <2004AGE5658>.

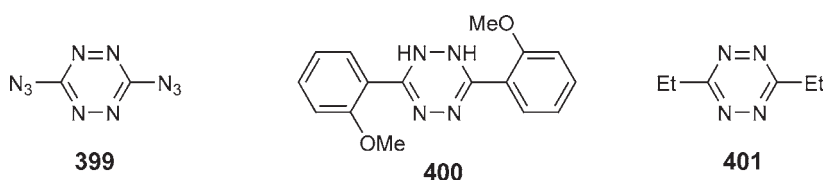
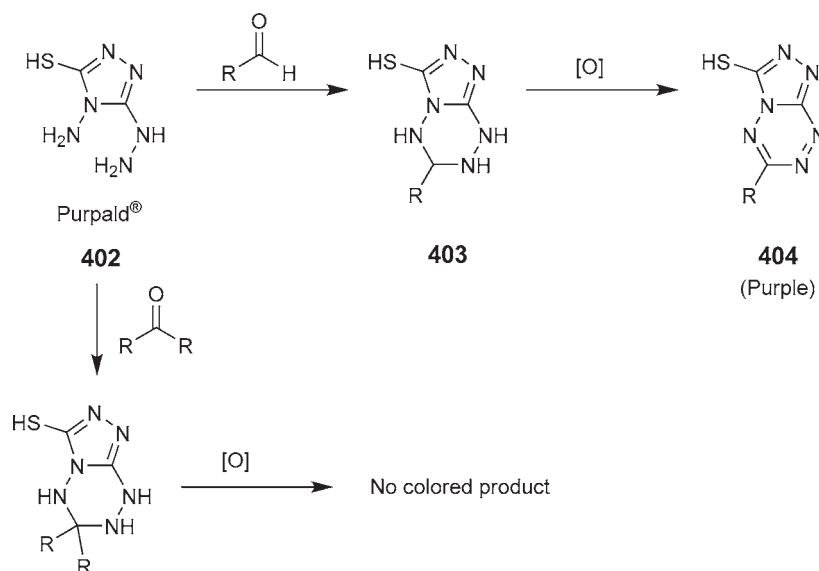


Figure 6

It is well known that heterocyclic compounds containing nitrogen atoms are good corrosion inhibitors for many metals and alloys in various aggressive media. 3,6-Bis(2-methoxyphenyl)-1,2-dihydro-1,2,4,5-tetrazine **400** is one such compound (Figure 6) <2000MI703>.

The use of 3,6-diethyl-1,2,4,5-tetrazine **401** as a new solvatochromic probe enabled the extension of the solvent acidity (SA) scale to carboxylic acids, phenols, haloalcohols, and halocarboxylic acids (Figure 6) <1999EJO885>.

4-Amino-3-hydrazino-5-mercapto-1,2,4-triazine (Purpald[®]) **402** is a well-established reagent for qualitative and quantitative detection of aldehydes. In the presence of an aldehyde or ketone, Purpald[®] is transformed into a fused tetrahydropyridine intermediate **403**. However, only with aldehydes, further oxidation of **403** takes place to give a deeply purple colored [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine-3-thiol **404** (Scheme 95) <2000ALD28>.



Scheme 95

References

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Biographical Sketch



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9.13

Other Tetrazines and Pentazines

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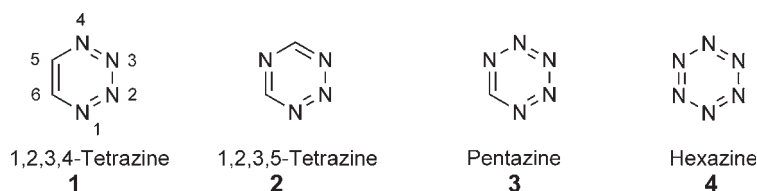
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9.13.1 Introduction

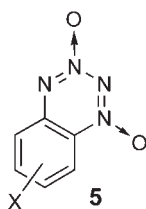
In CHEC-II(1996), due to the increased number of known tetrazine systems, tetrazine chemistry was divided into two chapters. The current edition continues this tradition. In the present chapter, only 1,2,3,4-tetrazine **1**, 1,2,3,5-tetrazine **2**, pentazine **3**, hexazine **4**, and their derivatives are considered, with the exception of fused structures that have a bridgehead nitrogen atom. Representatives of the latter are discussed in detail in appropriate chapters of Volume 10. A separate chapter on the chemistry of 1,2,4,5-tetrazine and its derivatives immediately precedes this one (Chapter 9.12).



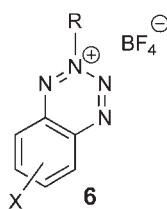
The number of relevant reference works has been growing steadily. Thus, when CHEC(1984) was published, there was a total of 27 pertinent publications. The second edition, CHEC-II(1996), had 30 references for tetrazines and pentazine and an additional 20 works on the chemistry of hexazine. Since 1994, there has been a total of 59 references covering the subject matter. The largest share belongs to works on the chemistry of 1,2,3,4-tetrazine systems, which have been discussed in 34 articles, including one major review in 2004 by Churakov and Tartakovskiy <2004CRV2601>.

Several review works have been published covering relevant theoretical issues, such as quantitative measures of aromaticity in heteroaromatic ring systems <2001CRV1421>, the role of π -delocalization in aromatic systems <2001CRV1501>, and the structural aspects of aromaticity <2001CRV1385>.

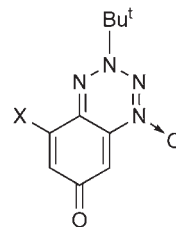
At the time of writing of this chapter, there has been no published work or evidence on the preparation of the parent monocyclic 1,2,3,4-tetrazine **1**. Numerous derivatives of the previously known 1,2,3,4-benzotetrazine-1,3-dioxide **5** have been prepared <2002RCB1841, 2002RCB1849>, as well as several new classes of compounds, incorporating core structures of 1,2,3,4-benzotetrazine **6**, 1,2,3,4-benzotetrazine-6(2*H*)-one **7** <1996MC22, 2002EJO3435>, and benzo-1,2,3,4-tetrazine 1-oxide (BTO) **8** <1994MC122>. Structure **9** is an interesting example of a bipolar spiro σ -complex <2002RCB668>.



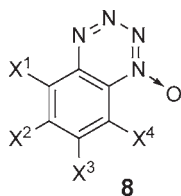
a: X = H; b: X = 6-Br; c: X = 7-Br
d: X = 5,7-(Br)₂; e: X = 6,7-(Br)₂
f: X = 6,8-(Br)₂; g: X = 5-NO₂
h: X = 7-NO₂; i: X = 5,7-(NO₂)₂
j: X = 6-OMe; k: X = 6-NMe₂; l: X = 8-Br



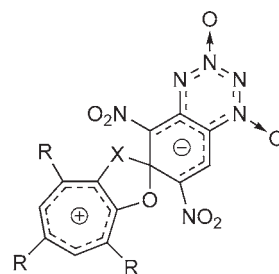
a–g: R = *t*-Bu; h–i: R = Me
a: X = H; b: X = 7-Br; c: X = 6-Br; d: X = 7-Me
e: X = 6-Me; f: X = 5,7-(Br)₂; g: X = 5,7-(Cl)₂
h: X = H; i: X = 5,7-(Br)₂



7a: X = H
7b: X = Br

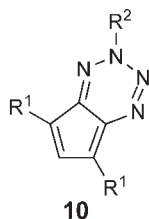


- 8**
a: $X^1, X^2, X^3, X^4 = H$; **b:** $X^1, X^3 = Br$; **c:** $X^1, X^2, X^3 = Br$
d: $X^1 = Br$; $X^3, X^4 = Me$; **e:** $X^1, X^3 = Br$; $X^2 = Me$
f: $X^3 = Br$; **g:** $X^2, X^3 = Br$; **h:** $X^1 = Br$; $X^3 = Me$
i: $X^2 = Br$; **j:** $X^3 = NO_2$; **k:** $X^1 = NO_2$
l: $X^1 = Br$; $X^3 = NO_2$; **m:** $X^2, X^4 = Br$; **n:** $X^1, X^3, X^4 = Br$

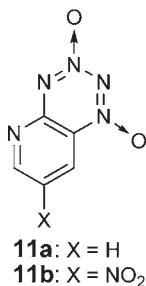


- 9a:** $R = CH_3$; $X = O$
9b: $R = H$; $X = NCH_2Ph$

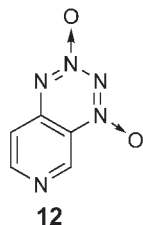
Other reported fused derivatives of 1,2,3,4-tetrazine include 2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **10** <1994CB1479>, pyrido[2,3-*e*]-1,2,3,4-tetrazines **11** and pyrido[3,4-*e*]-1,2,3,4-tetrazine **12** <2004RCB2577>, and 7-hydroxy-2*H*-pyrazolo[3,4-*e*]-1,2,3,4-tetrazines **13** <2005MI687>.



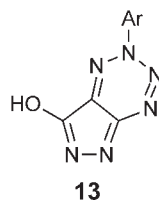
- a-g, o:** $R^1 = H$; **h-n, p:** $R^1 = t-Bu$
a, h: $R^2 = C_6H_5$; **b, i:** $R^2 = 4-CH_3OC_6H_4$; **c, j:** $R^2 = 4-NO_2C_6H_4$
d, k: $R^2 = 2-CH_3C_6H_4$; **e, l:** $R^2 = 2-CH_3-5-NO_2C_6H_3$
f, m: $R^2 = 2-CH_3-4-NO_2C_6H_3$; **g, n:** $R^2 = 2,4-(NO_2)_2C_6H_3$



- 11a:** $X = H$
11b: $X = NO_2$



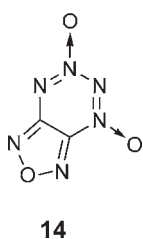
12



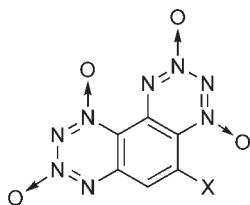
- a:** $Ar = Ph$
b: $Ar = 2-BrC_6H_4$
c: $Ar = 4-CH_3OC_6H_4$
d: $Ar = 2-NO_2C_6H_4$

13

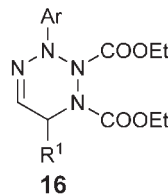
Structure **14**, a furazano-1,2,3,4-tetrazine 4,6-dioxide, although prepared previously, was reported in the literature during the period covered in this review <1995MC227>. The tricyclic 1,2,3,4-tetrazino[5,6-*f*]-1,2,3,4-benzotetrazines **15** were reported in 1999 <1997OL721>. Structures **16** are tetrahydro-1,2,3,4-tetrazines, with R^1 being a carbohydrate moiety <1999JOC6297>.



14



- 15a:** $X = Cl$
15b: $X = NHCH_3$

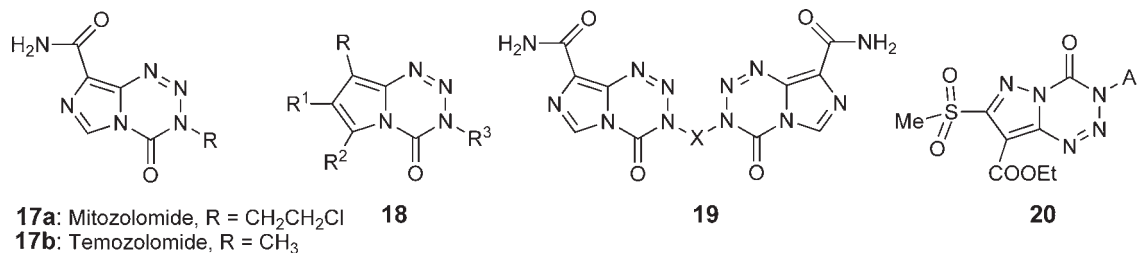


16

- $R^1 = \text{carbohydrate moiety}$
a, e: $Ar = Ph$; **b:** $Ar = 4-ClC_6H_4$; **c:** $Ar = 4-CH_3C_6H_4$;
d: $Ar = 4-CH_3OC_6H_4$; **f:** $Ar = 4-BrC_6H_4$

The reader will find some information on compounds **11–15** in the current chapter, mostly concerning structural features of those molecules compared to other 1,2,3,4-tetrazine derivatives. However, their comprehensive description is the subject of Chapters 10.14 **13** and **14**, 10.20 **11** and **12**, and 10.23 **15**.

While there were no reports on the preparation of the parent 1,2,3,5-tetrazine **2**, or any of its monocyclic derivatives, during the period covered by this review, a number of fused bicyclic systems have been prepared, all of them containing a bridgehead nitrogen atom, such as **18** <1999S2082>, **19** <2000J(P1)4432>, and **20** <2005JHC609>. They are structurally similar to mitozolomide **17a** and temozolomide **17b**, first prepared in the late 1970s and considered to be efficient antineoplastic agents <1979TL4253>. Please consult Chapters 11.15, 11.20, and 11.21 for further details on the chemistry of heterocyclic structures with a fused 1,2,3,5-tetrazine ring and a bridgehead N-atom.



There are no published works from the last decade on the preparation of the parent pentazine **3** and hexazine **4** systems or their derivatives. Both compounds have received extensive theoretical treatment, including some hexazine derivatives, such as the *N*-oxides <2001PCA7693> or transition metal complexes <2002CPL531>.

9.13.2 Theoretical Methods

The parent azine systems discussed in this chapter, compounds **1–4**, have not been prepared experimentally, but there has been continuing interest in their theoretical analysis. The past 10 years have seen the incorporation of computational chemistry into the mainstream of chemical research, facilitated by the advancement of computer hardware, and computational software and methods. Hence, not surprisingly, recent studies have been performed using advanced methods, such as MP2, CCSD, and a considerable number of density functional theory (DFT) calculations. Azines have been investigated in terms of structural features, aromaticity, kinetic and thermodynamic stability, and decomposition reactions.

9.13.2.1 Structure and Properties

Williams and Whitehead calculated heats of formation for several azoles, azines, and benzoazoles, using semi-empirical (AM1, PM3, and MNDO) and *ab initio* calculations (MNDO=modified neglect of diatomic overlap) <1997JMT9>. The latter were performed at the RHF/4-31G and RHF/6-31G** levels, and the resultant values were averaged, bringing them into very close agreement with experimental results. The semiempirical methods (AM1, PM3, and MNDO) were found to consistently underestimate the azines' heats of formation, but the predictions were improved upon the introduction of a correction, which works well for azines with up to four N atoms, but not for pentazine and hexazine.

The absolute energies of 12 monocyclic azines with general formula N_{*n*}(CH)_{6-*n*} (*n* = 1–6), were calculated at 0 and 298 K, using the G3 model and its variation G3(MP2) <2002JSC257>. Applying an atomization scheme, the authors were able to calculate the heats of formation of the studied compounds (ΔH_{f0} and ΔH_{f298}). The calculated heats of formation were found to be well within ± 10 kJ mol⁻¹ of the available experimental data. Energy and enthalpy results showed 1,2,3,4-tetrazine (C_{2v} geometry) to be the least stable of the three tetrazine isomers, while 1,2,3,5-tetrazine (C_{2v} geometry) was the most stable one. The enthalpy of formation difference at 298 K is $\Delta \Delta H_{f298} = 86.0$ kJ mol⁻¹ using G3 and $\Delta \Delta H_{f298} = 84.3$ kJ mol⁻¹ using G3(MP2).

Structural parameters of azines, calculated at the MP2(fc)/6-31G* and B3LYP/6-31G* levels, were reported in a recent comprehensive theoretical study <2004CJC50>, with results for relevant azines shown in Figure 1. Both B3LYP and MP2 calculations showed that hexazine (*D_{6h}*) is a hilltop, whereas hexazine (*D₂*) is a minimum, in agreement with the prior MP2-based results of von R. Schleyer and co-workers (MP2(fc)/6-31G*/MP2(fc)/6-31G*) <1996JPC13447>. The latter study demonstrated that the choice of level of theory could have a substantial impact on the results. At the RHF/6-31G* level, N₆ (*D_{6h}*) is actually predicted to be a minimum, matching the results of Engelke at the RHF/4-31G and RHF/4-31G* levels of theory <1992JPC10789>.

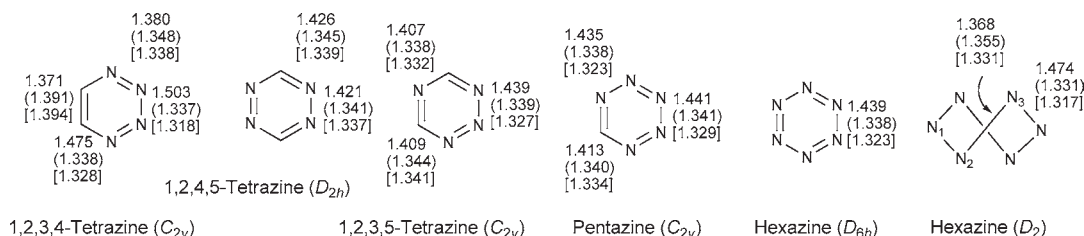


Figure 1 Structural parameters for tetrazines, pentazine, and hexazines. Wiberg bond orders from HF/3-21G//MP2(fc)/6-31G* calculations. Bond lengths (in angstroms, Å) from MP2(fc)/6-31G* (data in parentheses) and B3LYP/6-31G* (data in square brackets). Values from <2004CJC50>.

A study by Tobita and Bartlett <2001PCA4107> has utilized DFT methods and coupled cluster theory (singles, doubles, and noniterative triples) in order to analyze the stationary points on the potential energy surface (PES) of hexazine. Several structures were analyzed and are shown in **Figure 2**. The DFT methods (PW91/aug-cc-pVDZ and B3LYP/aug-cc-pVDZ) predict that D_2 hexazine, hexaazadewarbenzene (C_{2v}), and hexaazaprismane (D_{3h}) are all minima on the PES. The planar hexazine (D_{6h}) is a transition state, while earlier MP2 calculations predicted it to be a second-order saddle point. Using CCSD(T), the only predicted minima are hexaazadewarbenzene and D_2 hexazine (the latter is a stable structure only when the cc-pVTZ basis set is used). Energetically, the most stable isomer is D_2 hexazine, whose enthalpy of formation is more than 100 kcal mol⁻¹ lower than any of the other cyclic isomers. However, it is about 27 kcal mol⁻¹ higher in energy than the open-chain diazide (C_{2h}).

Hexazine (D_{6h})	Hexazine (D_2)	Hexaazadewarbenzene (C_{2v})	Hexaazaprismane (D_{3h})	Diazide (C_{2h})
Number of imaginary frequencies	0 (HF/4-31G*) ^a 2 (MP2/6-31G*) ^{a,b} 1 (PW91 or B3LYP/ aug-cc-pVDZ) ^c	0 (MP2/6-31G*) ^{a,b} 0 (PW91 or B3LYP/ aug-cc-pVDZ) ^c 0 (CCSD(T)/cc-pVTZ) ^c	0 (HF/4-31G*) ^a 0 (MP2/6-31G*) ^a 0 (PW91 or B3LYP/ aug-cc-pVDZ) ^c 0 (CCSD(T)/ aug-cc-pVDZ) ^c	0 (PW91 or B3LYP/ aug-cc-pVDZ) ^c 0 (CCSD(T)/ aug-cc-pVDZ) ^c
ΔH_f^c (kcal mol ⁻¹)	152.5 (PW91) 188.3 (B3LYP) 211.7 (CCSD(T)/ cc-pVTZ)	187.6 320.1 244	267.1 305.9 323	132.5 161.5 189

Figure 2 Stationary points on the potential energy surface of N_6 and their heats of formation ΔH_f (kcal mol⁻¹).

^aRef. <1992JPC10789>. ^bRef. <1996JPC13447>. ^cRef. <2001PCA4107>.

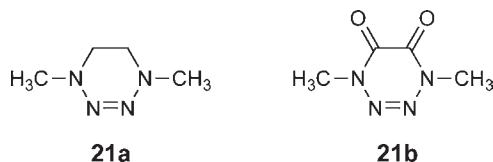
Doerksen and Thakkar reported optimized geometries (MP2/6-31G*), dipole moments, and static dipole polarizabilities for 12 azines <1996IJQ421>. The MP2-predicted bond lengths for the tetrazines were compared to prior CISD data <1991JOC539> and were found to differ from them by an average of 1.6 pm for 1,2,3,4-tetrazine and 1.1 pm for 1,2,3,5-tetrazine. Dipole moment and static dipole polarizability results for hexazine (MP2/6-31G) were reported by Archibong and Thakkar in a study involving benzene and 10 heteroaromatic molecules <1994MP557>. Quadrupole and octopole moments of various heteroaromatic rings, including azines, were calculated at the MP2/6-31G level, with theoretical results in good agreement with available experimental or other computational data <1999PCA10009>.

MRINDO/S calculations of electronic spectra of triazines and tetrazines, completed by singly excited configuration interaction, revealed the importance of the outer (Rydberg) atomic orbitals <2000THAC434>. According to the calculations, n-to- π^* transitions do not show any intensity.

Jimenez and co-workers conducted extensive semiempirical calculations (PM3) in order to rationalize the stereochemical outcome of some hetero-Diels–Alder reactions leading to the preparation of chiral tetrahydrotetrazine derivatives **16** <1999JOC6297>. The process was found to occur with high facial stereoselectivity when the starting

compound had a *threo*-configuration of the C-1'-C-2'- fragment of the sugar moiety, while low selectivity was observed when the configuration in the sugar residue was *erythro*. The stereoselectivity was attributed to considerable differences in TS energies.

Electronic structure calculations and conformational analysis were performed on several tetrahydrotetrazines, including compounds **21a** and **21b** <1997JMT157>. Results from both HF (with 6-31G*, 6-31+G, and 6-31+G* basis sets) and DFT calculations (B3LYP with each of the three basis sets) showed that **21b** exists as a single planar conformation, while **21a** is a mixture of two low-energy conformations: a half-chair and an unsymmetrical boat. The relative energies of the two conformations depend on the method and basis set used for the calculations.



Bartlett and co-workers studied computationally the effect of attachment of one or more oxygen atoms to N₄ and N₆ rings, employing SCF, MBPT(2), CCSD, CCSD(T), and B3LYP with the 6-31G* basis set for geometry optimizations, followed by single-point calculations with the aug-cc-pVDZ basis set <2001PCA7693>. Calculations predicted increasing stability in the order N₆O, N₆O₂, N₆O₃, with computed barriers to fragmentation of 1.2, 13.8, and 62.4 kcal mol⁻¹ correspondingly. N₆O₃ is a highly symmetrical molecule (*D_{3h}*), with all N–N bonds equal to 1.363 Å (CCSD(T) calculation).

Another route to stabilizing the planar N₆ ring, through coordination with a metal center in M(η^6 -N₆) complexes (M = Ti, Zr, Hf, Th), was also studied theoretically <2002CPL531>. Calculations were performed at the B3LYP/6-311+G(d) level for N, Ca, Sc, and Ti. The Stuttgart small-core pseudopotentials (electron core potential, ECP) with corresponding basis sets were used for elements with Z > 36, namely the 12-VE ECPs for Zr and Hf and 30-VE ECP for Th. Optimized geometries were obtained for the M(η^6 -N₆) systems, with *C_{6v}* geometry, corresponding to an η^6 -complex of a metal atom with a planar N₆ ring. The complexes were found to be higher in energy than a (metal atom + 3N₂) by approximately 70–130 kcal mol⁻¹; however, they were all substantially below the energy of any noncoordinated N₆ isomer. The stabilization of the planar N₆, upon complexation, was attributed to a favorable interaction of the ring π -system with the metal d- and f-orbitals.

Hexazine (*D_{6h}*), together with other electron-deficient aromatic compounds, was the subject of a theoretical study focused on anion– π interactions <2003MI1344>. Structures of chloride anion complexes of the studied compounds were optimized at the MP2/6-31++G** level, followed by analysis of the charge density and distribution of critical points, using the atoms-in-molecules (AIM) model. Good correlation was found between the quadrupole moment *Q_{zz}* of the aromatic ring and the electrostatic contribution to the total binding energy. In addition, a correlation was found between the computed molecular polarizability and the polarization contribution to the total binding energy.

The hexazine radical anion, N₆^{•-}, was the subject of study in work by Wayner and co-workers <1995JPC94>. The radical anion was generated by combination of an azide anion with an azide radical at the diffusion control limit (*k* = 1.2 × 10¹⁰ M⁻¹s⁻¹). The equilibrium constant for the formation of N₆^{•-} at room temperature in acetonitrile was determined to be 200 M⁻¹. Its stabilization energy, relative to N₃[•] + N₃⁻, based on the temperature dependence of the equilibrium constant, was calculated to be 4.4 kcal mol⁻¹. Spectroscopically, the species is characterized by a broad visible absorption band at 700 nm and an infrared (IR) band at 1842 cm⁻¹. Calculations at the ROHF/6-31+G*, UHF/6-31+G*, and UMP2/6-31+G* level led to several optimized minimum geometries. The global minimum is a *D_{2h}* six-membered cyclic structure with two long N–N bonds (2.76 and 2.88 Å at the ROHF/6-31+G* level) that connect two essentially intact azide units. The formation of N₆^{•-} was also observed spectroscopically in reactions of the azide anion with radical cations <1994JA1141>.

9.13.2.2 Aromaticity

Fully unsaturated six-membered rings, with one or more nitrogen centers present, can be formally considered as analogs of benzene, and therefore aromatic. However, treatment of aromaticity in general has always involved an element of ambiguity, due to the fact that it is not a clearly defined, measurable quantity. Aromaticity has been discussed from the standpoint of chemical properties, such as stability of the cyclic structure relative to an acyclic analog, or the degree of electron delocalization (σ - or π -electrons, or both), or magnetic criteria, such as magnetic susceptibilities and chemical shifts.

In a work of von R. Schleyer *et al.* <1997JA12669>, aromaticity of several cyclic systems, including N_6 (D_{6h} symmetry), was treated on the basis of the nucleus-independent chemical shifts (NICSs), which were proposed a year earlier by von R. Schleyer *et al.* as a new aromaticity/antiaromaticity criterion <1996JA6317>. NICS values were calculated at the SOS-DFPT-IGLO level (PW91/IGLO-III TZ2P, as implemented in the de Mon nuclear magnetic resonance (NMR) program), on B3LYP/6-311+G**-optimized geometries. Data were obtained both at the ring centers as well as 0.5 Å above the ring, and the total NICS values were separated into contributions from the σ - and π -bonds (NICS(σ) and NICS(π)). Interestingly, the NICS(tot) value for N_6 at the ring center was computed to be only +0.2, compared to -8.9 for benzene, and was related to the compensatory effects of the paratropic ring current (due to the ring σ -bonds) and the diatropic ring current (due to the ring π -bonds). The NICS(π) value for hexazine was found to be comparable to that of benzene (-20.4 and -20.7 correspondingly, at the ring center), while its NICS(σ) value was considerably larger (+24.6 vs +13.8 at the ring center), the substantial difference being attributed to the smaller ring radius of N_6 .

Giambiagi *et al.* proposed a multicenter bond index, I_{ring} , involving the ($\sigma + \pi$) electron population, as a measure for aromaticity, in a study of a large number of carbocyclic and heterocyclic systems, including 12 azines <2000PCP3381>. The computational results were derived from semi-empirical calculations. I_{ring} values for seven of the azines, including 1,2,3,4-tetrazine and 1,2,4,5-tetrazine, were close to 0.088, the same as benzene, while 1,2,3,5-tetrazine had a lower I_{ring} value (0.086). Planar hexazine, on the other hand, showed an I_{ring} value of 0.090, slightly higher than that for benzene.

In the work of Fabian and Lewars <2004CJC50>, aromaticity of azines was treated on the basis of results from (1) homodesmotic ring-opening reactions, (2) electron distribution as indicated by bond order-bond length variation, and (3) ring current effects as indicated by calculated NICSs. The homodesmotic ring-opening reactions were designed to assess the stabilization of the cyclic structures with respect to their open-chain analogs (which is one definition of aromaticity) and it appears from the results that, with the exception of 1,2,3,4-tetrazine, the studied systems are either highly destabilized (hexazine D_2 and hexazine D_{6h}) or equally stable (pentazine) with respect to the acyclic analogs. One conclusion would be that there is a progressive reduction of the degree of aromaticity with an increase of the nitrogen content. However, based on the Wiberg bond orders (Figure 1), the authors calculated the Bird index for aromaticity, I , and its values were found to be 88.5 for 1,2,3,4-tetrazine, 97.5 for pentazine, 89.6 for hexazine (D_2), and 100 for hexazine (D_{6h}), compared to a value of 100 for benzene, which would indicate that all of the studied systems have a high degree of delocalization and considerable aromatic character, especially the planar hexazine. The NICS results further reinforced this view. Overall, the authors concluded that all azines are aromatic, in the sense of a present diatropic ring current and evenness of electron distribution. The progressively decreasing stability was attributed to the unfavorable effect of the increasing number of lone pairs at the ring centers.

Shaik and co-workers, in an extensive treatment of aromaticity from the standpoint of balance between π -distortivity and σ -resistance to distortion, analyzed numerous four- and six-membered ring structures, including hexazine (D_{6h} symmetry) <2001CRV1501>. They concluded that hexazine's instability was due to its higher (compared to benzene) π -distortivity ($\Delta E_\pi = -13.3 \text{ kcal mol}^{-1}$ as opposed to $-9.1 \text{ kcal mol}^{-1}$ for benzene) and lower σ -resistance ($\Delta E_\sigma = +13.7 \text{ kcal mol}^{-1}$ vs. $+16.3 \text{ kcal mol}^{-1}$ for benzene). As a result, the two opposing trends are almost perfectly balanced and N_6 is virtually indifferent toward distortion of the symmetric hexagonal structure.

In work by Sadlej-Sosnowska <2004JPO303>, an attempt was made to establish relationships between different magnetic aromaticity parameters, as well as relationships between magnetic and structural aromaticity parameters. Among the studied systems were several azines, including 1,2,3,4-tetrazine and pentazine. Magnetic parameters were calculated by using either the GIAO (gauge-independent atomic orbital) method (NICS values) or the IGAIM (individual gauges of atoms in molecules) method, at the B3LYP/6-31++G** level. Overall, the study established that some of the magnetic parameters correlate well, within a particular set of compounds (e.g., azines), while others are orthogonal (i.e., do not correlate). Varying degrees of correlation were also observed between magnetic and structural aromaticity indices. NICS values for relevant azine systems, collected from several published sources, are listed in Table 1.

A different treatment of aromaticity of six-membered ring compounds was offered by Sakai <2002PCA10370>. Using a combination of configuration interaction (CI), localized molecular orbital (LMO), and complete active space self-consistent field (CASSCF) analyses, termed the CiLC method, the author calculated the relative weights of the singlet coupling and polarization configurations for several ring structures, including hexazine (D_{6h} symmetry). Based on the results, the author proposed a connection between aromaticity and electronegativity of the ring constituent atoms. Strongly electronegative centers tend to hold tightly their valence electrons, disfavoring delocalization, the opposite being true for weakly electronegative elements. Hence, the aromatic character is reduced in the sequence $B_6 > C_6H_6 > N_6$.

Table 1 NICS values for tetrazine, pentazine, and hexazine systems, from several literature sources. Values are listed for NICS at the ring center (NICS(0)), 0.5 Å above the ring center (NICS(0.5)), and 1 Å above the ring center (NICS(1))

Compound	NICS(0)	NICS(0.5)	NICS(1)
Benzene	−8.9 ^a −11.54 ^b	−10.7 −13.27	−12.81 −12.47
1,2,3,4-Tetrazine	−4.05 −2.69 ^c	−9.61	−10.81 −10.60
1,2,4,5-Tetrazine	−1.83		
Pentazine	−1.67 −0.63	−8.35	−12.14 −10.65
Hexazine (<i>D</i> _{6h})	+0.2 +0.29	−7.0 −7.61	
Hexazine (<i>D</i> ₂)	−6.81	−12.64	−14.79

^aValues from PW91/IGLO-III TZ2P//B3LYP/6-311+G** calculations <1997JA12669>.^bBold values from GIAO HF/6-31G*//MP2/6-31G* calculations <2004CJC50>.^cItalicized values from GIAO B3LYP/6-311++G**// B3LYP/6-311++G** calculations <2004JPO303>.

Bond orders for 324 bonds in 60 heterocyclic molecules, including 12 azines, were calculated at the HF/6-31G(d) and MP2/6-31G(d) levels of theory <2002IJQ534>. It was found that the MP2-derived bond orders were smaller by an average of 17%, compared to those derived from HF calculations. The *ab initio* results were further compared to the Gordy bond orders, derived on the basis of an empirical relationship. The latter were found to be much larger than the *ab initio* values, and the authors' recommendation was that Gordy bond orders should not be used in aromaticity studies.

9.13.2.3 Stability and Reactivity

Calculated activation and reaction energies for the fragmentation of azines into three two-heavy atom molecules were reported by Fabian and Lewars <2004CJC50>. The results are summarized in Table 2. They predict that 1,2,3,5-tetrazine should be considerably more stable than 1,2,3,4-tetrazine, and that both of them could be isolated below ambient temperature. The kinetic stability of pentazine is marginal and the barrier toward decomposition of hexazine (*D*₂) is either close to zero or even negative, questioning the very possibility for existence of the molecule. All fragmentation reactions of the tetrazines, pentazine, and hexazine have large negative reaction energies. For most of the azines with contiguous N-fragments (including 1,2,3,4-tetrazine), the activation energy barriers to fragmentation were found to correlate linearly with the reaction energies, in accordance with the Bell–Evans–Polanyi (BEP) principle. However, pentazine and hexazine were found to deviate significantly from the correlation, exhibiting unexpectedly high activation barriers (i.e., kinetic stability).

Table 2 Activation energies and reaction energies (in parentheses) for fragmentation of tetrazines, pentazine, and hexazine into three two-heavy atom molecules

Compound	MP2(fc)/6-31G*	B3LYP/6-31G*	CCSD(T)/6-31G* ^a
1,2,3,4-Tetrazine ^b	57.6 (−333.4)	97.6 (−266.7)	92.4 (−327.3)
1,2,3,4-Tetrazine ^c	70.8 (−319.4)	88.0 (−212.9)	59.0 (−310.3)
1,2,3,5-Tetrazine	109.2 (−241.9)	141.4 (−130.7)	115.7 (−228.8)
Pentazine	26.7 (−586.1)	23.2 (−462.6)	12.1 (−567.4)
Hexazine (<i>D</i> ₂) ^d	2.3 (−911.4)	−1.2 (−773.9)	−9.3 (−887.5)

^aSingle-point calculation on an MP2(fc)/6-31G* geometry.^bFor a decomposition to C₂H₂ + 2N₂.^cFor a decomposition to 2HCN + N₂.^dActivation energy results without the ZPE correction are 7.6, 0.6, and −4.0 kJ mol^{−1}. Results in kJ mol^{−1}.

All data from Ref. 2004CJC50.

In recent work, Ho and Li reported a G3(MP2) study of the concerted cycloaddition reactions of ethylene and a number of heteroaromatic systems, including 11 azines <2005JMT195>. The calculations indicated certain trends: (1) reactions with formation of a new C–C σ -bond had lower barriers compared to processes with formation of a C–N σ -bond; (2) ring centers with the greatest amount of positive charge were found to be the most favored reaction sites; (3) pathways with the least disruption of the ring aromaticity were favored.

9.13.3 Experimental Structural Methods

9.13.3.1 X-Ray Analysis

Jimenez *et al.* obtained an X-ray structure of compound **16b**, produced by a [4+2] cycloaddition of diethyl azodicarboxylate and a 1,2-diaza-1,3-diene, containing a carbohydrate substructure (Figure 3). The structural analysis was conducted with the particular goal to verify the absolute configuration of C-6 in the ring, which turned out to be *R*. The conformation of the tetrahydropyrimidine ring resembles a half-boat and the dihedral angles between its mean plane and those of the aromatic ring and the sugar moiety are 153.2° and 71.3°, respectively <1994AXC1972>.

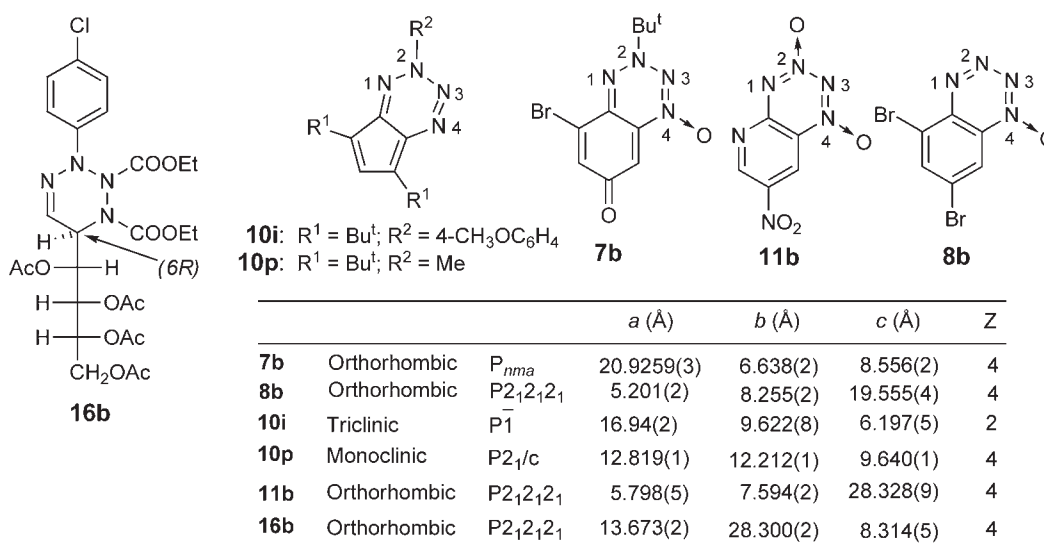


Figure 3 Selected crystallographic data for compounds **7b**, **8b**, **10i**, **10p**, **11b**, and **16b**. Data from <1994AXC1972>, <1994CB1479>, <1994MC122>, <1996MC22>, and <2004RCB2577>.

The X-ray structures of two 2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **10i** and **10p** showed that both compounds possess planar geometry <1994CB1479>. Similarly, analysis of **7b**, **8b**, and **11b** showed that each of them possesses a virtually planar bicyclic system <1994MC122, 1996MC22, 2004RCB2577>. An alternating pattern of the N–N bonds was observed in **7b**, **10i**, **10p**, and **11b**, while in compound **8b** the distances N–2–N–3 and N–3–N–4 are almost identical (Table 3).

Table 3 Selected bond lengths (Å) from the X-ray crystal structures of compounds **7b**, **8b**, **10i**, **10p**, and **11b**

Compound	C–N-1	N-1–N-2	N-2–N-3	N-3–N-4	C–N-4
7b	1.33	1.32	1.35	1.31	1.44
8b	1.36	1.30	1.35	1.34	1.41
10i	1.31	1.33	1.36	1.30	1.34
10p	1.31	1.32	1.36	1.30	1.36
11b	1.36	1.31	1.38	1.32	1.39

Data from <1994CB1479>, <1994MC122>, <1996MC22>, and <2004RCB2577>.

9.13.3.2 NMR Spectroscopy

9.13.3.2.1 ^1H - and ^{13}C NMR spectroscopy

^1H and ^{13}C NMR observations were utilized to analyze compounds exhibiting ring-chain tautomerism, such as **6a–g**/**22a–g** and **10d**/**23d**, ultimately determining the ratio of open and cyclic structures, depending on the particular substituent(s) X (**Figure 4**). In the case of **6a–g**, determinations were based on characteristic chemical shift values for the *t*-Bu group, taken to be δ 1.41 $\pm$ 0.02 ppm for the open form **22** and δ 2.16 ppm for the cyclic form **6**, both derived from compounds that were shown to exist entirely in the open-chain or cyclic form, respectively <2002EJO3821>. Variable-temperature studies showed the equilibrium being shifted in favor of the cyclic structure. ^{13}C NMR studies led to the same qualitative conclusions, although the actual ratios were slightly different. In the case of **10d**, the signal of H-6 was followed <1994CB1479>. It appears at δ 8.19 ppm in the cyclic form, which has a 10π -electron aromatic cyclopenta[*e*]-1,2,3,4-tetrazine substructure, and at δ 6.20 ppm in the open form **23d**, reflecting the cycloalkene character of the latter.

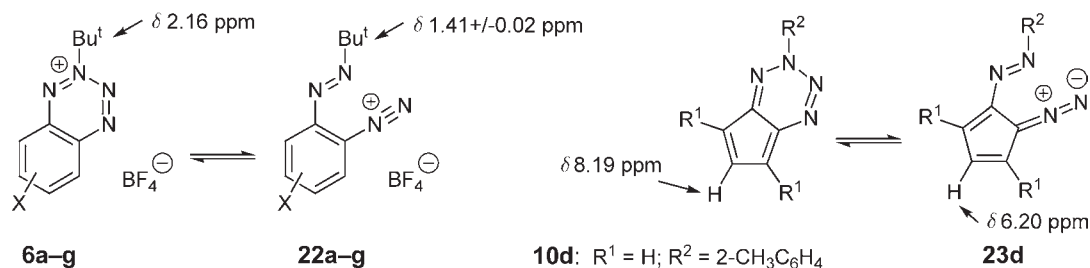


Figure 4 Characteristic chemical shifts in the cyclic and acyclic forms of compounds **6a–g** and **10d**. Data from <1994CB1479> and <2002EJO3821>.

Churakov and co-workers provided full ^1H and ^{13}C NMR assignments for a range of benzo-1,2,3,4-tetrazine 1,3-dioxides **5** (BTDOs), and for the recently prepared pyrido-1,2,3,4-tetrazine 1,3-dioxide **11a** (X = H) and its 7-nitro derivative **11b** <2002EJO3821, 2004RCB2577>. ^{13}C NMR assignment was used also to confirm the structure of **14** <1995MC227>.

The spirocyclic structure of **9b** (X = NCH_2Ph ; R = H) was confirmed by the AB quartet of the methylene hydrogens of the PhCH_2N^- group. Interestingly, temperature increase caused the conversion of the AB quartet into a singlet, indicating a fast process of (*R*)/(*S*) interconversion at the spirocyclic chirality center, which was found to occur with a rate constant $k_{298} = 12 \text{ s}^{-1}$ <2002RCB668>.

Double irradiation experiments were used to assign the signals in the ^1H NMR spectra of the tetrahydrotetrazine adducts **16**, reported by Jimenez *et al.* <1999JOC6297>. The ^{13}C spectra were used for additional structure confirmation. The chemical shifts for the carbons in the carbohydrate unit had the typical values observed in acyclic carbohydrate moieties.

9.13.3.2.2 ^{14}N and ^{15}N NMR spectroscopy

The high nitrogen content in tetrazine derivatives has made natural the use of nitrogen NMR spectroscopy in structure elucidation/confirmation. Values of ^{14}N and ^{15}N shifts for compound **5a** (X = H) and several of its bromo and nitro derivatives were summarized in a recent work of Churakov *et al.* <2002EJO2342>. The ^{15}N spectrum of **5a**, using samples with natural isotope content, showed four distinct N signals, as did the ^{14}N spectrum. In the latter case the N-centers connected to oxygen atoms (N-1 and N-3) showed as two narrow peaks, while the other two signals (N-2 and N-4) were very broad. This seems to be the typical pattern for several classes of fused 1,2,3,4-tetrazine derivatives, since it was also observed in the ^{14}N NMR spectra of **14** and the more recently prepared **11a** and **11b** <1995MC227, 2004RCB2577>. The structures of two representatives of the novel heterocyclic system 1,2,3,4-tetrazino[5,6-*f*]-benzo-1,2,3,4-tetrazine 1,3,7,9-tetraoxide (TBTDO, **15a**: X = Cl and **15b**: X = NHCH_3) were also confirmed by NMR studies <1997OL721>. ^{14}N NMR spectra showed four signals for the N(O) centers, in the same region as those shown by the closely related BTDOs.

Nitrogen NMR was also used as an additional tool to study ring-chain tautomerism. Thus, in the case of **10b**, both tautomeric forms were observed in the ^{15}N spectrum <1994CB1479>.

9.13.3.3 Mass Spectrometry

Jimenez and co-workers utilized mass spectrometry (MS) data as evidence for the proposed structures of their 1,2,3,4-tetrahydrotetrazine adducts **16** <1999JOC6297>. Three different fragmentation patterns were observed: (1) the loss of a COOEt unit, followed by subsequent elimination of AcOH and acetate units; (2) elimination of ketene and acetate units; and (3) initial elimination of an ArN₂ – fragment, followed by loss of acetate and acetic acid. In the case of **16b** in particular, the most abundant peaks were observed at m/z 570 and 568 [M–AcOH]⁺, 557 and 555 [M–COOEt]⁺, 489 [M–ArN₂]⁺, 141 and 139 [ArN₂]⁺, 73, 60, and 43.

A characteristic fragmentation pattern was established for a number of BTDOs **5**. Electron impact spectra of all studied compounds exhibited the fragments [M–N₂O]⁺ and [M–2N₂O]⁺, corresponding to a stepwise loss of two N₂O molecules <2002EJO2342>. Structures **15a** and **15b** gave the expected molecular ions in their mass spectra <1997OL721>.

9.13.3.4 IR/Raman, UV/Vis, and Photoelectron Spectroscopy

Analysis of the vibrational spectra of fused 1,2,3,4-tetrazine *N*-dioxides, such as **5** and **14**, showed strong vibrational interaction between the two N=N(O)– units. The stretching vibrations, at $\nu = 1548$ and 1420 cm^{-1} , involve the predominant participation of the N=N bonds and much weaker contribution by the N–N and N–O bonds. These vibrations give strong absorption in the IR spectra but not in the Raman spectra <1995MC100, 1995RCB2092>.

Studies of the ultraviolet (UV) spectra of BTDOs **5** led to assignment of the transitions in the tetrazine dioxide unit, which are manifested by two absorption bands, corresponding to a $\pi\text{--}\pi^*$ and an $n\text{--}\pi^*$ transition, respectively <1997MC174>. Introduction of electron-donating groups in the fused benzene ring, particularly at C-7, led to bathochromic shifts of both bands. The experimental results were compared with data from CNDO/S calculations.

Circular dichroism (CD) studies were used to characterize epimeric pairs of 1,2,3,4-tetrahydrotetrazine adducts **16**, with opposite configurations at C-6 <1999JOC6297>. CD spectra of all pairs of C-6 epimers were found to be approximately mirror images, demonstrating that the sign of CD and its ellipticity was practically dependent only on the absolute configuration at C-6, with little influence of the rest of the chirality centers. CD spectra were used subsequently to identify structures with analogous absolute configuration at C-6.

Photoelectron (PE) spectra of **21a,b** were recorded and compared to computational results <1997JMT157>. Analysis of the PE spectra was found to be complicated, due to the presence of multiple, adjacent heteroatomic centers and the resultant accumulation of vicinal lone pairs. In general, good correspondence with experimental ionization potentials was observed only at the B3LYP/6-31+G* level of theory.

9.13.4 Thermodynamic Aspects

9.13.4.1 Melting Points

As a rule, BTDOs **5** are quite stable and melt without decomposition, in the range of $170\text{--}250^\circ\text{C}$ <2002EJO2342>. In contrast, compound **14** melts at 112°C with decomposition <1995MC227>. Decomposition is also observed in the case of TBTDOs **15a** (m.p. 140°C dec) and **15b** (decomposes at 210°C , prior to melting) <1997OL721>. The spiro- σ -complexes **9** melt slightly above 200°C , with decomposition <2002RCB668>. Pyrido-1,2,3,4-tetrazines **11a** and **11b** are stable yellow compounds melting without decomposition at $228\text{--}229^\circ\text{C}$ and $189\text{--}190^\circ\text{C}$, respectively <2004RCB2577>.

9.13.4.2 Ring–Chain Tautomerism

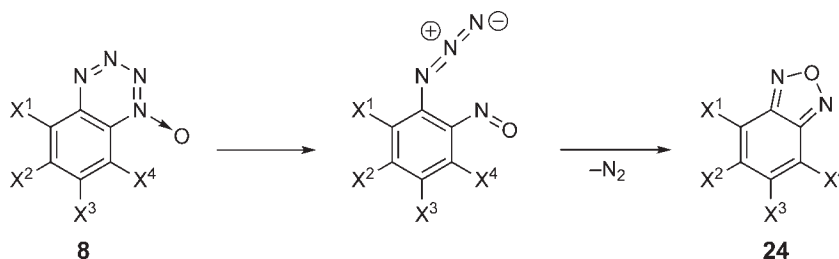
As discussed in Section 9.13.3.2.1, 2-aryl-2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **10** exist in equilibrium with 1-arylazo-2-diazocyclopentadienes **23** (Figure 4), and the two tautomers have been observed by NMR and/or IR spectroscopy <1994CB1479>. NMR data were used to elucidate the percentages of the cyclic and acyclic forms. With $R^1 = \text{H}$ and $R^2 = \text{Ar}$, the cyclic form is generally favored, both with electron-donating substituents (98% for $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$) and electron-withdrawing ones (87% for $\text{Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4$). The clear exceptions are *o*-,*p*-disubstituted systems (6% for $\text{Ar} = 2\text{-Me-4-NO}_2\text{C}_6\text{H}_3$ and 2% for $\text{Ar} = 2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3$). A similar trend is observed for structures with $R^1 = t\text{-Bu}$ and $R^2 = \text{Ar}$. Only the cyclic form was observed in cases with $R^2 = \text{Me}$. Variable-temperature NMR observations of dimethylformamide (DMF) solutions showed a clear preference for the open form at higher temperatures, consistent with the entropy effect on the equilibrium. In the case of **10d** ($R^1 = \text{H}$; $R^2 = 2\text{-CH}_3\text{C}_6\text{H}_4$), the Gibbs activation energy for the tautomeric conversion was determined to be $\Delta G^\ddagger_{333} = 72.1 \pm 1\text{ kJ mol}^{-1}$.

Ratios of the cyclic and acyclic forms were calculated also for tautomeric equilibrium mixtures of structures **6** (Section 9.13.3.2.1; Figure 4). The ratios were not affected by the nature of the alkyl group (**6a–g**: R = *t*-Bu; **6h–i**: R = Me), but changed significantly upon variation of the substituent(s) X. Highest percentages of the cyclic form were observed in 5,7-dibromo or 5,7-dichloro derivatives (100% for **6f** and **6g** and 95% for **6i**). For monosubstituted derivatives, the amount of the cyclic form varies between 45% and 85% and does not seem to depend on the electronic demands of the substituent <2002EJO3821>.

9.13.5 Reactivity of Fully Conjugated Rings

9.13.5.1 Unimolecular Thermal and Photochemical Reactions

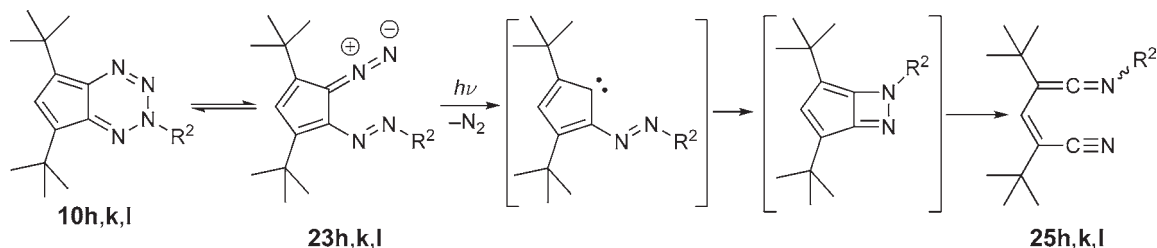
BTOs **8** are thermally unstable and decompose via ring opening, loss of N₂, and subsequent closure to benzofurazans **24** (Scheme 1) <1994MC122, 2002EJO3435>. Their low thermal stability made impossible the observation and/or isolation of some target structures, including **8a** (X¹ to X⁴ = H) as well as several brominated and nitrated derivatives. BTO decomposition times were found to range from 20 min at 20 °C in the case of **8f** (X³ = Br) to 12 h at 50 °C for **8o** (X¹ = Br, X³ = morpholino). Electron-donating substituents at the 7-position (X³) stabilize the corresponding BTO derivative <2002EJO3435>.



Scheme 1

In contrast, BTDOs **5** exhibit high thermal stability, which is attributed to the favorable positioning of the oxygen atoms, preventing ring–chain tautomerism and subsequent decomposition. Elimination of the highly stable N₂ molecule is also impossible. Instead, they decompose via the loss of N₂O, which is, however, not as favorable thermodynamically <2002EJO2342>.

Photolysis of several derivatives of **10** led to the formation of iminoketenes **25** <1994CB1479>. The suggested mechanism involves a unimolecular decomposition process triggered by an initial loss of N₂ from the azodiazio form **23** (Scheme 2). The structure of the iminoketenes **25** was confirmed by X-ray analysis.



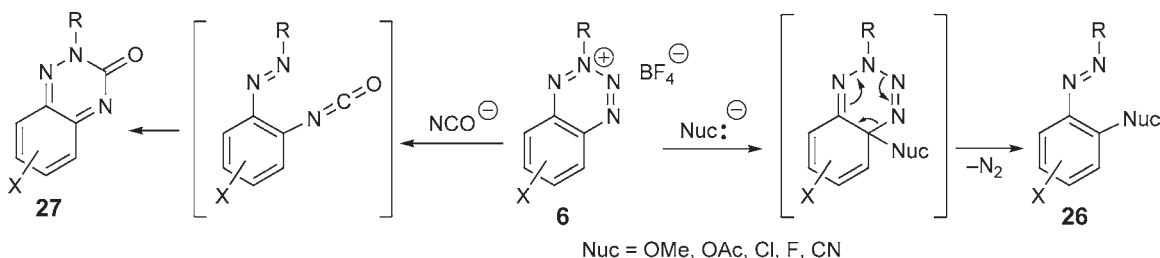
Scheme 2

9.13.5.2 Electrophilic Attack at Nitrogen

2*H*-Cyclopenta[*e*]-1,2,3,4-tetrazine **10a**, upon treatment with HBF₄, formed a ring-opened salt through protonation at N-2. The ring-opened, diazonium character of the salt was demonstrated by an intense absorption in the IR spectrum at 2185 cm^{−1} <1994CB1479>.

9.13.5.3 Nucleophilic Attack at Carbon

Tetrazinium salts **6** have been shown to react with a number of O-centered nucleophiles, halides and cyanide, to yield azo compounds **26**, whose formation is postulated to occur *via* a nucleophilic addition complex (Scheme 3). An azo compound is most likely the product when isocyanate is used as a nucleophile, but it undergoes further closure to the thermodynamically more stable triazinone **27**. The type of product generated with amine nucleophiles was found to depend both on the amount of cyclic tautomeric form of the corresponding salt **6** and the nature of the amine.



Scheme 3

9.13.5.4 Reduction

Reduction of BTDOs **5** with $\text{Na}_2\text{S}_2\text{O}_4$ or SnCl_2 led to the generation of benzotriazoles <2002OL3227>. The process is suggested to proceed via an intermediate *N*-nitrosotriazole, which is quickly hydrolyzed. Theoretical studies (RHF/6-31G*), labeling experiments (^{15}N -label at the 3-position), and isolation of *N*-nitrosated products are all in support of the proposed mechanism. The release of NO has been linked to the biological activity of some BTDOs (Section 9.13.12).

9.13.6 Reactivity of Nonconjugated Rings

1,2,3,6-Tetrahydro-1,2,3,4-tetrazines **16** were found to undergo efficient cleavage in the presence of trifluoroacetic acid, to yield acyclic 1,2-bis(hydrazones) <2002JOC2378>. The authors offered a mechanistic rationale to account for the significant difference in reactivity of **16** and some close structural analogs ($\text{R}^1 = \text{CONHPh}$), studied earlier by Ferguson *et al.* <1991J(P1)3361>. The latter, in similar reaction conditions, gave cyclic rearranged products with ring contraction, 2,5-dihydro-1*H*-1,2,3-triazoles. The relative acidity of the hydrogen at C-6 was identified as the main cause for the difference in product outcome.

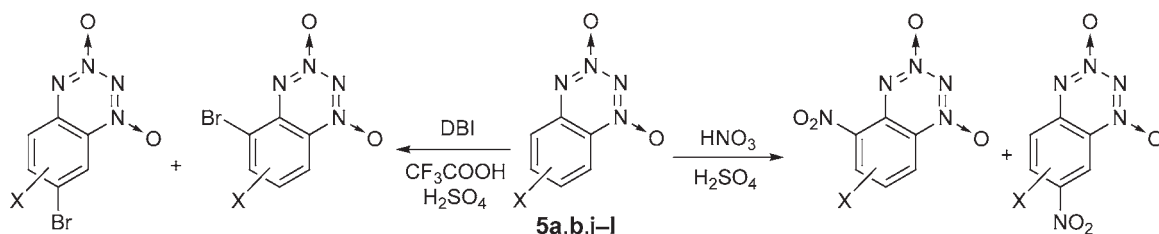
9.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms

9.13.7.1 Fused Benzene Rings

9.13.7.1.1 Benzo-1,2,3,4-tetrazine 1,3-dioxides

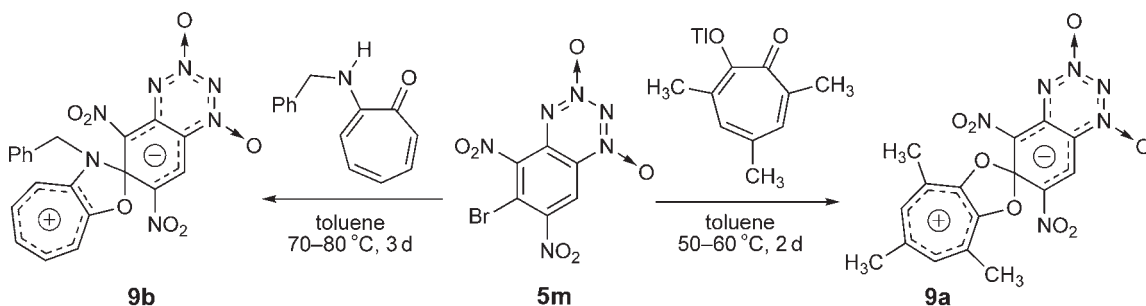
9.13.7.1.1(i) Electrophilic aromatic substitution

BTDOs **5** are stable compounds, and the 1,2,3,4-tetrazine 1,3-dioxide (TDO) substructure survives a variety of conditions. Thus, BTDOs undergo electrophilic aromatic substitution reactions, such as nitration and bromination, which result in the generation of a number of bromo and nitro derivatives <2002RCB1841>. Nitration was conducted with $\text{HNO}_3/\text{H}_2\text{SO}_4$ or $\text{HNO}_3/\text{oleum}$ and led to generation of mixtures of isomers, with reactivity changing in the order $5 \approx 7 > 8 > 6$ position (Scheme 4). BTDOs were brominated using dibromoisocyanuric acid (DBI) in $\text{CF}_3\text{COOH}/\text{H}_2\text{SO}_4$ (5:1) or H_2SO_4 . The observed order of position reactivity was similar to that for nitrations, with a somewhat reduced selectivity between positions 5 and 7.

**Scheme 4**

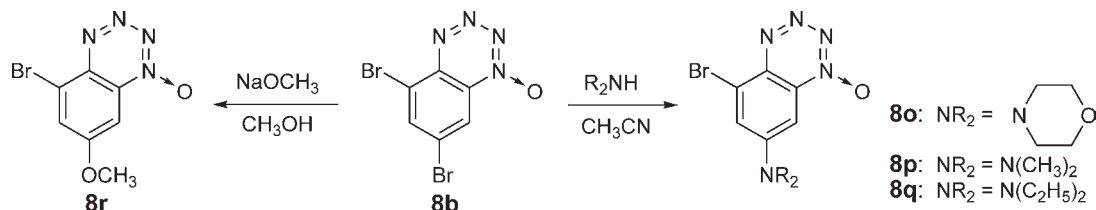
9.13.7.1.1(ii) Nucleophilic aromatic substitution

Bromo or nitro derivatives of BTDO undergo facile reactions of nucleophilic aromatic substitution, with replacement of bromine or the nitro group by methylamino ($\text{CH}_3\text{NH}_2/\text{DMSO}$), dimethylamino ($(\text{CH}_3)_2\text{NH}/\text{DMF}$), azido (NaN_3/DMF), or methoxy groups ($\text{KOH}/\text{CH}_3\text{OH}$) (DMSO = dimethyl sulfoxide). Studies on both monobrominated and dibrominated BTDOs led to an order of position reactivity, $6 > 8 > 7 > 5$, which is opposite to the order observed in electrophilic aromatic substitution processes [<2002RCB1849>](#). Displacement of bromine in 6-bromo-5,7-dinitrobenzo[*e*]-1,2,3,4-tetrazine 1,3-dioxide **5m** by 3,5,7-trimethyltropolone (Tl salt) or 2-(*N*-benzylamino)tropone led to the generation of the spiro- σ -complexes **9a** and **9b** (Scheme 5) [<2002RCB668>](#).

**Scheme 5**

9.13.7.1.2 Benzo-1,2,3,4-tetrazine 1-oxides

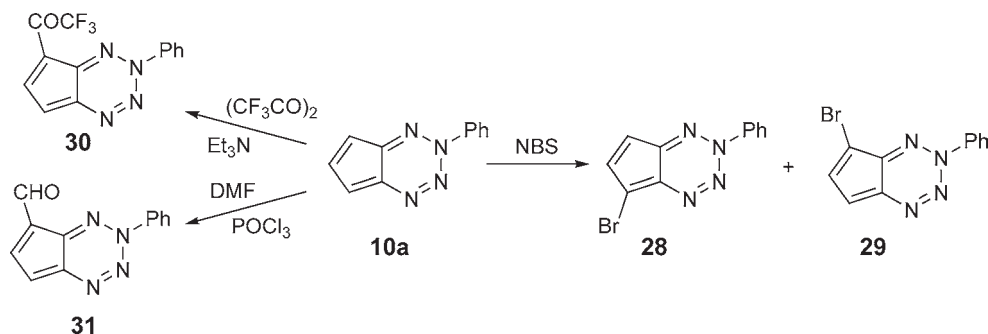
Bromo derivatives of BTO, such as **8b–d**, undergo nucleophilic aromatic substitution reactions with retained integrity of the BTO core [<2002EJO3435>](#). Several BTO derivatives were produced from **8b**, with exclusive replacement of Br at position 7 (Scheme 6). Competitive replacement of Br at the 6- and 7-positions was observed in the case of **8d**.

**Scheme 6**

9.13.7.2 Fused Cyclopentadiene Rings

9.13.7.2.1 2*H*-Cyclopenta[*e*]-1,2,3,4-tetrazines

Electrophilic aromatic substitution reactions of compounds **10** occur in a fashion characteristic for heterocyclic analogues of azulene, and are specific at positions 5 and 7 [<1994CB1479>](#). Thus, **10a** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$) was successfully brominated, formylated, and acylated, as shown in Scheme 7.



Scheme 7

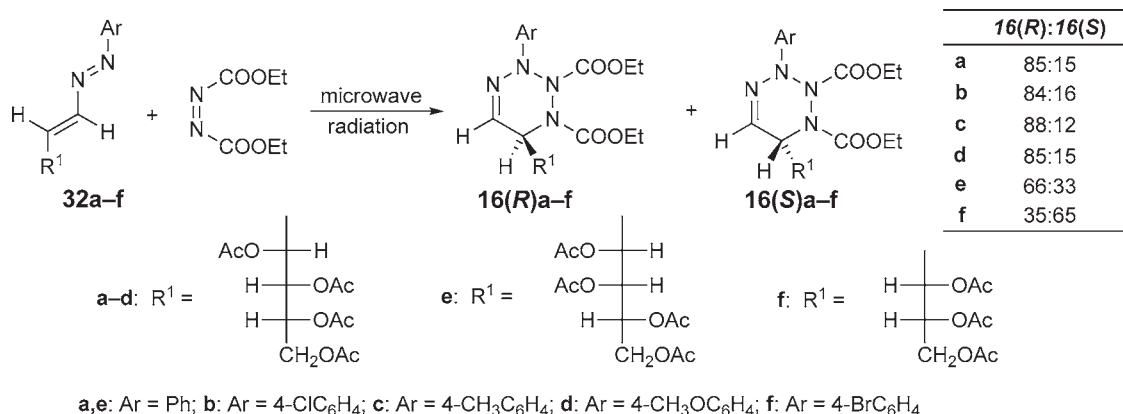
9.13.8 Reactivity of Substituents Attached to Ring Heteroatoms

Tetrazinium salts **38** are generated as intermediates in the formation of BTOs **8** (Section 9.13.9.2.3; Scheme 11). They are unstable and undergo elimination of *t*-butyl cation to furnish the corresponding BTOs <2002EJO3435>.

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

9.13.9.1 [4+2] Cycloaddition

The preparation of 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **16** was accomplished via hetero-Diels–Alder reactions of chiral 1,2-diaza-1,3-butadienes **32** with diethyl azodicarboxylate (Scheme 8) <1999JOC6297>. Reactions proceeded slowly in benzene at ambient temperature but were greatly accelerated by microwave irradiation. The stereochemical outcome was found to depend greatly on the configuration at the C-1'–C-2' linkage in the carbohydrate moiety. *threo*-Configuration at that linkage led to high diastereoselectivity of the addition process, with a strong preference for the (*6R*)-isomer of the product in the cases with (*R*)-configuration at C-1' in the starting diene (tetrazine products **16a–d**) while *erythro*-configuration led to product mixtures with lower diastereomeric ratios (tetrazine product **16e**). Results were rationalized on the basis of PM3 computational results (Section 9.13.2.1).



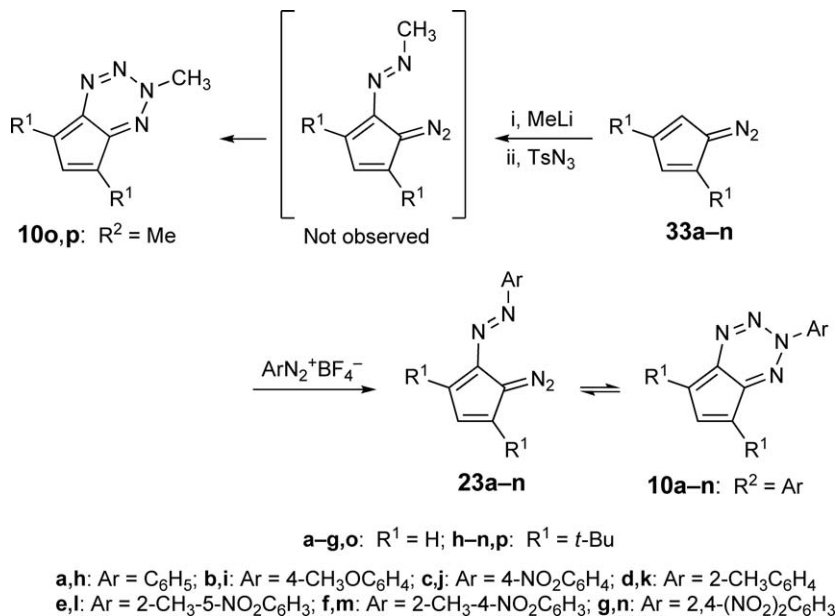
Scheme 8

9.13.9.2 Ring Closure of a Single Component via Reaction between Electrophilic and Nucleophilic Centers

9.13.9.2.1 N–N bond formation by coupling of azo and diazo functional groups

2-Azodiazocyclopentadienes **23**, the open-chain tautomers of 2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **10**, were generated through coupling of arenediazonium salts with diazocyclopentadienes, or via reaction of diazocyclopentadienes

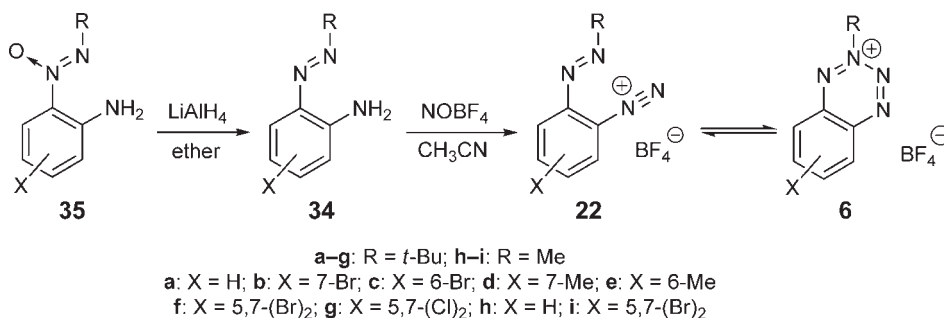
33 with MeLi, followed by a diazo transfer using tosyl azide, as shown in [Scheme 9](#) <1994CB1479>. In the latter case, the open-chain forms were not observed ([Section 9.13.4.2](#)).



Scheme 9

9.13.9.2.2 N–N bond formation by coupling of azo and diazonium functional groups

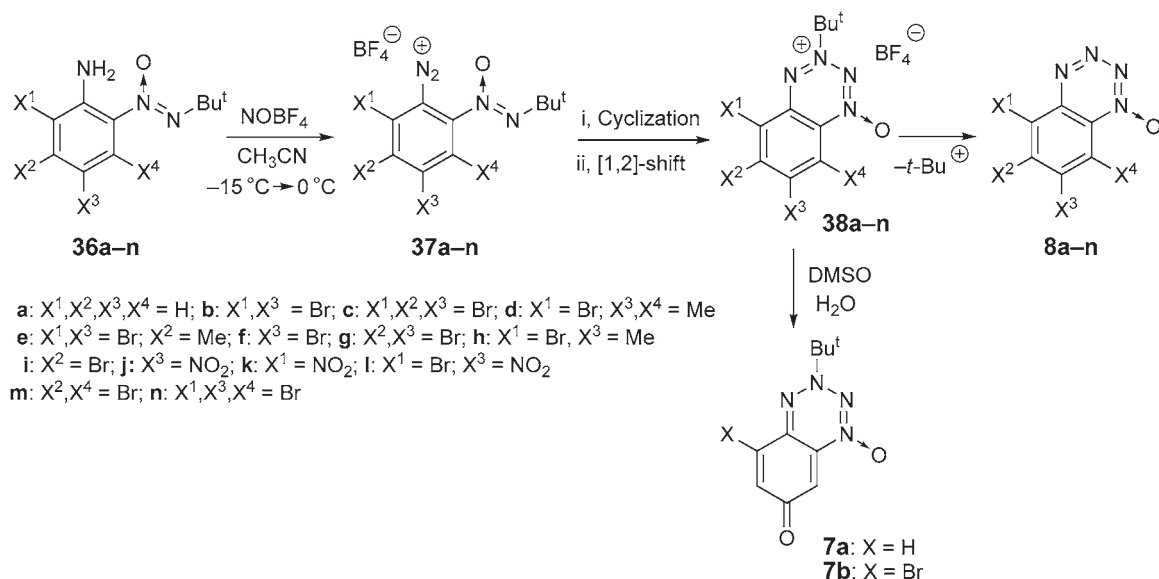
2-Alkyltetrazinium salts **6** were prepared via diazotization of the corresponding *ortho*-azoanilines **34** with NOBF₄, leading to the generation of *ortho*-azodiazonium salts **22** ([Scheme 10](#)). The latter are in equilibrium with the cyclic structures **6** ([Sections 9.13.3.2.1 and 9.13.4.2](#)) <2002EJO3821>. The starting *ortho*-azoanilines were prepared by reduction of *ortho*-(alkylazoxy)anilines **35** with LiAlH₄ <2002RCB311>.



Scheme 10

9.13.9.2.3 N–N bond formation by coupling of azoxy and diazonium functional groups

BTOs **8** were prepared utilizing the synthetic sequence outlined in [Scheme 11](#) <1994MC122, 2002EJO3435>. *ortho*-(*t*-Butyl)-azoxyanilines **36** are diazotized with NOBF₄ to yield diazonium salts **37**. Salts **37**, via cyclization and subsequent facile [1,2]-shift of the *t*-butyl group, yield tetrazinium salts **38**, which undergo elimination of *t*-butyl cation to form BTOs **8**. The rate of cyclization of diazonium salts **37** to form **38** was found to be strongly dependent on the substituent(s) X¹ to X⁴. Thus, for the nonsubstituted structure **37a** (X¹ to X⁴ = H), cyclization was observed only at elevated temperature (1 h at 50 °C), leading to mixtures of **38a** and benzofurazan **24a**. The fact that the BTOs

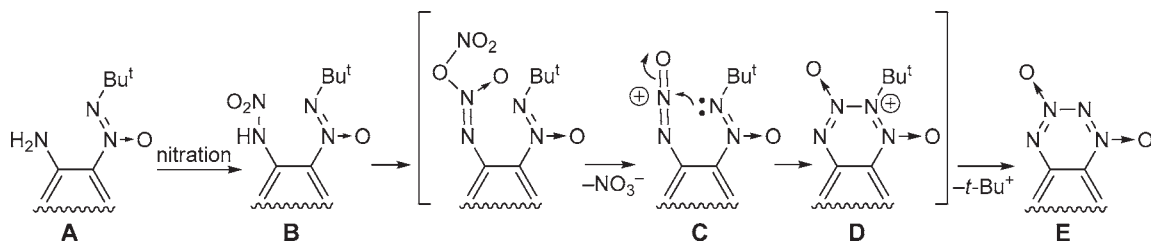


Scheme 11

were not observed in certain cases was accounted for on the basis of their low thermal stability and facile conversion to benzofurazans **24** (Section 9.13.5.1; Scheme 1). Further evidence for the structure of salts **38** was derived by treatment of **38b** and **38f** with a DMSO–water mixture, leading to the generation of the quinonoid compounds **7a** and **7b** correspondingly. The structure of **7b** was confirmed by X-ray analysis (Section 9.13.3.1).

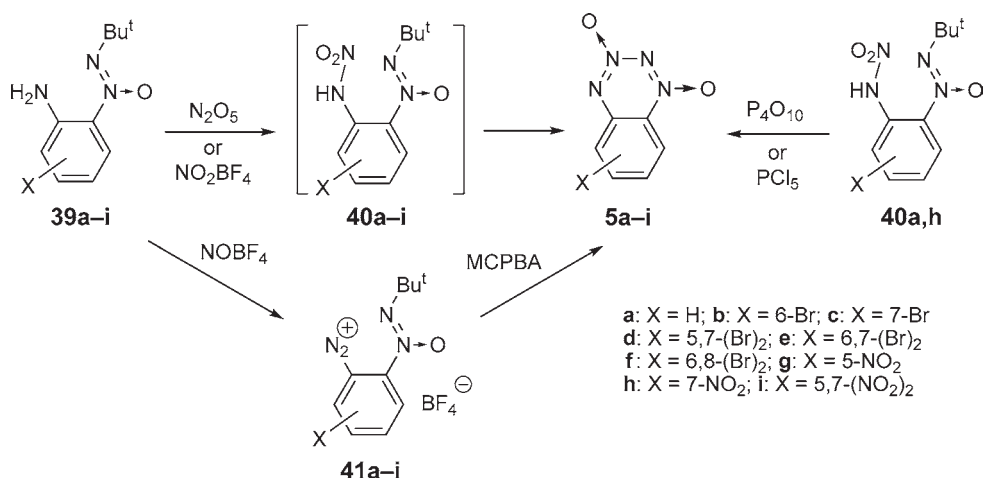
9.13.9.2.4 N–N bond formation by coupling of azoxy and oxodiazonium functional groups

The coupling of azoxy and oxodiazonium functional groups has been utilized in the preparation of compounds containing the TDO substructure, fused to an aromatic ring (benzene, pyridine, furazan). A common methodology is followed, as outlined in Scheme 12. An aromatic amino compound **A**, containing an *ortho*-(*t*-butylazoxy) group, is nitrated to produce an *N*-nitroamine **B**, which, through further nitration and nitrate elimination, yields an oxodiazonium cation **C**. Cyclization of **C** and subsequent loss of *t*-butyl cation from cyclic intermediate **D** leads to the generation of the TDO ring **E** <2004RCB2577>.



Scheme 12

Following the common methodology, BTDOs **5** were prepared from *ortho*-(*t*-butylazoxy)anilines **39**, via nitration with N_2O_5 or NO_2BF_4 (Scheme 13) <2002EJO2342, 2002RCB1841, 2002RCB1849>. Yields were found to depend strongly on both the reagent and solvent. The parent compound **5a** was prepared in highest yield using $\text{N}_2\text{O}_5/\text{CH}_3\text{NO}_2$. Acetonitrile was found preferable for the bromo derivatives **5b–f**, which precipitate at lower temperatures, thus facilitating product isolation. The nitro derivatives **5g–i** were generated in significant yields as by-products in the preparation of **5a** when NO_2BF_4 was used as a nitrating agent or in strongly acidic conditions ($\text{N}_2\text{O}_5/\text{CF}_3\text{COOH}$).



Scheme 13

Mechanistically, their formation can be explained either by rearrangement of the intermediate *N*-nitroamines in acidic medium or by the direct nitration of **5a**. Alternatively, BTDOs are prepared from anilines **39** by diazotization and treatment of diazonium salts **41** with *meta*-chloroperbenzoic acid (MCPBA). A third methodology consists of a P₄O₁₀- or PCl₅-promoted ring closure of *N*-nitroanilines **40**, achieved in the case of **5a** and **5h** <2000RCB482>.

9.13.10 Ring Syntheses by Transformations of Another Ring

There are no literature references from the covered period that report preparations of the target compounds by transformations of other heterocyclic structures.

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

BTDOs **5** have been prepared following three different routes (Section 9.13.9.2.4; Scheme 13): (1) treatment of *ortho*-(*t*-butylazoxy)anilines **39** with N₂O₅ or NO₂BF₄ (nitration method) <2002EJO2342, 2002RCB1841, 2002RCB1849>; (2) treatment of *ortho*-(*t*-butylazoxy)anilines **39** with NOBF₄, followed by MCPBA (oxidation method) <2002EJO2342>; and (3) treatment of *ortho*-(*t*-butylazoxy)-*N*-nitroanilines **40** with P₄O₁₀ or PCl₅ <2000RCB482>. Overall, BTDOs were obtained in similar yields following either the nitration or oxidation method, the greatest difference being observed in the case of **5a** (nitration method: 41% yield; oxidation method: 70% yield). An advantage of the oxidation method for generation of BTDOs is the absence of nitrated by-products.

9.13.12 Important Compounds and Applications

Several BTDOs, namely **5g**, **5h**, and **5i**, were investigated in terms of their ability to generate nitric oxide (NO) and activate guanylate cyclase <2002MI396, 1998RU2123526>. All of the studied compounds were found to be thiol-dependent NO donors as well as guanylate cyclase activators. All of them inhibited ADP-induced aggregation of human platelets (IC₅₀ = 10.0, 1.3, and 2.0 μM for **5g**, **5h**, and **5i**, respectively). BTDOs **5a**, **5b**, **5c**, and **5e** have exhibited antimetastatic properties <2002RU2192857>. Compounds **5b** and **5c** have been shown to irreversibly and selectively inhibit the activity of H,K-adenosinetriphosphatase in the microsomal fraction of stomach mucosa <2002RU2186108>.

9.13.13 Further Developments

Valence bond theory and ring current maps were used to study the electronic structure of several homo- or heterocyclic benzene analogs, including hexazine N_6 (D_{6h}) <2005IC5266>. The valence bond calculations were conducted at the VB/6-31G(d,p) level of theory, on B3LYP optimized structures, using TURTLE as implemented in the GAMESS-UK package. Magnetic properties for the studied structures were obtained at the coupled HF level, within the CTODC-DZ formalism, using the 6-31G(d,p) basis set, leading to maps for the α , π and the $(\alpha + \pi)$ contributions to the current density. The results indicated that all homonuclear structures, including hexazine, resemble benzene and are characterized with resonance between two Kekulé structures. The resonance energy for hexazine was calculated to be 97.8 kJ mol^{-1} and was greater than the corresponding value for benzene (81.4 kJ mol^{-1}). All homonuclear structures were found to possess induced diatropic ring current.

Mosquera and co-workers conducted local aromaticity studies, using n-center delocalization indices, in order to evaluate the role of aromaticity on the relative stability of position isomers for various mono- and polycyclic structures, including all tetrazine isomers, pentazine and hexazine <2006T12204>. Calculations were carried out at the B3LYP/6-311++G(d,p) level, to obtain molecular geometries, energies and molecular orbitals. The program NDELOC, developed by the authors, was used to compute the n-center delocalization indices. The results indicated that the order of stability within a series of position isomers, such as the tetrazines, is not controlled by aromaticity but by other structural factors. Thus, within the tetrazine series, the most stable isomer was the least aromatic one.

Churakov *et al.* recently prepared the first nonannulated 1,2,3,4-tetrazine-1,3-dioxide derivative *via* nucleophilic displacement by azide of all bromine and nitro groups in 6,8-dibromo-5,7-dinitro-1,2,3,4-benzotetrazine-1,3-dioxide, followed by thermolysis of the resultant 5,6,7,8-tetraazido-1,2,3,4-benzotetrazine-1,3-dioxide <2006RCB1648>.

A set of new 1,2-dihydro-1,2,3,4-tetrazine derivatives was prepared by a reaction of substituted 2-azido-1,3,5-triazines with methyl or ethyl cyanoacetate <2006CHE965>.

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Biographical Sketch



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9.14

Other Six-membered Rings with Four or Five Nitrogen, Oxygen, or Sulfur

C. L. Francis

CSIRO, Melbourne, VIC, Australia

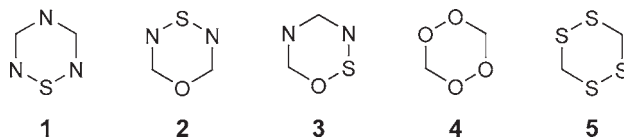
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9.14.1 Introduction

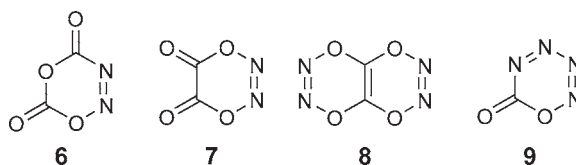
Reviews of the chemistry and applications of the ring systems covered in this chapter appeared in two chapters in CHEC(1984) <1984CHEC(3)943, 1984CHEC(3)1039>. In CHEC-II(1996), these ring systems were combined in a single chapter <1996CHEC-II(6)967>. For the present edition, this chapter covers new developments reported from

1995–2006. The last decade has witnessed new reports on over 30 different heterocycles within the scope of this chapter and, for most of these rings, there were very few reports dealing with each of them. However, the chemistry of five of these heterocycles has been studied in some detail. These were the 1,2,4,6-thiatriazines **1** (long known and relatively common, but undergoing renewed interest due to the herbicidal activity of new derivatives), 1,4,3,5-oxathiadiazines **2**, 1,2,3,5-oxathiadiazines **3**, 1,2,4,5-tetroxanes **4** (significant recent interest due to the impressive antimalarial activity of some derivatives), and 1,2,4,5-tetrathianes **5**.

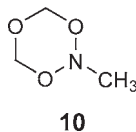


9.14.2 Theoretical Methods

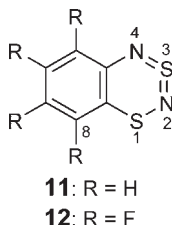
From an AM1 and *ab initio* study of cyclic copolymers of dinitrogen and carbon dioxide, it was concluded that only the MP2(FC)/6-31G* results are likely to be reliable and none of the structures, which include dioxadiazines **6–8** (and oxatetrazine **9**), are kinetically stable at room temperature <1999JMT(469)77>.



Molecular orbital (MO) calculations at the restricted Hartree–Fock (RHF)/6-31G** level of theory on *N*-methyl-1,3,5,2-trioxazine **10** indicate that it should be almost as stable as *s*-trioxane and, by analogy, it should decompose thermally into MeNO + 2CH₂O <1998CC583>.

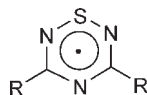


The crystal structures of 1,3λ⁴δ²,2,4-benzodithiadiazines **11** and **12** were discussed in CHEC-II(1996) and indicated that **11** is planar in the solid phase, whereas **12** is nonplanar in the heterocyclic ring <1996CHEC-II(6)967>. However, *ab initio* calculations at the B3LYP/6-31G* level suggested that for the free molecules the geometrical situations are reversed; **11** has a nonplanar geometry, in which the heterocyclic ring is bent along the S(1)–N(4) line and S-1 lies out of the plane of the benzene ring, while **12** is planar. Gas electron diffraction (GED) experiments using the SARACEN method (structural analysis restrained by *ab initio* calculations for electron diffraction) of structural analysis quite convincingly demonstrated the nonplanarity of **11** in agreement with the density functional theory (DFT) calculations. The effect of the fluorine atoms on the planarity of the heteroatomic ring was also investigated by extending the B3LYP/6-31G* calculations to some mono- and difluoro derivatives of dithiadiazines **11**. These calculations indicated that the fluorine atom in the 8-position is alone responsible for the flattening of the heteroatomic ring <2001CEJ3592>.



Gas-phase electron-transfer processes for the 1,2,4,6-thiatriazinyl radicals **13** were investigated using the Hartree–Fock (HF) and B3LYP methods with the 6-31G(d) basis set augmented with diffuse functions. The calculated

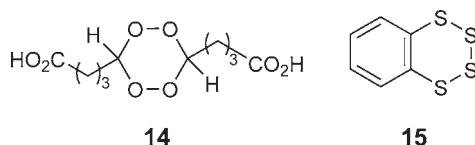
ionization potentials (I_p) and free energy changes were compared subsequently with the experimental I_p and electrochemical redox potentials. The DFT method performed better than the HF method giving excellent correlations for vertical I_p and $E_{1/2}^{\text{red}}$ but not for $E_{1/2}^{\text{ox}}$ or E_{cell} <2001PCA7626>.



13: R = Cl, Ph

The theoretical value of the enthalpy of formation of the tetroxane **14**, 276.27 kcal mol⁻¹, was in good agreement with the experimental value, 262.47 kcal mol⁻¹ <2005BMC5826>.

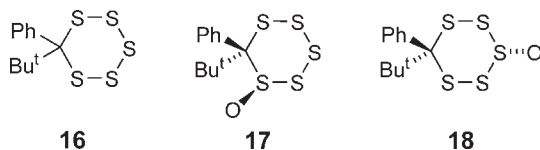
The stability of benzotetrathiine **15** was estimated by MM2 calculations and the results suggested the compound to be very labile because of the small torsional angle of 50° for C–S–S–S <1999PAC489>.



14

15

DFT calculation of the nuclear magnetic resonance (NMR) chemical shifts of pentathiane **16** and 16 isomers of the monoxides were found to be in practical agreement with the experimental data of the pentathiane and the isolated 1- and 3-oxides **17** and **18**, respectively <2002BCJ319>.



16

17

18

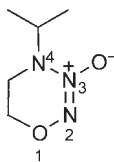
Theoretical calculations have been used frequently, often in conjunction with X-ray crystallography and NMR spectroscopy, to predict and determine preferred ring conformations, particularly in the cases of tetroxanes and tetrathianes (see Section 9.14.4.5).

9.14.3 Experimental Structural Methods

9.14.3.1 X-Ray Crystallography

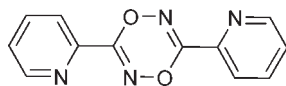
Due to the lack of contiguous NMR-responsive nuclei in the core heterocycles of most of the compounds described in this chapter, X-ray structural studies are often critical in confirming the exact connectivity of the atoms that constitute the heterocyclic ring.

The crystal structure of the 1,2,3,4-oxatriazine 3-oxide **19** was reported to be orthorhombic with space group *P* 21 21 21 <2005JA5388>.

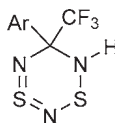


19

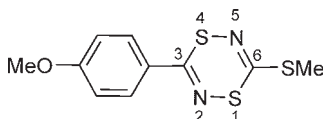
The crystal structure of 3,6-di(2-pyridyl)-1,4,2,5-dioxadiazine **20** solved and refined well, but the central ring was disordered with respect to the positions of the nitrogen and oxygen atoms, despite the fact that the outer pyridine rings did not show any such disorder <2003EJI405>.

**20**

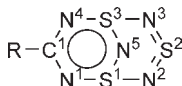
The crystal structure of 1,3,2,4,6-dithiatriazine **21** (Ar = Ph) was reported to be triclinic with space group *P* 2. This molecule is nonplanar and not aromatic <1996JHC295>.

**21**

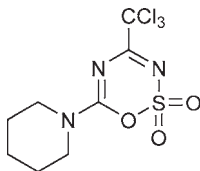
In the crystal structure of 1,4,2,5-dithiadiazine **22**, the dithiadiazine ring is folded by 48.3(2)° along the S(1)–S(4) vector, which is a similar conformation to that previously observed in other 1,4,2,5-dithiadiazines, as well as isoelectronic 1,4,2-dithiazines and most 1,4-dithiines. The benzene ring in **22** forms a dihedral angle of 26.4(2)° with the S(1)–N(2)–C(3)–S(4) plane, while the N(5)–C(6)–SMe torsion angle of –9.1(6)° implies conjugation between the methylthio group and the N(5)=C(6) bond <1997J(P1)1157>.

**22**

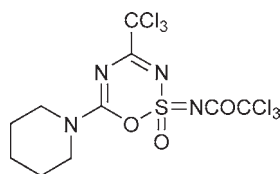
A detailed examination of bonding parameters from the crystal structures of the bicyclic compounds **23** found that the C(1)–N(1), N(1)–S(1), and S(1)–N(5) bond lengths lie in the range between those of single and double bonds, while the S(1)–N(2) bonds might be considered as single bonds and the N(2)–S(2) bonds as double bonds. The bicyclic framework is best described as a dithiatriazine bridged by a sulfur diimide group. The C(1)–N(1) bond lengths are increased by electron-donating R and shortened by electron-accepting substituents. The neighboring N(1)–S(1) bonds show the reverse effect. Directly bonded amino groups significantly increase the S(1)–N(2) bond length. The experimentally determined influence of the different substituents on bond lengths and on the NCN bond angle was quite well reflected by theoretical calculations (RHF, MP2, and B3LYP). The best fit for bond lengths was found with the RHF calculations. The influence of the substituents was explained in terms of the (extended) frontier orbital model <2003EJI3211>.

**23**

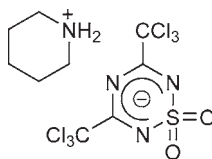
The crystal structure of 1,2,3,5-oxathiadiazine-2,2-dioxide **24** was mentioned briefly in CHEC-II(1996) <1996CHEC-II(6)967>. The S–O bond length of 1.632 Å is significantly longer than the analogous bond (1.610 Å) in the cyclic trimer SO₃ and this is consistent with the observation that this bond, rather than the C–O bond, ruptures in reactions of **24** with nucleophiles (see Section 9.14.5) <1997CHE1028>.

**24**

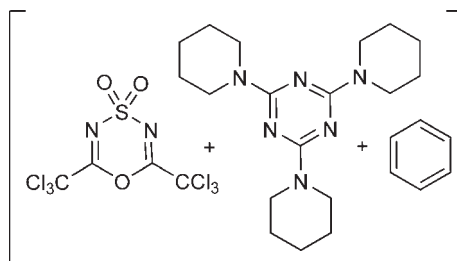
The crystal structure of **25** is monoclinic, space group $P2_1/C$, $Z=4$ <1999RJO157>. Some important features include the following: the OCNCN fragment in the central ring is planar within $0.02\text{ \AA}$ with the S-atom deviating from the mean square plane by $0.179\text{ \AA}$, the piperidino N deviates from the same plane by $0.127\text{ \AA}$, the two $\text{C}=\text{N}$ and one $\text{C}-\text{N}$ bond in the central ring are all of similar length, indicating delocalization of π -electrons over the entire CNCN fragment, and the piperidino $\text{N}-\text{C}(6)$ bond is shorter than the standard $\text{C}_{\text{sp}^2}-\text{N}_{\text{sp}^2}$ bond, suggesting that this bond also participates in the above electron density delocalization. The piperidino group of **25** adopts a chair conformation <2000RJO1523>.

**25**

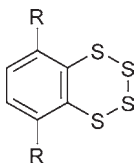
Salt **26** is monoclinic, space group $P2_1/C$, $Z=4$. The thiaziazine ring is planar, the piperidinium cation is in a chair conformation, and ionic fragments in the crystal are joined into a three-dimensional (3-D) structure by strong hydrogen bonds <2002RJO1702>.

**26**

The crystalline structure of supramolecular complex **27** (see Section 9.14.5) is formed by 1,4,3,5-oxathiadiazine 4,4-dioxide, symmetric triazine, and solvate benzene molecules, bound through van der Waals interactions, in a ratio of 2:2:1. No short intermolecular contacts between constituent molecules were found and the bond lengths in the triazine and oxathiadiazine components are similar to those found in structurally related compounds. The central NCOCN fragment in the oxathiadiazine dioxide component is almost planar and the S-atom deviates from this plane by $0.17\text{ \AA}$. The central oxathiadiazine ring appears folded along the $\text{N}-\text{N}$ line such that the dihedral angle between the mean square plane and the plane formed by the S-, N-, and N-atoms is 10.3° . The crystals are monoclinic, space group $P2_1/m$, $Z=4$ <1999RJO1410>.

**27**

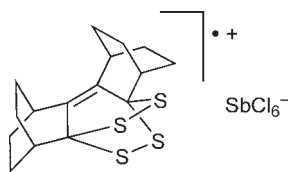
In the crystal structure of dimethoxybenzotetrathiane **28**, key metric parameters include: bond lengths ($\text{\AA}$) $\text{C}-\text{S}(1)$ 1.800(1), $\text{S}(1)-\text{S}(2)$ 2.028(6); bond angles ($^\circ$) $\text{C}-\text{S}(1)-\text{S}(2)$ $105.6(5)$, $\text{S}(1)-\text{S}(2)-\text{S}(3)$ $98.7(3)$; torsional angle ($^\circ$) $\text{C}-\text{S}(1)-\text{S}(2)-\text{S}(3)$ $60.4(5)$. This torsional angle is greater than the calculated value for the corresponding angle (50.1°) in the unsubstituted compound **15** (see Section 9.14.2), which suggests stabilization by the substituents <1999PAC489>.



15: R = H

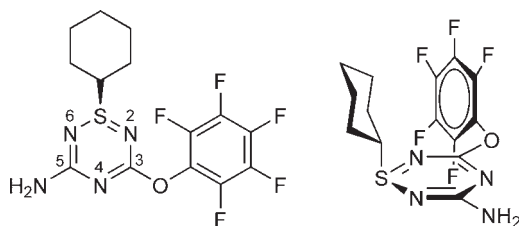
28: R = OMe

X-Ray analysis of the remarkably stable radical cation salt **29** indicated a strong transannular bonding interaction between the two disulfide linkages. Theoretical calculations (UB3LYP/6-31G^{*}) suggested that this transannular interaction could be described as the resonance between the limiting structures, each of them having a two-center three-electron bond between two sulfur atoms belonging to two different disulfide linkages: thus, both the spin and positive charge are equally delocalized to the four sulfur atoms, causing a great stabilization of **29**^{•+} <2002JA15038>.



29

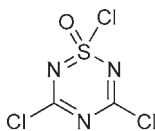
X-Ray structural determination of 1 λ^4 -1,2,4,6-thiatriazines shows that the heterocyclic system is not planar; the sulfur atom points out of the average plane of the other five atoms. The two S–N bonds are almost the same length (in the case of **30**, 1.625 and 1.662 Å) and the S-substituent is orthogonal to the average plane (99° for **30**).



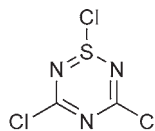
30

When the 3- and 5-positions are differently substituted, as in **30**, the sulfur atom becomes an asymmetric center and introduction of an asymmetric substituent leads to diastereomers. The configuration at the sulfur is very stable. The enantiomers of **30** were separated on a chiral column. No racemization has been observed under a range of conditions <2000JHC583, 2003C725>.

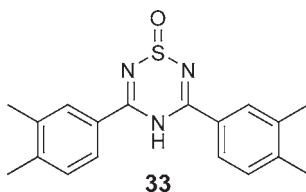
In the solid state, the six atoms of the thiatriazine ring in **31** and the 3,5-chloro atoms are all essentially coplanar, which is in contrast to the structure of **32** where the S-atom deviates significantly (ca. 0.314 Å) from the plane of the three N- and two C-atoms in the ring <2004AXEo2402>. The crystal structure of thiatriazine-S-oxide **33** is also nonplanar <2000T7153>. Compound **32** has significantly elongated S–N bond lengths (ca. 1.615 Å) compared to **31**, which has distances for the same bonds of around 1.58 Å. In **31**, the S–Cl bond lengths range from 1.99 to 2.01 Å, whereas in **32** this distance is slightly longer at 2.13 Å. The differences in bond lengths may be attributed to the higher formal positive charge on the S(vi) center in **31** compared to that on the S(iv) center in **32** <2004AXEo2402>.



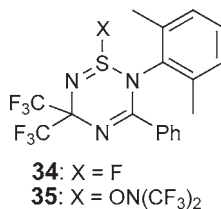
31



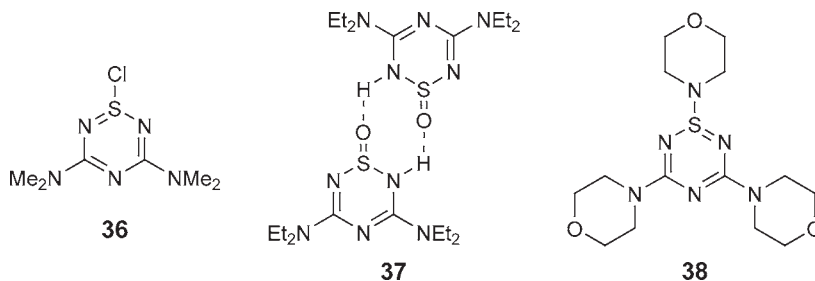
32



X-Ray crystallographic analysis of the dihydrothiazines **34** and **35** found intra-annular bond lengths to be C=N 1.27–1.28 Å, C–N 1.40–1.465 Å, S=N 1.50–1.52 Å, and S–N 1.68–1.69 Å (consistent with localized single and double bonds). The S-substituents were found to be in an axial position, presumably due to anomeric interactions with the nonbonding electron pairs of the adjacent N-atoms. This structural feature is consistent with the ^{19}F NMR spectra, which show nonequivalent CF_3 groups and, in the case of **34**, the lower field quartet was split further into doublets due to coupling with the sulfur-bonded fluorine <2000JFC(102)337>.

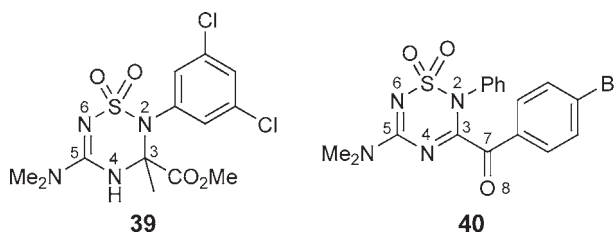


Notable features of the crystal structure of **36** are the S–Cl bond projecting almost perpendicular to the mean plane of the heterocycle and the exocyclic C–N bond lengths of 1.342 and 1.344 Å, while the endocyclic C–N bond lengths fall in the range 1.340–1.376 Å. This indicates significant double-bond character for the exocyclic C–N bonds, which is further evidenced by the fact that the C₂N moiety of the exocyclic amino group is oriented in a plane almost parallel to the mean plane of the ring itself. Similarly shortened exocyclic C–N bonds were observed in **37** and **38**. Partial saturation in the heterocycle **37** resulted in a lengthening of the endocyclic S–N(H) bond (1.713 Å). Hydrogen-bonding interactions between the NH and S=O bonds lead to a dimeric structure <1999IC3022>.



Interestingly, the exocyclic S–N bond length of **38** (1.694 Å) is comparatively longer than the ring S–N bond lengths (1.619, 1.620 Å) and is quite close to S–N(H) of **37**, which is more toward an S–N single bond. It can be concluded that, unlike the ring carbon and morpholino nitrogen in **38**, there is comparatively little π -interaction between the ring sulfur and attached morpholino nitrogen atoms <1999IC3022>.

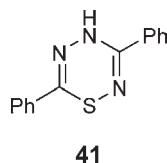
The 1,2,4,6-thiazine rings in **39** and **40** both adopt an envelope conformation. In the case of **39**, N-2 is 0.636(2) Å out of the SC(3)C(5)N(4)N(6) plane. The SN(2)C(3) plane subtends an angle of 46.3(1)° with the above plane. In the crystal of **39**, adjacent molecules are linked by an N–H...O hydrogen bond to form chains parallel to the a -direction <2005AXEo2694>.



In the crystal structure of **40**, the S-atom is 0.308(2) Å out of the N(6)C(5)N(4)C(3)N(2) plane. The N(6)SN(2) plane subtends an angle of 17.5(1)° with the above plane, confirming the nonaromatic character of this heterocycle.

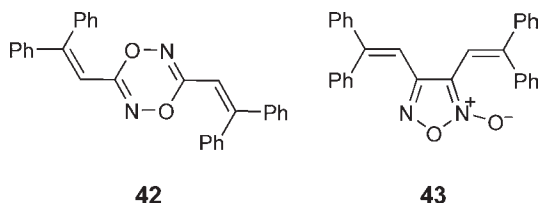
The coplanarity of the guanidinium-type unit defined by $\text{Me}_2\text{N}-\text{C}(5)\text{N}(4)\text{N}(6)$, together with the short $\text{C}(5)$ –exocyclic N and $\text{SN}(6)$ bond lengths (1.328(3) Å and 1.561(2) Å, respectively) indicate significant conjugation in this region. The torsion angle $\text{N}(4)\text{C}(3)\text{C}(7)\text{O}(8)$ is $95.5(2)^\circ$, thus limiting conjugation, and this is consistent with the unusually long $\text{C}(3)$ – $\text{C}(7)$ bond (1.528(3) Å). Interestingly, there appears to be intermolecular π -stacking between the ‘guanidinium region’ centered on C-5, the exocyclic N of another molecule, and the nonbrominated phenyl ring of a third molecule <2006AXEo3794>.

The 4*H*-1,2,4,5-thiatriazine **41** adopts an ‘open book’ conformation. The ring is folded along the S–N(4) axis by about 45° and the two halves of the open book are nearly coplanar. The phenyl rings are rotated relative to the planes defined by the adjacent thioiminy and amidinyl fragments by 8° and 30° , respectively. The higher torsional angle for the phenyl group at C-3 may reflect steric interaction with the N-4 hydrogen atom <2000JOC931>.

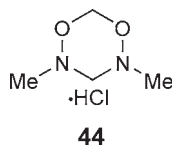


9.14.3.2 NMR Spectroscopy

The structure of 1,4,2,5-dioxadiazine **42** was distinguished from the isomeric furoxan structure **43** by ^1H NMR spectroscopy. The ^1H NMR spectrum of **42** showed a 2*H* singlet at δ 6.49 for the equivalent alkene protons, whereas the furoxan **43** showed two 1*H* singlets at δ 6.59 and δ 6.74 (δ values in ppm) <2000ARK683>.

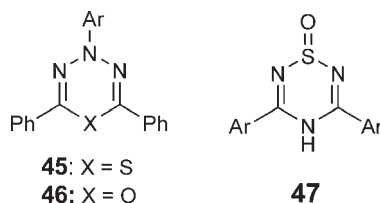


The ^1H NMR spectrum of the 1,5,2,4-dioxadiazine **44** in d_6 -DMSO at 25°C showed broadened signals at $\delta \sim 4.2$ and $\delta \sim 5.7$ for the methylene groups. At 60°C , these signals were singlets. This broadening can result from both intra- and intermolecular proton exchange of the acid and conformational processes <2004RCB1349>.

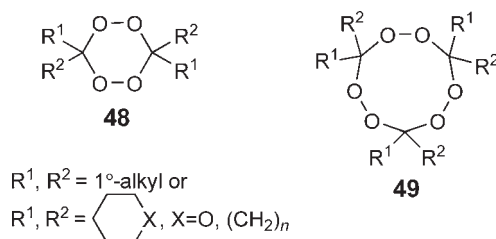


The hydrogen atom of the N–H group in thiatriazines **21** is exchangeable with D_2O in CDCl_3 and the ^{19}F NMR spectrum of **21** (Ar=Ph) exhibited only a singlet at -23.63 ppm, which indicated no special interaction such as hydrogen bonding with a hydrogen on the nitrogen atom <1996JHC295>.

The ^{13}C NMR spectrum of 1,3,4,5-thiatriazines **45** (Ar = substituted Ph) showed only nine signals due to the S–N(4) axis of symmetry, with the ring carbon signal at 141 ± 1.5 ppm <1994JCM350>. The corresponding signal in the oxatriazines **46** was at 146 ppm <1996CHEC-II(6)967>. Similarly, with the ^{13}C NMR spectra of 1,2,4,6-thiatriazine-*S*-oxides **47**, the number of signals was equivalent to half the total number of carbons of these compounds, indicative of the symmetrical structure <2000T7153>.

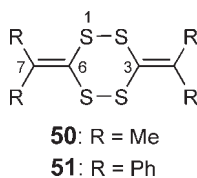


A reliable method for distinguishing between 1,2,4,5-tetroxanes **48** and 1,2,4,5,7,8-hexaoxonanes **49** by inspection of the chemical shifts, signal number, signal shape, and dynamic features in their NMR spectra has been developed. Such a method is useful because a common synthetic method for 1,2,4,5-tetroxanes **48** is the acid-catalyzed peroxidation of ketones (see Section 9.14.8.3) which sometimes affords 1,2,4,5,7,8-hexaoxonanes **49** as by-products or, in some cases, as sole products. In all of the ^1H NMR spectra, diagnostic tetroxane signals (two equatorial methylene groups) appeared downfield compared to the diagnostic hexaoxonane signals (half of an AB system for the diastereotopic methylene groups adjacent to the core ring). The equatorial and axial carbons in tetroxanes are not magnetically equivalent, whereas the corresponding carbons adjacent to the hexaoxonane ring are magnetically identical. With the ^{13}C NMR spectra of the tetroxanes, the two or four signals corresponding to these carbons were broadened, presumably due to conformational inversion, whereas only sharp signals (and fewer of them, in general) were observed for the hexaoxonanes. All tetroxanes displayed significant changes in peak shape and chemical shifts in their ^1H NMR spectra between 20 and 60 $^\circ\text{C}$, whereas the spectra of the hexaoxonanes were practically unaffected in the same temperature range <2001JHC463>.



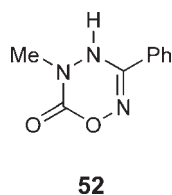
The very fast ring inversion of tetroxanes **48** at room temperature leads to broad NMR signals, but when some spectra were recorded at lower temperature (-40°C), the conformation of the ring froze and in cases where $\text{R}^1 \neq \text{R}^2$, a mixture of *cis*- and *trans*-isomers was revealed <2006BMC7790>.

The quaternary carbon atoms C-6 and C-7 in 1,2,4,5-tetrathianes **50** and **51** show a difference in chemical shift of about 10 ppm in the ^{13}C NMR spectra. The lower field signal was assigned to C-7 due to observed coupling ($^3J = 3.8\text{ Hz}$) between the *ortho*-protons of the phenyl ring and C-7 in a ^{13}C -, ^1H -gated decoupled NMR spectrum of **51** <1996CB663>.

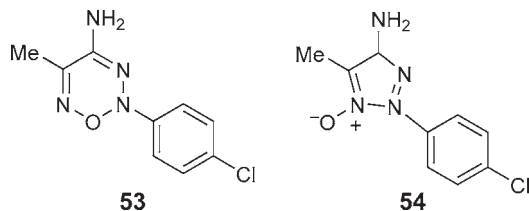


9.14.3.3 Mass Spectrometry

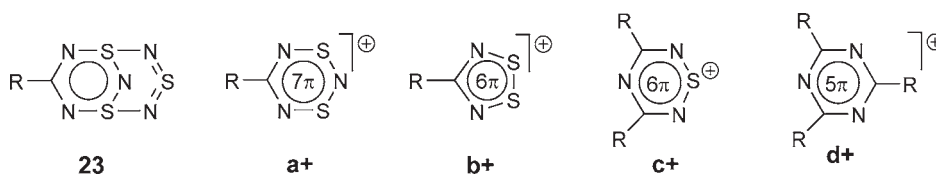
The electron impact (EI) mass spectrum of 1,2,4,5-oxatriazin-6-one **52** shows that the major fragmentation pathway involves rupture of the weak N–O bond, displacement of the H-atom, followed by loss of OH radical <1998ASJ180>.



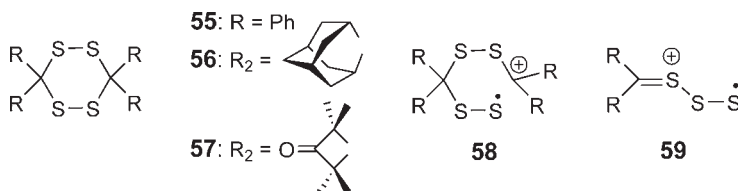
Of special importance in the EI mass spectrum of the 1,2,3,6-oxatriazine **53** is the peak at m/z 141 (60%) which is attributed to the fragment 4-ClC₆H₄NO. This is in accordance with structure **53** rather than the isomer, 1,2,3-triazole 1-oxide **54** <2005ICA(358)4511>.



The results from mass spectrometric analysis of the bicyclic systems **23** depend on the ionization method applied. With EI, molecular ions are mostly detected, but with low intensity. The peak representing the fragment $[M-N_3S]^+$ is always present. This corresponds to the stable 1,2,3,5-dithiadiazolium cation **b⁺**. The more gentle FI method allows for the detection of molecular ions and the direct degradation products **a⁺** and **b⁺** are observed, together with the ions (**c⁺**, **d⁺**) formed by recombination of the fragments <2003EJI3211>.

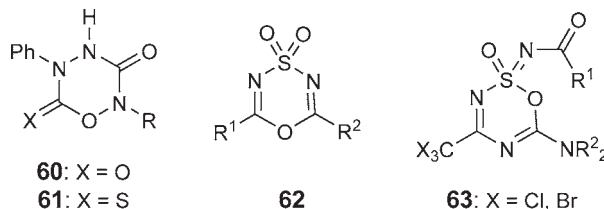


Detailed discussions of the mass spectra of 1,2,4,5-tetrathianes **55** and **56** <1997H(45)507> and **57** <1997LA1517> have been reported. Consistent with data reported for other compounds of this type, the molecular peaks – perhaps as the distonic radical ion **58** – were small but the diagnostic, and usually major, fragments corresponded to R₂CS₃⁺ **59** and R₂CS⁺.



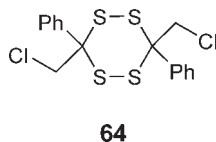
9.14.3.4 IR Spectroscopy

The IR spectra of 1,2,4,5-oxatriazine 3,6-diones **60** each show two carbonyl bands at 1751–1770 and 1627–1635 cm⁻¹, while thio analogs **61** are characterized by a carbonyl stretching vibration at 1655–1670 cm⁻¹ <2002HCO321>. The oxatriazinone **52** shows a carbonyl band at 1677 cm⁻¹ <1998ASJ180>. The 1,4,3,5-oxathiadiazine 4,4-dioxides **62** show two SO₂ bands at 1170–1210 and 1350–1400 cm⁻¹ and two C=N bands at 1635–1680 and 1720–1750 cm⁻¹ <2000RJO1523, 2002RJO889>. The 2,4,6-trisubstituted-1,2,3,5-oxathiadiazine 2-oxides **63** show two SO₂ bands at 1160–1200 and 1328–1380 cm⁻¹, two C=N bands at 1532–1580 and 1640–1670 cm⁻¹, and a C=O band at 1668–1730 cm⁻¹ <2000RJO1523>.



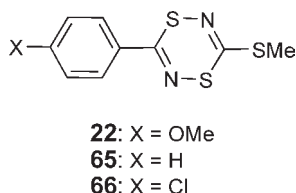
Complete assignment of the IR and Raman spectra of 3,3,6,6-tetramethyl-1,2,4,5-tetroxane (**48**: R¹ = R² = Me) <1999JRS479> and the vibrational IR spectrum of tetroxane diacid **14** <2005MSI1075> have been reported.

The most important contributions are the characterization of the bands located at 860 and 872 cm^{-1} in the IR and Raman spectra of **48** ($R^1 = R^2 = \text{Me}$) and the band at 943–936 cm^{-1} in the IR spectrum of **14** as the O–O stretching modes. The assignments were supported by theoretical calculations. Diagnostic bands in the IR spectrum of 1,2,4,5-tetrathiane **64** were the very strong $\nu_{\text{C-S}}$ band at 690 cm^{-1} , the $\nu_{\text{S-S}}$ band at 520 cm^{-1} , and a series of strong, narrow peaks at 750, 1000, 1190, and 1448 cm^{-1} due to skeletal vibrations of the saturated ring; these bands are typical of such structures <2004RJO766>.



9.14.3.5 UV Spectroscopy

Solution ultraviolet (UV) spectra of **22**, **65**, and **66** in acetonitrile demonstrate that the aryl substituent is conjugated with the heterocyclic ring: the value of λ_{max} shifts hypsochromically along the series **22** (391 nm), **65** (385–375 nm, broad band), and **66** (371 nm) <1997J(P1)1157>.



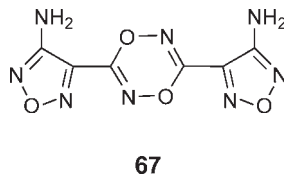
Absorption at 205 nm in the UV spectrum of tetroxane **14** has been assigned to the O–O group. There is a satisfactory agreement with the calculated value at the Zerner's intermediate neglect of differential overlap (ZINDO) semi-empirical level of calculation <2005MSI1075>.

The endocyclic S–S bonds in 1,2,4,5-tetrathiane **64** give rise to an absorption band at λ_{max} 526 nm due to electron transition between the sulfur d orbitals <2004RJO766>.

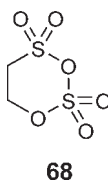
9.14.4 Thermodynamic Aspects

9.14.4.1 Solubilities and Chromatographic Behavior

The diamino compound **67** is poorly soluble in most organic solvents, though it can be recrystallized from a large volume of dioxane or acetonitrile, or reprecipitated from dimethyl formamide (DMF) with water <2004RJO884>.

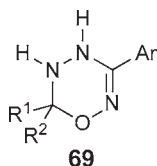


Carbyl sulfate (1,3,2,4-dioxadithiane-2,2,4,4-tetroxide) **68**, a useful reagent in various industrial processes, has sparing solubility or even insolubility in most organic solvents. Although it dissolves satisfactorily in protic solvents, the dissolution is accompanied by simultaneous decomposition <2001WO0160787>.

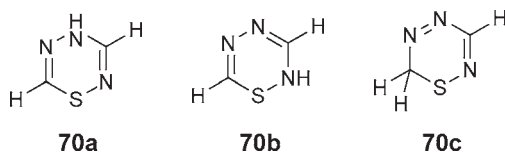


9.14.4.2 Tautomerism

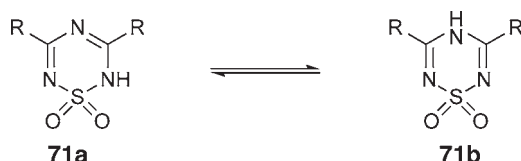
Only a few examples of oxatriazine systems capable of existing in tautomeric forms, such as **69**, have been reported and, according to their NMR and IR spectra, these compounds exist as formed and no tautomeric interconversions have yet been observed <2001AHC(81)253>.



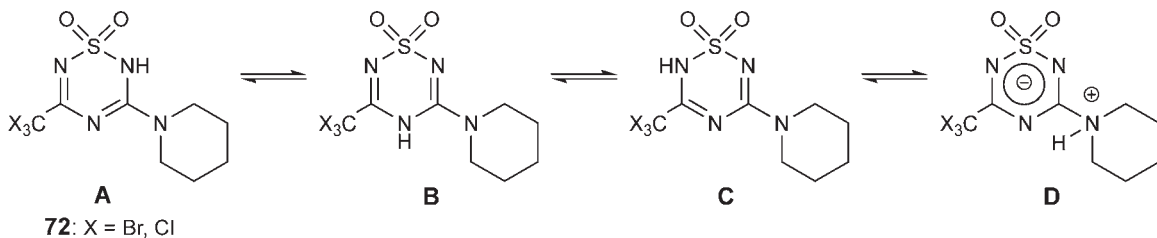
The thermodynamic stabilities of three possible annular tautomers of the parent 1,2,4,5-thiatriazine **70** were compared using *ab initio* HF/6-31G* calculations which showed the 4*H*-isomer **70a** to be the most stable (more stable than **70b** by 11.6 kcal mol⁻¹ and than **70c** by 15.5 kcal mol⁻¹), presumably because it allows low-energy distortion from planarity and adoption of the boat conformation <2001AHC(81)253>.



Some investigations of the tautomeric behavior of 1,2,4,6-thiatriazine-1,1-dioxides **71**, which can exist as N[2(6)]H **71a** and N(4)H **71b**, have been performed. The parent compound (R = H) exists predominantly in the 4*H*-form (**71b**), according to NMR data (and comparison with the 4-Me derivative). The symmetrical structure was also established for the 3,5-di(trifluoromethyl) derivative **71b** (R = CF₃) on the basis of a unique signal in the ¹⁹F NMR spectrum. *Ab initio* calculations also indicated the 4*H*-tautomer **71b** to be more stable than **71a** by 5.5 kcal mol⁻¹ (STO-3G*) or 2.8 kcal mol⁻¹ (3-21G*) <2001AHC(81)253>.

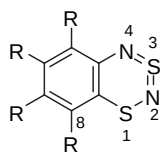


The thiatriazines **72** exist as a mixture of tautomeric forms **A–D** in a ratio of 1:1.5:1.5:1 according to the IR and ¹H NMR spectra <2000RJO1229>.



9.14.4.3 Aromaticity

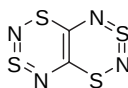
The 1,3λ⁴δ²,2,4-benzodithiadiazines **11** and **12** are mixed heterocyclic–carbocyclic compounds that combine true aromaticity in the all-carbon part (4n + 2π electrons) with a nonaromatic heterocyclic part, to give an overall antiaromatic structure (4nπ electrons) <2001CEJ3592>.



11: R = H

12: R = F

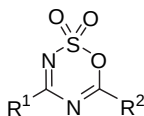
The molecular structure of dithiadiazine **73** was optimized at the RHF and DFT (B3LYP) levels in the 6-31G** basis set, known to be sufficient for semi-quantitative calculation of current density maps. These calculations predicted **73** to have planar equilibrium geometry and the intermediate bond lengths expected of delocalized systems. Current density maps were plotted at the planar RHF geometry for **73** and it was found that the molecule exhibited diatropic perimeter circulations and no cross-link π -current, in close analogy with naphthalene, where such a current is forbidden by symmetry. On the basis of the magnetic criterion, **73** can reasonably be regarded as aromatic <2004JA11202>.



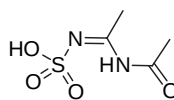
73

9.14.4.4 Stability

The stability of the 1,2,3,5-oxathiadiazine ring **74** depends considerably on the nature of the substituents R^1 and R^2 , particularly R^2 . Heterocycles **74** having both identical ($R^1 = R^2$) aryl, unsaturated, p-donor (dialkylamino) and different ($R^1 = \text{CCl}_3$, $p\text{-NO}_2\text{Ph}$; $R^2 = \text{dialkylamino}$) substituents are relatively stable. Where substituents R^1 and R^2 are both alkyl, only compounds where $R^1 = R^2 = \text{Bu}^t$ are obtained. Compound **74** ($R^1 = R^2 = \text{Me}$) is so labile that hydrolysis to the sulfamic acid **75** occurs during isolation. Compounds **74** with strong acceptor substituents R^2 are generally not obtained. The state of the C–O bond also affects stability of the ring in **74**. The C–O bond may be stabilized by resonance (making the moiety **A** in the ring flat) and this is favored by π - and p-donor substituents R^1 , which also cause decreased electrophilicity of C-6. Bulky groups $R^2 = \text{Bu}^t$ block access to these centers by nucleophilic reagents, thus contributing to ring stability. A change in the nature of substituents R^1 and R^2 leads to a change in orientation of reaction of rings **74**. When donor substituents R^1 are replaced by acceptor substituents, it is no longer the C–O bond that breaks, but rather the S–O bond (which is longer than usual – see Section 9.14.3.1) <1997CHE1028>.



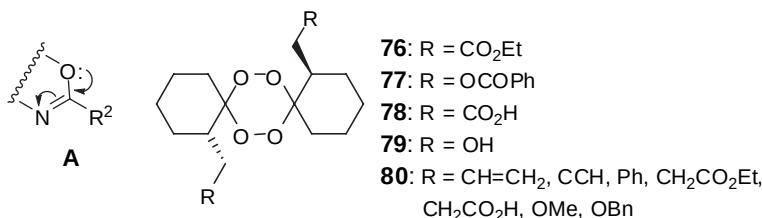
74



75

The strain energy for *s*-tetroxane **4** has been calculated (using high-level computational schemes) to be 2.2 kcal mol⁻¹ <2002JOC3884>.

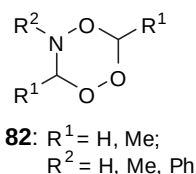
The 1,2,4,5-tetroxanes **76–80** are colorless crystalline solids, stable at room temperature for months if not years. The tetroxanes **76** and **77** bearing ester groups were hydrolyzed with 6 equiv of KOH in MeOH/H₂O/CH₂Cl₂ to the corresponding compounds **78** and **79** in yields of 72% and 60%, respectively <1999JME1477>. Several steroidal dispiro-1,2,4,5-tetroxanes derived from cholic acid derivatives, bearing methyl ester group(s) on the steroid moiety(ies), were treated with NaOH in refluxing isopropanol/water to afford the corresponding acids in 72–95% yield. Further transformations of the acids to various amides in good yields (60–96%) provided additional evidence of 1,2,4,5-tetroxane ring stability <2002JME3331, 2003BMC2761>.



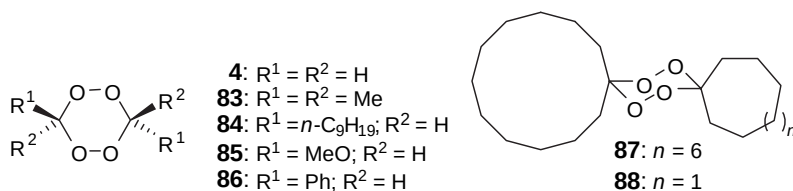
3,3,6,6-Tetraphenyl 1,2,4,5-tetrathiane **55** is stable in boiling benzene, but heating in refluxing mesitylene (150 °C) for 15 h caused complete degradation to thiobenzophenone and elemental sulfur <1997H(45)507>. The *cis*- and *trans*-isomers of 3,6-bis(1,1,3,3-tetramethyl-4-oxo-4-phenylbutyl)-1,2,4,5-tetrathiane **81** (see Section 9.14.4.5 for structures) were thermally stable in refluxing toluene and neither decomposed nor isomerized <2000BCJ729>.

9.14.4.5 Conformation

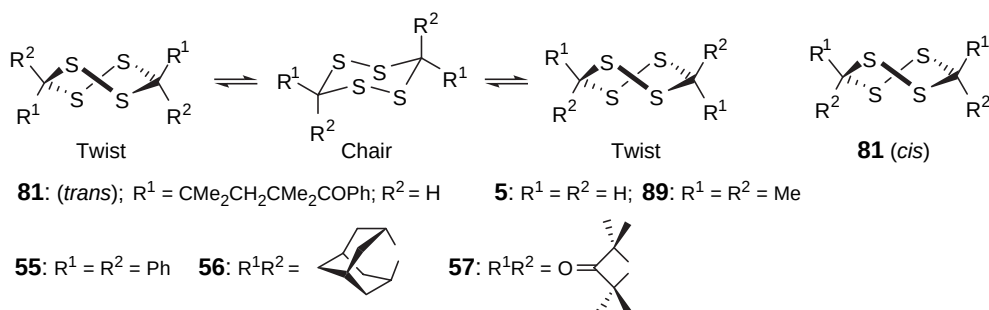
A theoretical conformational study of some alkyl and phenyl 1,2,4,5-trioxazines **82** with semi-empirical AM1, PM3, and modified neglect of diatomic overlap (MNDO/3) as well as an *ab initio* method with a limited basis set found reasonable agreement among the different calculation procedures suggesting a chair conformation to be the most stable for these molecules <1995JMT(334)249>. Molecular orbital calculations on *N*-methyl-1,3,5,2-trioxazine **10** also indicate a chair conformer being of lowest energy <1998CC583>.



Photoelectron spectra, detailed NMR studies, and X-ray structures prove that 1,2,4,5-tetroxane (*s*-tetroxane) **4** adopts the chair conformation <1998AHC(69)217>. A recent conformational study of **4** using different theoretical procedures (AM1 semi-empirical, *ab initio* RHF at 3-21+G and 6-311+G(d,p) basis set levels, and B3LYP density functional method at the same basis set levels) found general agreement between these methods and all of them predict the chair conformation to be the most stable conformer <2002PAS387>. A molecular dynamics/density functional conformational study of the tetramethyl tetroxane **83** suggested that a chair conformer is 2.78 kcal mol⁻¹ more stable than a twisted form. Boat forms are unstable according to these calculations <1999JRS479, 2000JMT(499)85>. Later, X-ray crystallographic studies confirmed that in the solid state, this molecule adopts a chair conformation <2004AXCo180, 2005JA1146>. In *trans*-dimethoxy tetroxane **85** and *trans*-diphenyl tetroxane **86**, the chair conformation with the two substituents located in the axial positions was found to be the most stable. A number of steroidal dispiro-1,2,4,5-tetroxanes and cyclohexano dispiro-1,2,4,5-tetroxanes were found also to exist in an all-chair conformation <2004AHC(86)41>. The conformation and geometric parameters of the symmetrical 1,2,4,5-tetroxane **87** with two 12-membered rings are similar to those observed in other symmetrical tetroxanes, whereas the chair-like conformation of the heterocycle in the unsymmetrical molecule with 7- and 12-membered spiro rings **88** is distorted; the torsion angles about the O–O bonds differ by 4° <2004S2356>. The *trans*-dinonyl tetroxane **84** (in a 3,6-diequatorial orientation where the alkyl chains are in an all-*trans*-conformation) and the *trans*-dimethoxy tetroxane **85** were studied by X-ray analysis. The latter compound was also the object of a detailed ¹H NMR study; in acetone-*d*₆ at –80 °C, a conformational equilibrium *ax,ax* ⇌ *eq,eq* (75%:25%; Δ*G*° = 0.42 kcal mol⁻¹) with a preference for the diaxial conformer was found, due to the anomeric effect which also dominates the conformational equilibrium of 3-methoxy-1,2,4,5-tetroxane; the axial conformer was found, in agreement with the X-ray structure <1998AHC(69)217>. The barriers to ring inversion of a range of 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes have been determined. The free energies of activation, Δ*G*‡, are in the range of 12.6–15.3 kcal mol⁻¹ <1998AHC(69)217>.



The conformational equilibria of the *cis/trans*-isomers of tetrathiane **81** have been studied in detail by both NMR spectroscopy and X-ray crystallography. On cooling the *trans*-isomer, the NMR resonances split into two signals each (intensity ratio 2.4:1); the major conformer was assigned to the twist form, the minor one to the chair conformer (Scheme 1). The free energy of activation of interconversion was estimated to be 13.3 and 12.8 kcal mol⁻¹, respectively. In the solid state only the chair conformer was observed. The *cis*-isomer exists exclusively as the twist conformer, both in solution and in the solid state <2004AHC(86)41>. 3,3,6,6-Tetramethyl-1,2,4,5-tetrathiane **89** exists as the twist conformer in the solid state according to X-ray studies and *ab initio* calculations at the HF/6-31+G*, MP2/6-31+G*, and B3LYP/6-31+G* levels of theory estimated the twist conformer of **89** to be 4 kJ mol⁻¹ more stable than the chair form and the calculated strain energy for twist-to-chair conversion was 61.1 kJ mol⁻¹. This study calculated also that the chair conformation of the parent 1,2,4,5-tetrathiane **5** is 10.7 kJ mol⁻¹ more stable than the twist form <2004PS2015>.

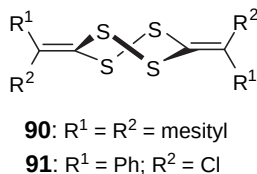


Scheme 1

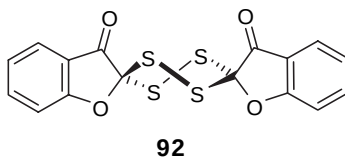
According to the ¹³C NMR spectra of 1,2,4,5-tetrathianes **55**, **56** <1997H(45)507>, and **57** <1997LA1517>, these molecules exist in a twist conformation, which inverts with $\Delta G \sim 16$ kcal mol⁻¹ (estimated by dynamic ¹H NMR spectroscopic studies).

In 3,3,6,6-tetrasubstituted-1,2,4,5-tetrathianes, such as those described above, the twist conformer is favored (more so for large R) over the chair conformer which suffers from *syn*-axial repulsion (S1/S5, S2/S4) between the lone pairs <1997H(45)507>.

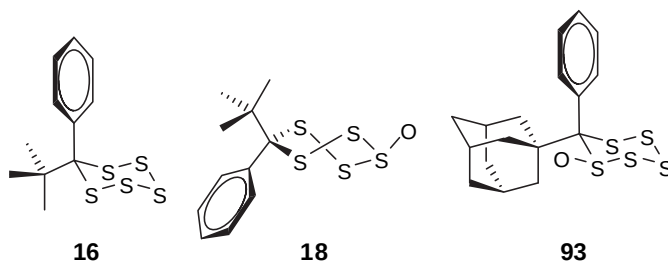
1,2,4,5-Tetrathiane **90**, which has 3,6-exomethylene moieties, exists in an imperfect twist conformation since the two C=C bonds are at an angle of 166°, rather than 180° <2004AHC(86)41>. The related compound **91** shows a closely similar structure <2002AXEo555>.



The bis-benzofuranone-substituted 1,2,4,5-tetrathiane **92** also has a twist conformation with the two coumaranone rings *syn*-oriented with the angle of twist between them being 38° as determined by X-ray studies. Molecular mechanics calculations (MM2) refined with AM1 calculations were consistent with the preference for *syn*-orientation and also the 38° twist angle. However, the calculations determined that the *anti*-isomer of **92** is energetically more stable than the *syn*-form, so the experimental results indicate kinetic reaction control in the formation of this compound <1996T1961>.



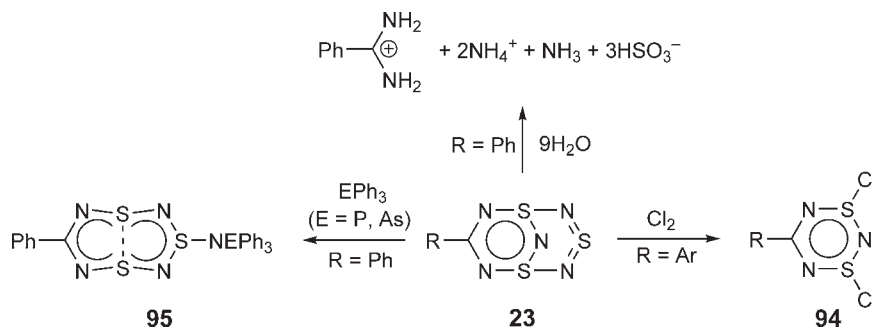
An X-ray crystallographic analysis of pentathiane **16** revealed a chair conformation in the solid state. X-Ray studies also showed that the 3-oxide **18** takes a twist conformation in the solid state with the oxygen atom *cis* to the Bu^t group, while the 1-oxide **93** adopts a chair conformation with the oxygen atom in an equatorial position <2002BCJ319>.



9.14.5 Reactivity of Fully Conjugated Rings

There are very little published data on the reactivity of 1,4,2,5-dioxadiazine derivatives, but some reactions of diamine **67** have been investigated (see Section 9.14.7). After heating compound **67** for 2 h in 98% H₂SO₄, 93–94% of the compound can be recovered <2004RJO884>.

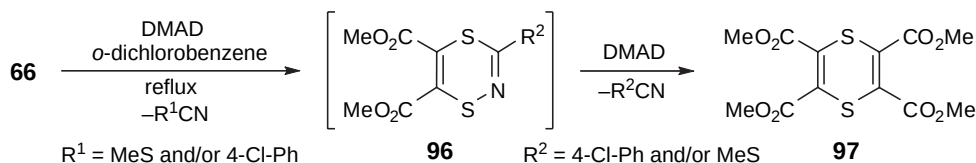
The bridged dithiatrizazine compounds **23** are stable at room temperature in an inert atmosphere; however, the bicyclic sulfur nitrogen framework does undergo chemical, photochemical, or thermal decomposition. In moist air, these compounds will slowly decompose (within a few days). Complete hydrolysis occurs according to Scheme 2 <2003EJI3211>.



Scheme 2

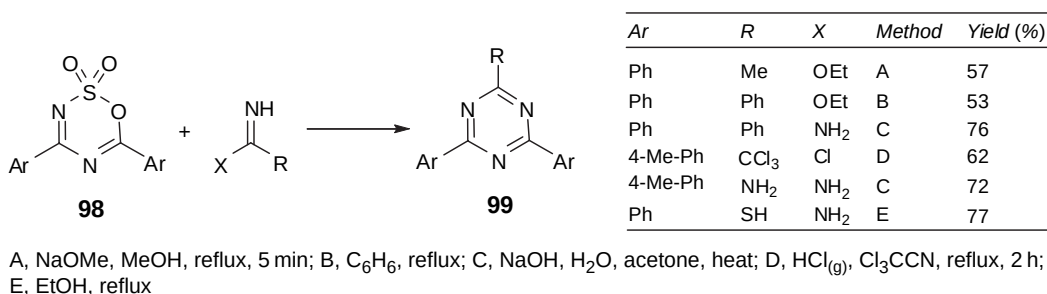
Aryl derivatives of **23** are readily degraded with chlorine to dithiatrizazines **94** with the rate being dependent on the aryl substituent. The phenyl derivative of **23** undergoes nucleophilic attack by triphenylphosphine or triphenylarsine and is transformed into the monocyclic eight-membered imino compound **95**, which has weak transannular S–S bonds (Scheme 2). Thermolysis and photolysis of compounds **23** affords the corresponding 1,2,3,5-dithiadiazolyl radicals. The trifluoromethyl derivative of **23** (R = CF₃) is astonishingly stable and does not react with bromine, chlorine, sulfonyl chloride, or (CF₃)₂NO. To date, no explanation has been found <2003EJI3211>.

When compound **66** was treated with DMAD (5 equiv) in refluxing *o*-dichlorobenzene (180 °C), the 1,4-dithiine-2,3,5,6-tetracarboxylate **97** (12%) was isolated. The likely pathway to formation of **97** is reaction of **66** with DMAD with loss of a nitrile fragment (MeSCN and/or 4-Cl-PhCN) to afford either or both of two possible intermediates **96**, which, as would be expected from the reactions of 1,4,2-dithiazines, reacts further with DMAD to yield **97** and a nitrile fragment (Scheme 3). The methoxy- and unsubstituted analogs **22** and **65** did not react under the same conditions, indicating that an electron-withdrawing *para*-substituent on the aryl group increases the reactivity of the heterocycle <1997J(P1)1157>.



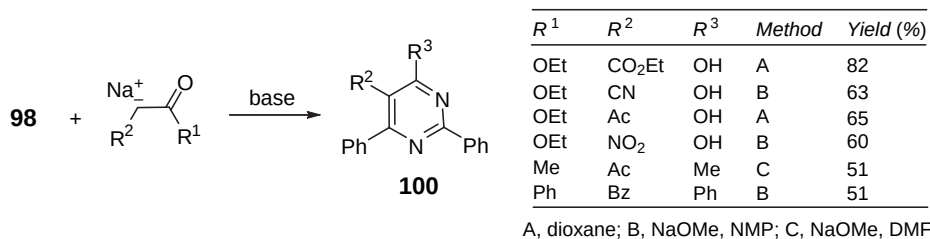
Scheme 3

The chemical behavior of 4,6-diaryl-1,2,3,5-oxathiadiazine 2,2-dioxides **98** is determined mostly by the presence of an SO_3 moiety in the ring as well as several electron-deficient centers (C-4, C-6, S) capable of competing for nucleophilic agents. Reaction of **98** with amidines, imidates, or related reagents results in the S–O segment being replaced by a C=N fragment to give *s*-triazines **99** (Scheme 4) <1997CHE1028, 2004SOS(17)449>.



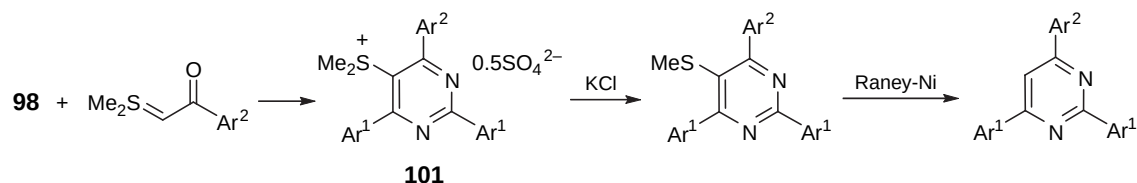
Scheme 4

Reaction of **98** (Ar = Ph) with sodium salts of active methylene compounds affords the 5-substituted pyrimidines **100** in good yield, presumably via attack by the ylide at C-6 (Scheme 5) <1997CHE1028, 2004SOS(16)379>.



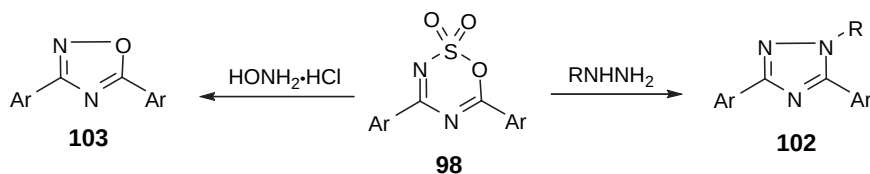
Scheme 5

Treatment of **98** with carbonyl-stabilized sulfur ylides furnishes pyrimidines **101**, which can be further manipulated (Scheme 6) <1997CHE1028, 2004SOS(16)379>.



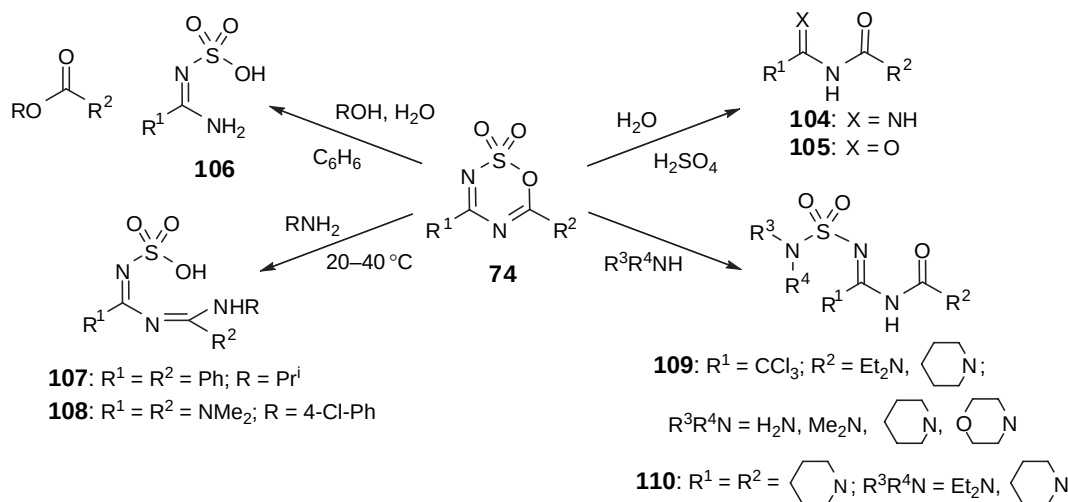
Scheme 6

Compounds **98** are converted relatively easily to five-membered heterocycles. 1,2,4-Triazoles **102** are obtained in high yield by reactions of **98** with hydrazine derivatives (aryl hydrazines, semicarbazide, thiosemicarbazide, benzhydrazide, and aminoguanidine) (Scheme 7). The corresponding reaction with hydroxylamine hydrochloride affords 1,2,4-oxadiazoles **103** also in high yield (Scheme 7) <1997CHE1028>.



Scheme 7

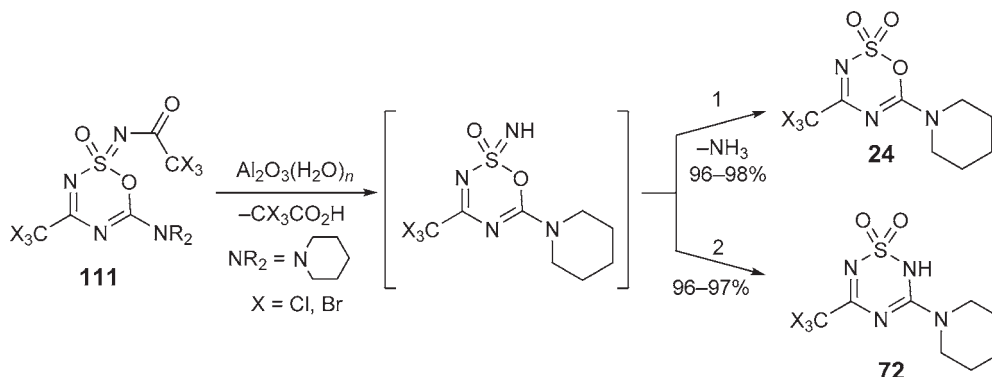
1,2,3,5-Oxathiadiazine 2,2-dioxides **74** react readily with aqueous acid to produce (depending on substituents and conditions) *N*-acylamidines **104** or imides **105** (Scheme 8). Reaction of **74** ($R^1 = R^2 = \text{aryl}$) with alcohols in benzene in the presence of a small amount of water affords *N*-sulfamidines **106** (Scheme 8). Treatment of **74** with amines results in rupture of the C–O bond and formation of products such as **107** and **108** (Scheme 8) <1997CHE1028>.



Scheme 8

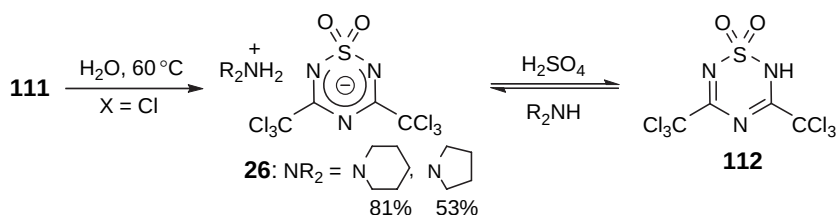
Oxathiadiazines **74** with amino substituents at C-6 can be converted easily to sulfonylamidines **109** or sulfonylguanidines **110** when treated with ammonia or amines (Scheme 8). The strong donor group R_2N significantly decreases the electrophilicity of C-6 and reaction of the nucleophilic reagent at sulfur becomes preferred, resulting in rupture of the S–O bond <1997CHE1028>.

At room temperature and below, hydrolysis of oxathiadiazines **111** with water bound to γ -alumina affords 1,2,3,5-oxathiadiazine 2,2-dioxides **24**, $\text{CX}_3\text{CO}_2\text{H}$, and ammonia (path 1), while at 30–50 °C, elimination of the CX_3CO group is accompanied by a rearrangement (path 2) to furnish the 1,2,4,6-thiatriazine 1,1-dioxides **72** (Scheme 9) <2000RJO1229>.



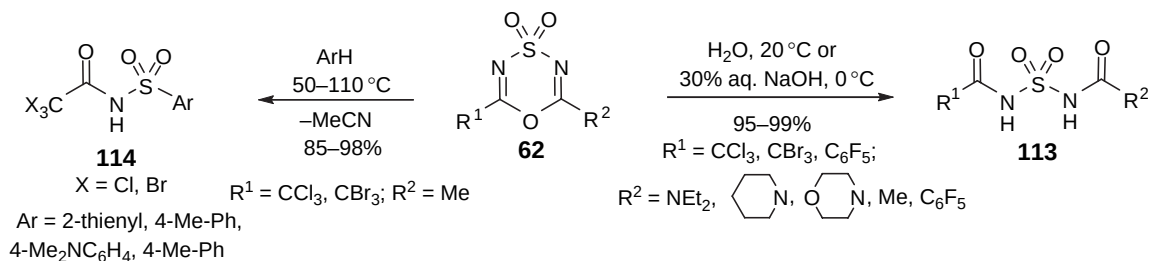
Scheme 9

Heating the 2,4,6-trisubstituted-1,2,3,5-oxathiadiazine 2-oxide **111** ($\text{X} = \text{Cl}$, $\text{NR}_2 = \text{piperidino}$ or pyrrolidino) at 60 °C in benzene, toluene, or chloroform with an equimolar amount of water resulted in conversion to the salts **26** (Scheme 10). This process apparently involves initial hydrolysis of the trichloroacetamide fragment followed by an unusual substitution of the piperidino or pyrrolidino moiety by the CCl_3 group with concomitant loss of CO_2 . Treatment of salts **26** with sulfuric acid affords the 1,2,4,6-thiatriazine 1,1-dioxide **112** which revert to salts **26** with piperidine or pyrrolidine <2002RJO1702>.



Scheme 10

The 2,6-disubstituted-1,4,3,5-oxathiadiazine 4,4-dioxides **62** readily undergo hydrolysis to give the acyclic compounds **113** in almost quantitative yield (Scheme 11) <2000RJO1523, 2002RJO889>.

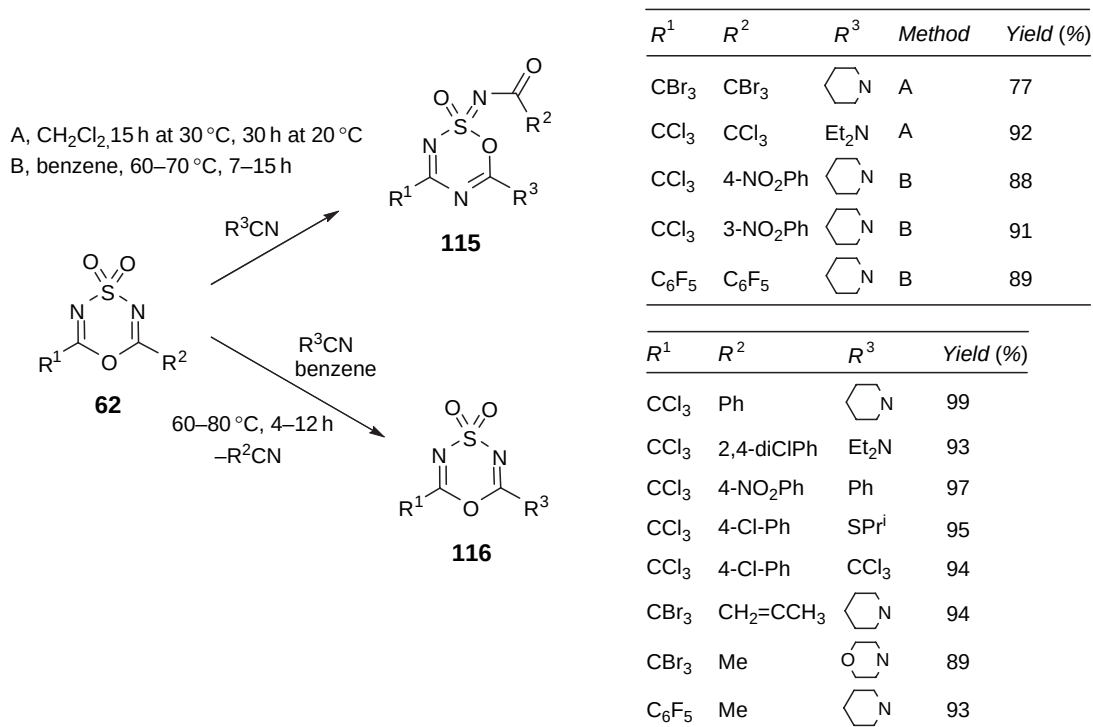


Scheme 11

Heating 6-methyl-1,4,3,5-oxathiadiazine 4,4-dioxides **62** ($R^1 = \text{CCl}_3, \text{CBr}_3$; $R^2 = \text{Me}$) with some aromatic or heteroaromatic compounds in either benzene, toluene, or anisole affords the corresponding *N*-trihaloacetylarenesulfonamides **114** (Scheme 11) <2004RJO282>.

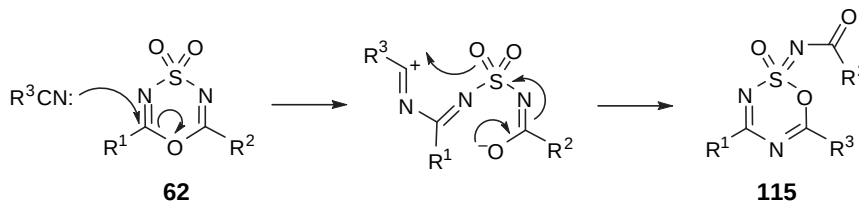
The 1,4,3,5-oxathiadiazine 4,4-dioxides **62** bearing strongly electron-withdrawing substituents at both the 2- and 6-positions react with substituted cyanamides to yield 2,4,6-trisubstituted-1,2,3,5-oxathiadiazine 2-oxides **115**, generally in high yield (Scheme 12) <2000RJO1523, 2002RJO889>.

However, with 1,4,3,5-oxathiadiazine 4,4-dioxides **62** bearing less strongly electron-withdrawing, or -donating, substituents at R^2 , in reactions with a wider range of cyano-containing compounds including benzonitriles and thiocyanates, a ‘transimination’ reaction occurs resulting in replacement of the imine fragment $R^2\text{C}=\text{N}$ in **62** by the corresponding fragment $R^3\text{C}=\text{N}$ from the reagent affording products **116** (Scheme 12) <2000RJO1523, 2002RJO889>.



Scheme 12

Compounds **62** having two strong electron-acceptor substituents react with cyanamides ($R^3 = \text{R}_2\text{N}$) through the carbon bearing the stronger acceptor R^1 . A probable reaction pathway is shown in Scheme 13 <2002RJO889>.



Scheme 13

Compounds **62** having weaker electron-accepting or -donating substituents can react with cyano compounds through the sulfur atom. In this case, the reaction can follow a type of [4+2] cycloaddition via transition state **A**, or through formation of reactive species **B** (Scheme 14) <2002RJO889>.

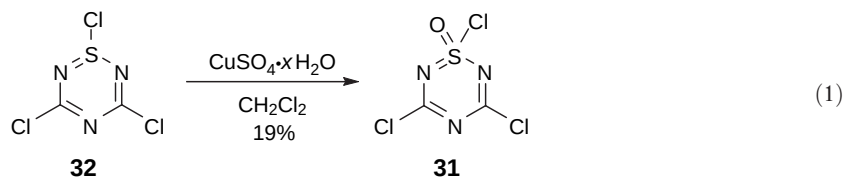


CX3C1=NC(=O)S(=O)(=O)N1C=CX3
 $\xrightarrow[20\text{ }^{\circ}\text{C}]{\text{RCN, C}_6\text{H}_5\text{Z}}$
CX3C1=NC(=O)S(=O)(=O)N1C=C(R)C(=O)C
 $\xrightarrow[53-92\%]{\text{2RCN, C}_6\text{H}_5\text{Z, 60 }^{\circ}\text{C}}$
CX3C1=NC(=O)S(=O)(=O)N1C=C(R)C(=O)C
+
C1=NC(=C(R)N(R)N1C=C(R)C(=O)C
+
C6H5Z

62: X = Cl, Br
115
27
 R = NEt₂, N, N
 Z = H, CH₃, Cl, CN

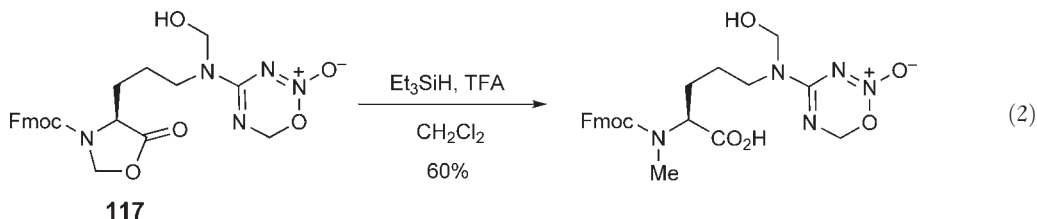
Scheme 15

The trichlorothiatriazine **32** was oxidized to **31** in $\leq 20\%$ yield by treatment with $\text{CuSO}_4 \cdot x\text{H}_2\text{O}$ ($x = 4-6$) in CH_2Cl_2 (Equation 1). Interestingly, no oxidation occurred when the anhydrous cupric salt was used, nor with the alternative oxidants *m*-chloroperbenzoic acid (MCPBA) or KMnO_4 [<1999IC70>](#).

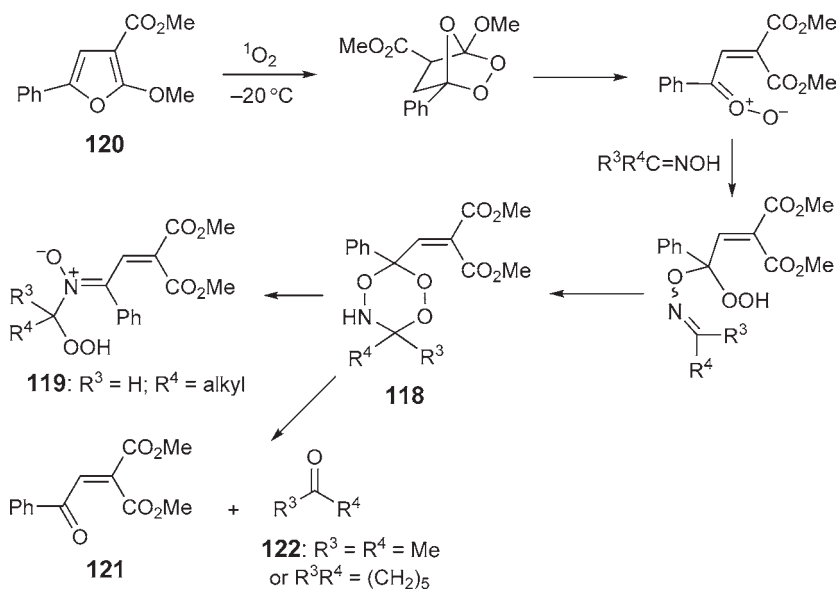


9.14.6 Reactivity of Nonconjugated Rings

The 1,2,3,5-oxatriazine 2-oxide moiety of **117** survived treatment with triethylsilane and trifluoroacetic acid (TFA) while the oxazolidinone moiety was reductively cleaved (Equation 2) <2003JOC2652>.

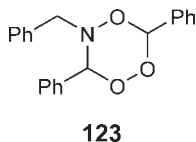


The 1,2,4,5-trioxazines **118** were observed and characterized as intermediates in the preparation of *N*-hydroperoxyalkyl nitrones **119** from alkoxyfuran **120** and aldoximes (Scheme 16). When ketoximes were used in similar reactions, the alternative products, ketodiester **121** and ketones **122**, were formed <1998JOC9528>.



Scheme 16

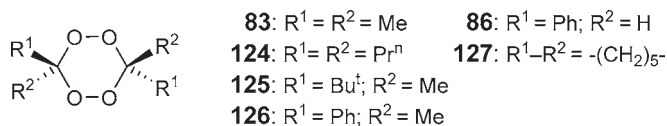
An investigation of the thermal decomposition of 1,2,4,5-trioxazine **123** in various solvents confirmed the main products as benzaldehyde and benzaldehyde oxime and showed the rate-determining step to be rupture of the O–O bond <1996IJK21>.



Kinetic studies of the thermal decomposition reactions (130–185 °C) of tetramethyl tetroxane **83** in methyl *tert*-butyl ether <2004IJK302>, tetrasubstituted tetroxanes **124–126** in toluene <2004H(63)2231>, **126** in dioxane, acetonitrile, and isopropanol/benzene <2000MOL365>, and **83** and **86** in THF <2002AFF676> concluded that the reactions followed first-order kinetics up to 50–60% conversion and followed a mechanism involving initial rupture of one O–O bond leading to an intermediate biradical which underwent C–O bond ruptures to give the ketone as the principal organic product. The reactivity of **126** is higher in polar solvents than in nonpolar solvents and the higher relative reactivity of **125** was attributed to steric hindrance.

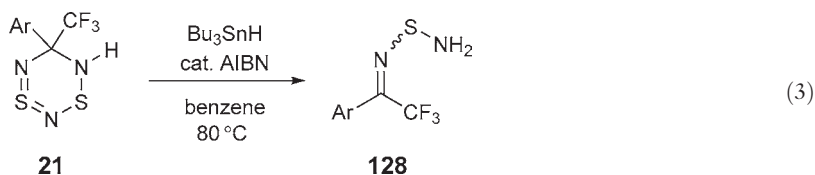
A theoretical investigation of the thermolysis of tetroxane **83** by the AM1 MO method using the unrestricted Hartree-Fock (UHF) approach was consistent with the above experimental data in that the mechanistic route involving initial O–O bond cleavage had a lower activation energy (130 kJ mol^{-1}) for the rate-determining step <1996JMT(363)339>.

Treatment of **127** in hexafluoroisopropanol (HFIP) with catalytic amounts of strong acids resulted in rapid (within a few seconds) and quantitative rearrangement to ϵ -caprolactone. Upon addition of water to the HFIP, the rearrangement becomes increasingly sluggish and ϵ -hydroxycaproic acid becomes increasingly prominent as a side product. This reaction using catalytic *p*-TsOH in anhydrous HFIP finds use as part of a smooth and efficient Baeyer–Villiger oxidation of cyclohexanone to ϵ -caprolactone with the tetroxane **127** as an intermediate <2002AGE4481>.

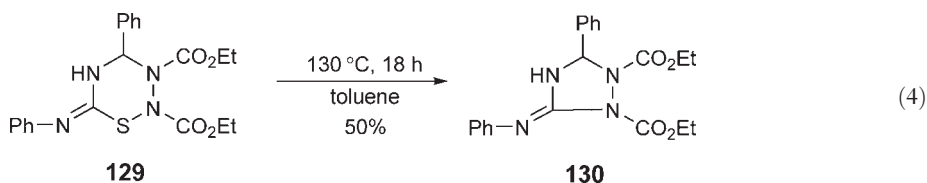


The 1,3,2,4,6-dithiatriazine **21** ($\text{Ar} = \text{Ph}$) is inert to concentrated hydrochloric acid and TFA in dichloromethane at room temperature and does not react with 4-biphenylcarbonyl chloride in the presence of triethylamine <1996JHC295>.

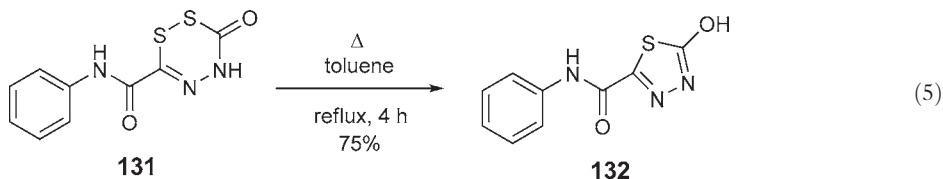
However, dithiatriazines **21** are readily converted to the corresponding aminosulfenamides **128** in excellent yields by treatment with tributyltin hydride (6 molar equiv) in the presence of catalytic amounts of azobisisobutyronitrile (AIBN) in benzene at 80°C (Equation 3) <1996JHC295>.



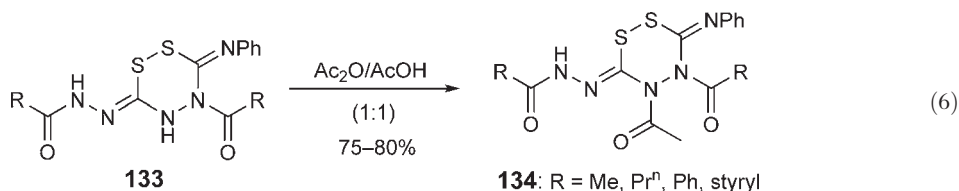
When a degassed toluene solution of the 1,2,3,5-thiatriazine **129** was heated at 130°C for 18 h in a sealed tube, sulfur extrusion and carbon–nitrogen bond formation occurred giving triazoline **130** in moderate yield (Equation 4) <1995S985>.



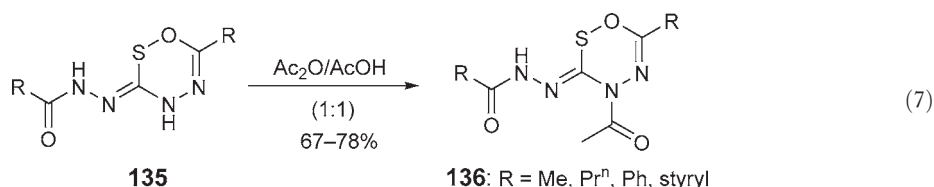
Heating a toluene solution of 1,2,4,5-dithiadiazin-3-one **131** resulted in extrusion of a sulfur atom and formation of the hydroxythiadiazole **132** (Equation 5) <2003PS1283>.



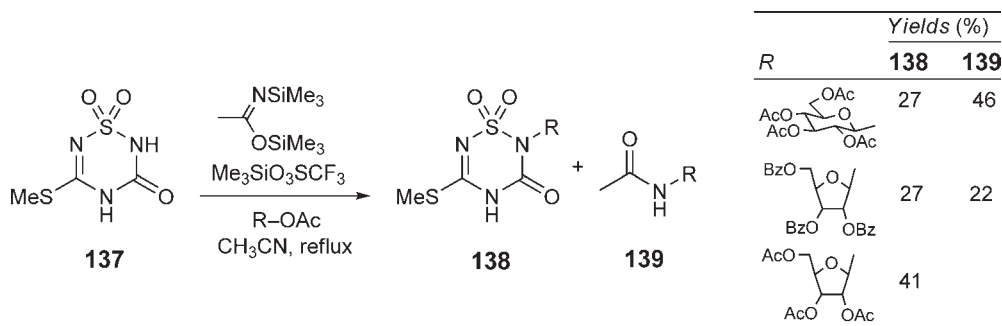
The 1,2,4,5-dithiadiazines **133** can be acetylated with acetic anhydride in acetic acid, giving compounds **134** in good yield (Equation 6) <2005ASJ2800>.



The 1,2,4,5-oxathiadiazines **135** can be similarly acylated providing derivatives **136** (Equation 7) <2004IJH151>.

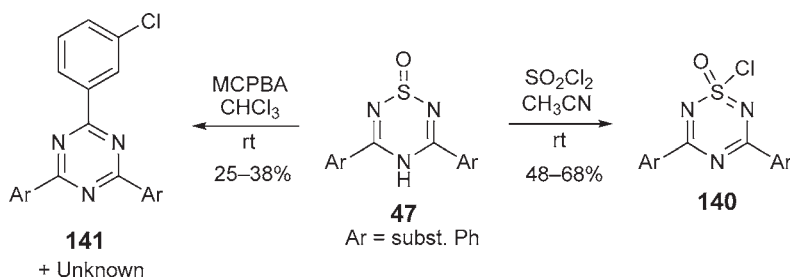


Glycosylation of 1,2,4,6-thiatriazin-3-one 1,1-dioxide **137** with penta-*O*-acetyl- β -D-glucopyranose, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose, and tetra-*O*-acetyl- β -D-ribofuranose was carried out in refluxing acetonitrile, using *N,O*-bis(trimethylsilyl)acetamide as silylating agent and trimethylsilyltriflate as catalyst. The reactions were regioselective, with glycosylation only occurring at N-2 to give **138**, as established by extensive NMR analysis (Scheme 17). Glycosylated acetamides **139** were also formed in the reaction, except in the case of the tetraacetyl ribofuranose, which probably reacted more rapidly with **137** than the other sugar derivatives <1998NN901>.



Scheme 17

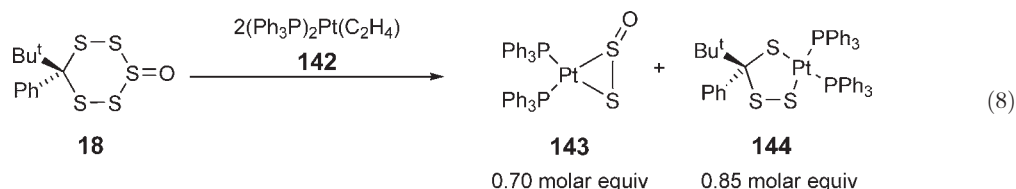
The 3,5-diaryl-1,2,4,6-thiatriazine 1-oxides **47** were converted to the 1-chloro derivatives **140** with sulfuryl chloride (Scheme 18). Treatment of **47** with MCPBA gave the unexpected 1,3,5-triazine product **141** and an unknown by-product (m.p. > 300 °C) (Scheme 18). No 1,2,4,6-thiatriazine 1,1-dioxides were isolated. A mechanism for formation of **141** was proposed <2000T7153>.



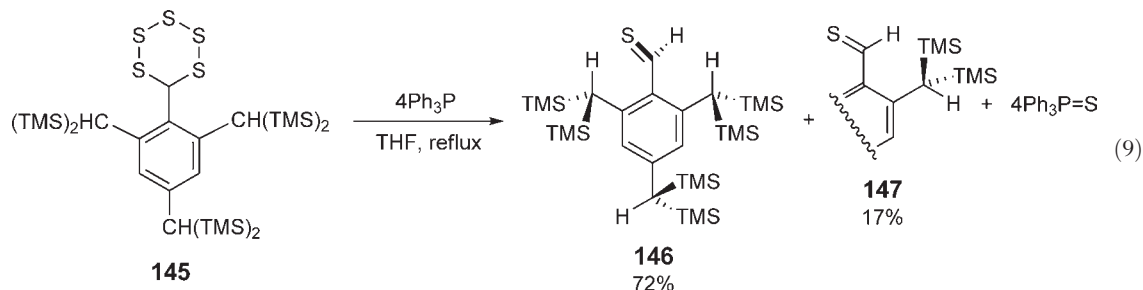
Scheme 18

Oxidation of the *tert*-butyl-substituted pentathiane **16** with trifluoroperacetic acid in dichloromethane at -20 °C gave the 3-oxide **18** as the sole isolated product in 25% yield, whereas oxidation of the corresponding 1-adamantyl derivative using dimethyldioxirane afforded a 57% yield of 1-oxide **93** (see Section 9.14.4.5) <2002BCJ319>.

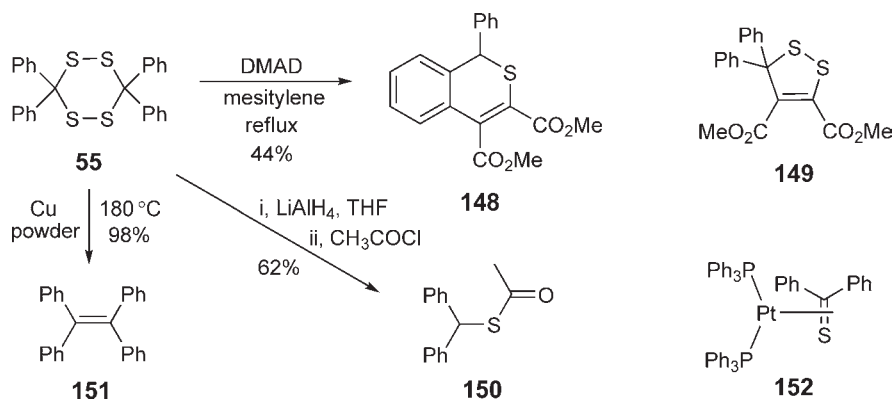
Reaction of **18** with 2 molar equiv of the Pt(0) complex **142** furnished the S₂O complex **143** and the dithiolato–thiolato complex **144** in 0.70 and 0.85 molar equiv, respectively (Equation 8) <2003EJI3716>.



Treatment of the 2,4,6-trisubstituted pentathiane **145** with 4 molar equiv of triphenylphosphine in refluxing THF afforded, after flash column chromatography at low temperature, the first rotational isomers of thiobenzaldehydes, **146** and **147** (Equation 9). The structures of both these compounds were confirmed by X-ray crystallography and their interconversion was studied kinetically <1997CEJ62>.



Treatment of 1,2,4,5-tetrathiane **55** with DMAD in refluxing mesitylene produced the benzothiopyran **148**, that is, the Diels–Alder adduct of thiobenzophenone and DMAD (Scheme 19). When the reaction was carried out in chloroform in a sealed tube at 150 °C, a 36% yield of **148** was obtained, along with 26% of dithiole **149**, perhaps via a competing acid-catalyzed pathway <1997H(45)507>.

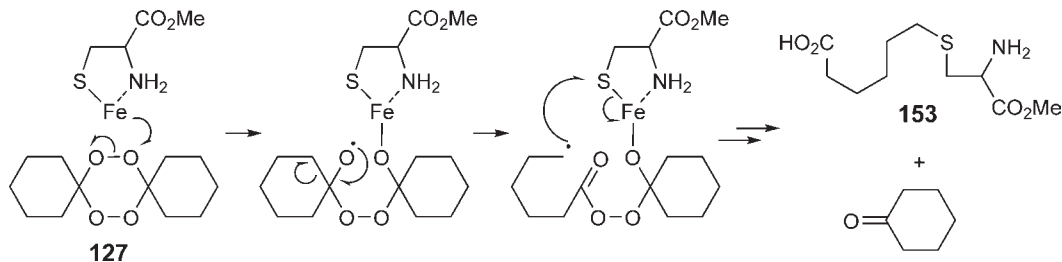


Scheme 19

The reduction of **55** with LiAlH_4 and subsequent acetylation afforded the diphenylmethyl thioacetate **150**, while heating with copper powder in diglycol diethyl ether caused desulfurization to tetraphenylethylene **151** (Scheme 19) <1997H(45)507>. Treatment of **55** with a fourfold excess of $(\text{Ph}_3\text{P})_2\text{Pt}(\eta^2\text{-C}_2\text{H}_4)$ in either THF or toluene solution yielded $[\text{Pt}_2(\text{Ph}_3\text{P})_4(\mu\text{-S}_2)]$ and the platinum(0) compound **152** (Scheme 19) <2000ZNB453>.

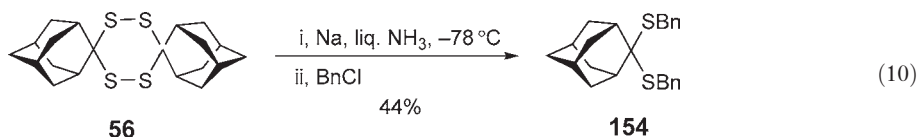
The tolerance of cyclohexano dispiro-1,2,4,5-tetroxane **127** to hydride reduction has been investigated. The substrate was recovered (85%) after treatment with LiAlH_4 in THF for 2 h at 28 °C and in 64% yield after treatment at 50 °C. Treatment with LiBH_4 in refluxing ether for 10 h resulted in 85% recovery and LiBHEt_3 and $\text{LiAlH}(\text{OBu}^t)_3$ were also well tolerated. However, diisobutylaluminum hydride (DIBAL-H) cleaved **127** much more readily and only 42% of the substrate was recovered after 3 h treatment at 26 °C in CH_2Cl_2 <2005JOC4240>.

Treatment of **127** with cysteine–iron in the presence of excess of methyl cysteine led to formation of a sulfur-alkylated methyl cysteine derivative **153** in 33% yield (Scheme 20), suggesting a possible mechanism for antimalarial action by tetroxanes <2003CHJ875>.

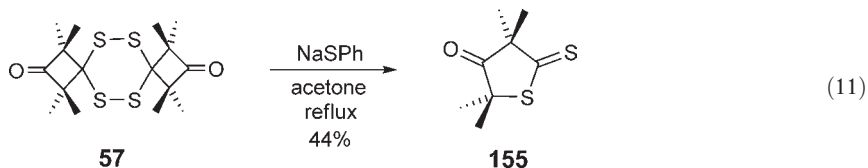


Scheme 20

The disulfide bonds of **56** were cleaved by treatment with sodium in liquid ammonia; subsequent benzylation afforded **154** (Equation 10) <1997H(45)507>.



Treatment of **57** with 1.2 equiv of sodium thiophenolate in refluxing acetone afforded a 44% yield of the dithiolactone **155** (Equation 11) <1997LA1517>.



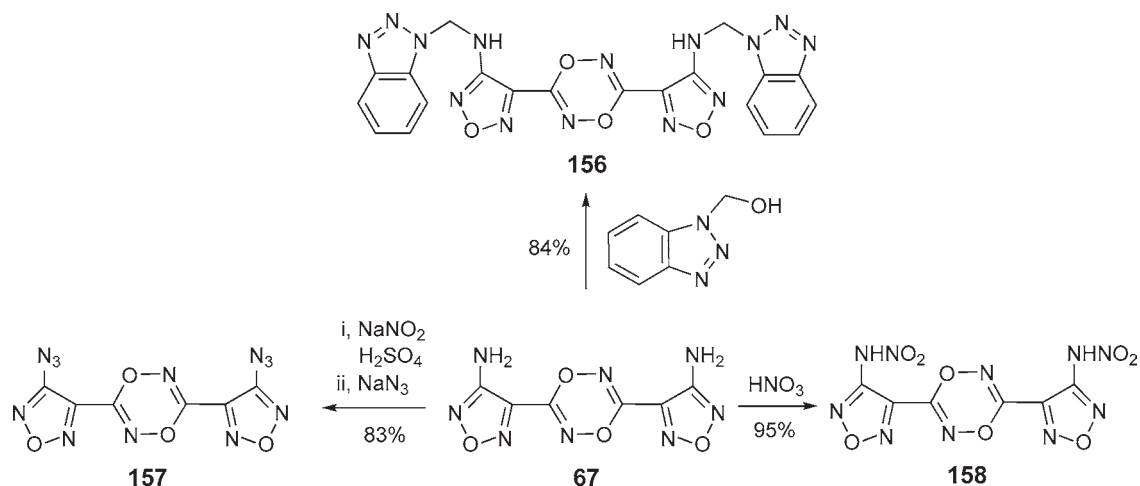
9.14.7 Reactivity of Ring Substituents

The basicity of the amino groups in **67** is reduced due to the effect of the oxadiazole ring. Diamine **67** was not acylated with acetic anhydride even on heating, but it did react with 1-hydroxymethylbenzotriazole to give compound **156**. Treatment of compound **67** with nitrosylsulfuric acid afforded the corresponding diazonium salt, which was converted into diazide **157**. Reaction of **67** with concentrated nitric acid provided the *N,N'*-dinitroamine **158**, which is stable in acidic and weakly basic media (Scheme 21). Disodium and bis-amine salts of **158** were obtained, with NaHCO₃ and various nitrogenous bases, respectively; however, aqueous Na₂CO₃ led to decomposition of the initial nitroamine. A cautionary note that such derivatives are explosive was also offered <2004RJO884>.

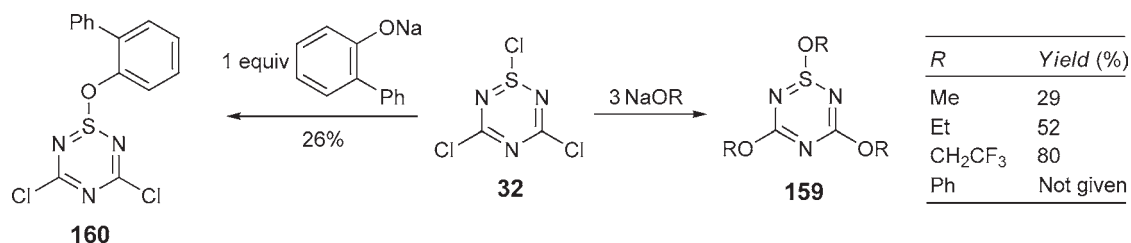
The 1,3,5-trialkoxy-substituted 1 λ^4 -1,2,4,6-thiatriazine derivatives **159** were obtained as air-stable, colorless liquids by reaction of 1,3,5-trichloride **32** (easily prepared in one step from sodium dicyanamide and thionyl chloride) with 3 equiv of a sodium alkoxide at 0 °C (Scheme 22). A similar reaction with 1 equiv of sodium 2-phenylphenoxide resulted in exclusive substitution at sulfur to give **160** (Scheme 22). The reaction with sodium phenoxide showed preferential, but not exclusive, substitution at sulfur <1999IC70>.

Trialkoxy derivatives of the S(vi) ring could not be obtained by oxidation of **159**; however, treatment of **31** with 3 equiv of NaOCH₂CF₃ produced **161** in excellent yield. Thermolysis of **161** resulted in an O $\rightarrow$ N migration of a CH₂CF₃ group to give **162** (Scheme 23) <1999IC70>.

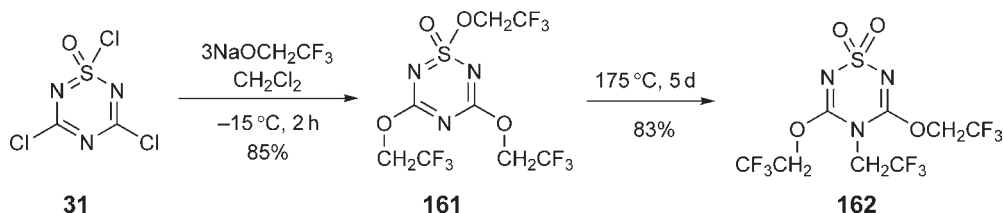
Reactions of trichlorothiazine **32** with aliphatic tertiary amines and diamines proceeded readily and resulted in dealkylation of the tertiary amine giving preferentially the *C*-dialkylamino-substituted derivatives. For example, treatment of **32** with 2 equiv of tetramethylmethylenediamine proceeds in diethyl ether at room temperature to give



Scheme 21



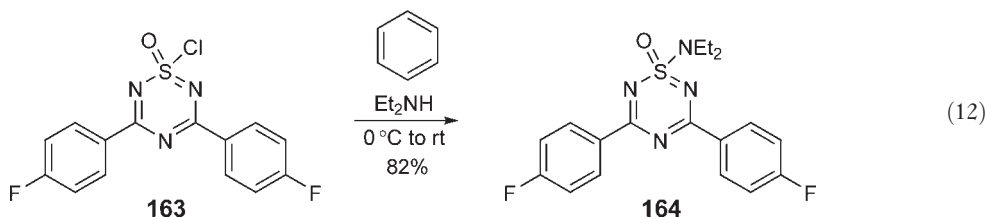
Scheme 22



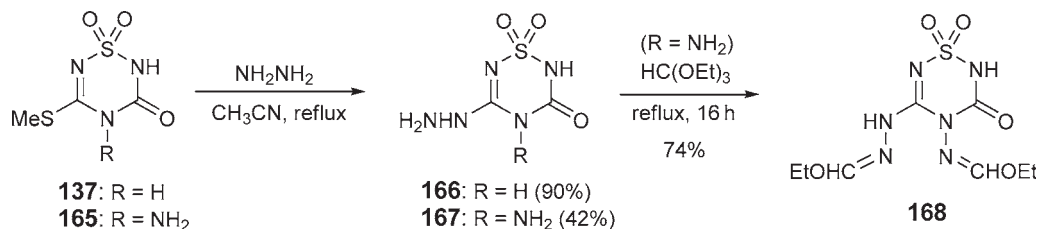
Scheme 23

the bright yellow, air-sensitive compound **36** in 70% yield. Triethylamine in similar reactions exposed to air/moisture led to good yields of the partially hydrolyzed product **37**. The dealkylation process occurring during their formation is favored since a C–N single bond of the tertiary amine is cleaved and another C–N bond having partial double-bond character is formed. This also considerably reduces the available electron density on the amino nitrogen, so further dealkylation of the amino substituent is not favored <1999IC70>.

Reaction of **36** with 2 equiv of morpholine in toluene gave the *S*-morpholino derivative while treatment of **32** with excess of morpholine afforded **38** <1999IC3022>. Reaction of the $1\lambda^6$ -1-chloro-1-oxo-1,2,4,6-thiatriazine **163** with diethylamine gave **164** (Equation 12) <2000T7153>.



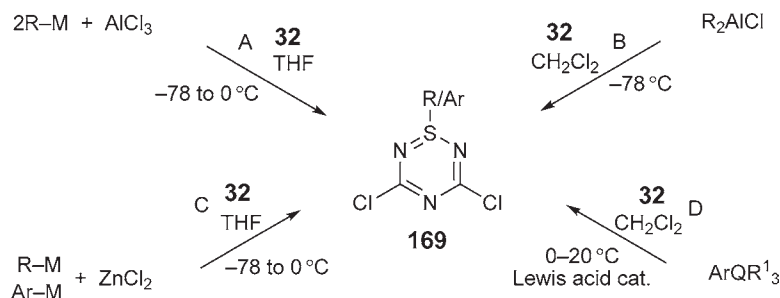
The methylthio group of compounds **137** and **165** underwent nucleophilic displacement by hydrazine to give 5-hydrazino derivatives **166** and **167**, respectively (Scheme 24) <1996H(43)2199>.



Scheme 24

Attempted substitution with propylamine yielded only the corresponding propylammonium salts of the heterocycles. Both primary amino groups of **167** reacted with an excess of ethyl orthoformate to give disubstituted derivative **168** and no traces of any cyclic products were observed (Scheme 24). Attempted condensation of the amino group of **165** with aryl aldehydes was unsuccessful <1996H(43)2199>.

A variety of trisubstituted 1,2,4,6-thiatriazines with a tetravalent sulfur atom bearing a carbon-based substituent can be synthesized from the trichlorothiatriazine **32**. Since the sulfur-bound chlorine atom is the most reactive, it can be displaced first to produce **169** (Scheme 25). The chlorine atoms at C-3 and C-5 of **169** can be displaced sequentially to produce trisubstituted compounds having three different substituents. This approach is the subject of two reviews by Stoller, the earlier of which gives also a historical overview of prior strategies employed in synthesizing such heterocycles <2000JHC583, 2003C725>.



Scheme 25

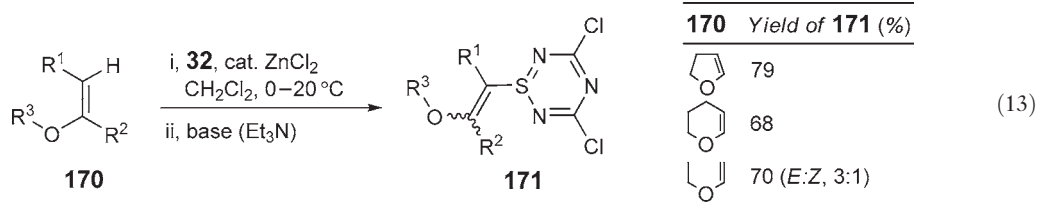
Treatment of **32** with alkyllithium or alkylmagnesium reagents (even with Ce, Cr, Cu, or Mn additives) at low temperature yielded none or little of the desired products **169**. Modification of the reagents by addition of zinc chloride or aluminium chloride, or use of preformed chlorodialkylaluminium, led to much higher yields (up to 95%) (Table 1). Alkenyl, aryl, or heteroaryl groups can be introduced in a similar way (Scheme 25). The yield is better with zinc reagents (<50% with the aluminium reagents), which is important in the case of valuable R groups. The stability of products **169** was good to acceptable in most cases <2000JHC583, 2003C725>.

An alternative method for replacing the sulfur chlorine by an aromatic moiety is an *ipso*-thia-desilylation or *ipso*-thia-destannylation achieved under very mild conditions with the trialkylsilyl or trialkylstannyl derivative with Lewis acid catalysis (e.g., AlCl_3) (method D, Scheme 25). It is noteworthy that the position bearing the tin group is much more activated than the one with silicon <2000JHC583>.

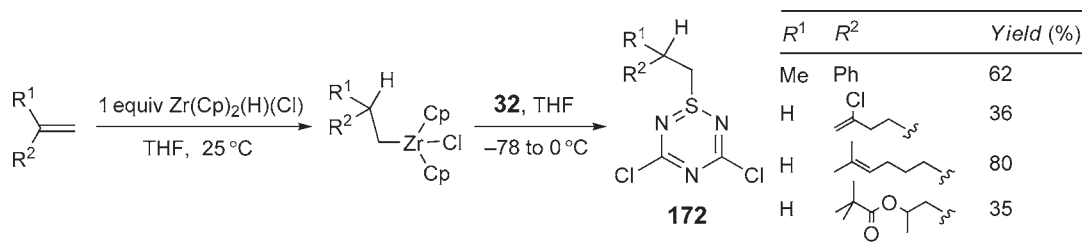
Some electron-rich olefins, such as enol ethers **170**, react directly with **32** under mild conditions with Lewis acid catalysis. The first product of the reaction results from addition of the S-Cl bond to the olefin, the sulfur atom being attached to the carbon β to the oxygen and the chlorine in the α -position. If the β -carbon carries a hydrogen atom, elimination of HCl can be effected with mild bases such as triethylamine to regenerate a double bond. The reaction works with both cyclic and acyclic enol ethers, the latter case giving (*E*):(*Z*)-mixtures of products **171** (Equation 13) <2000JHC583>.

Table 1 Yields of trisubstituted 1,2,4,6-thiatriazines **169** (Scheme 25)

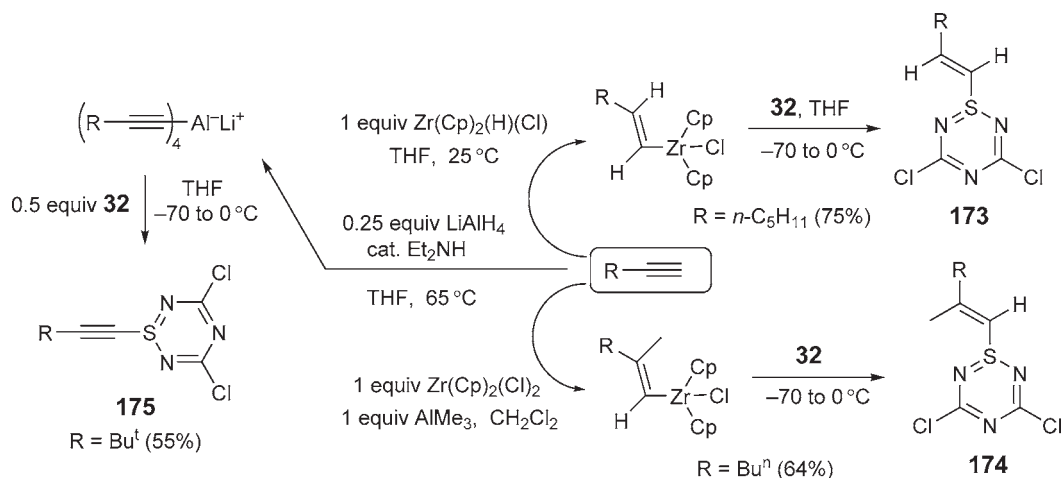
<i>R/Ar</i>	<i>M/QR</i> ¹ ₃	<i>Method</i>	<i>Yield (%)</i>
CH ₃ (CH ₂) ₄	Al	A	90
Ph(CH ₂) ₂	Al	A	80
Cyclohexyl	Al	A	73
Cyclohexen-1-yl	Al	A	60
Me, Et	Al	B	90–95
Vinyl	MgCl	C	73
PrO(CH ₂) ₃	MgCl	C	36
SiMe ₃ CH ₂	MgCl	C	87
Bu ^t	Li	C	50
Pr Et	MgCl	C	37
	MgBr	C	28
3,5-Di-Me-Ph	MgBr	C	74
4-Vinyl-Ph	MgCl	C	95
5-Bu ⁿ -thien-2-yl	Li	C	91
Benzo[<i>b</i>]furan-2-yl	MgCl	C	68
Ph	SiMe ₃	D	86
2,4-Di-Cl-Ph	SiMe ₃	D	58
5-SiMe ₃ -thien-2-yl	SnBu ⁿ ₃	D	91



For incorporation of 1-substituents containing sensitive functional groups (e.g., esters or halides) which are not compatible with organolithium or organomagnesium reagents, the milder organozirconocene derivatives may be employed to give **172** (Scheme 26) <2000JHC583>.

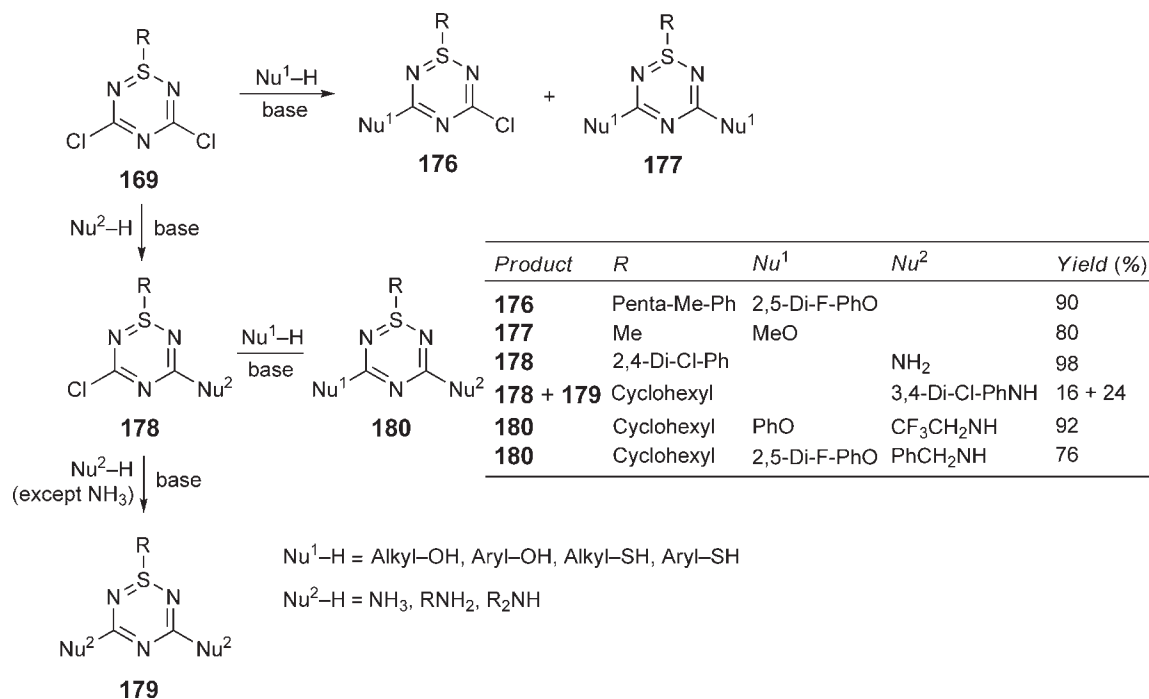
**Scheme 26**

This type of reaction can be used also to introduce alkenyl groups onto the sulfur atom. In one variation, a terminal alkyne is treated with Schwartz' reagent to generate an (*E*)-alkenylzirconocene which reacts stereospecifically with **32** to give **173** (Scheme 27). In another variation, the terminal alkyne is treated with zirconocene dichloride and trimethylaluminum to form a β -methylated- α -alkenyl zirconocene derivative. The sequence is stereo- and regio-specific, producing **174** (Scheme 27). Use of lithium tetraalkynylalanes (from terminal alkynes and LiAlH₄) allows incorporation of an sp carbon at the sulfur to afford compounds **175** (Scheme 27). Two alkynyl groups are transferred in moderate to good yield <2000JHC583>.



Scheme 27

The 1-substituted 3,5-dichlorothiazines **169** react further with alkyl alcohols, phenols, and mercaptans, usually nonselectively, leading to mono- and disubstituted products **176** and **177** (Scheme 28). The reaction with amines is more selective, since the introduction of the first amino substituent deactivates the last substitution, giving **178** as the major or sole product. If the amine is nucleophilic enough, the last substitution can proceed, affording **179**. In the case of ammonia, disubstitution does not occur and derivatives **178** are formed almost quantitatively (Scheme 28) <2000JHC583>.

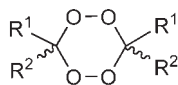


Scheme 28

Subsequent reaction of **178** with alcohols, phenols, or mercapto compounds, in the presence of base and trimethylamine, gives the trisubstituted product **180**. The chlorine atom of **178** is deactivated by the amino group and the trimethylamine is used to activate this position by the introduction of a trimethylammonium moiety which can be displaced by the O- or S-nucleophile <2000JHC583>.

Reactions of **169** such as those described above can be carried out typically in THF at room temperature in the presence of a base. Typical bases used are the amines themselves in excess, Et₃N (for anilines and mercaptans), sodium hydroxide (for phenols), and sodium alkoxides (for alcohols) (Scheme 28) <1997WO9725318, 2000JHC583>.

Reaction of the 1,2,4,5-tetroxane **181** with AgBF₄ in acetic acid afforded the substitution product **182** in 41% yield. In contrast to **181**, which gave violent explosions, **182** could be heated to its melting point of 119°C without decomposition <1995JOC8062>.



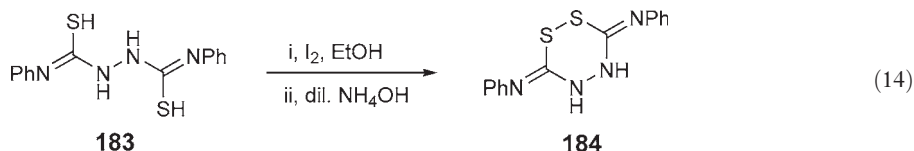
181: R¹ = Me; R² = Cl

182: R¹ = Me; R² = MeCO₂

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

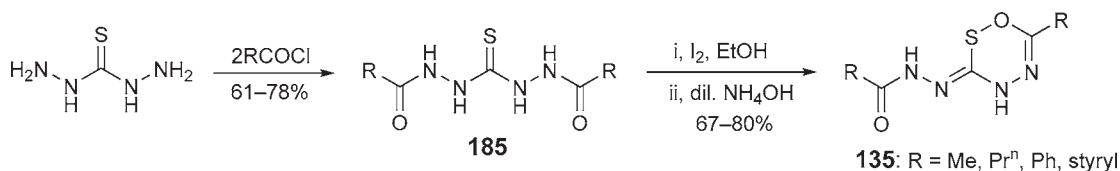
9.14.8.1 Formation of One Bond

The symmetrical 1,2,4,5-dithiadiazine **184** was prepared from 1,6-diphenyl-2,5-dithiobiurea **183** by oxidative cyclization with iodine (Equation 14) <2002IJH153>.



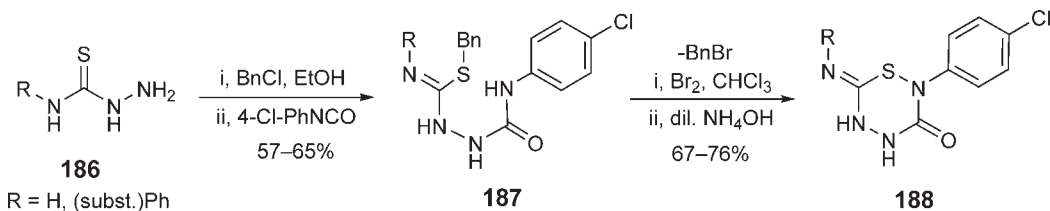
A more general route to nonsymmetrical derivatives of this type is outlined in Section 9.14.8.2.2.

Iodine-mediated oxidative cyclization methodology can also be applied to the synthesis of 1,2,4,5-oxathiadiazines **135** from the 1,5-bis-acylated thiocarbonylhydrazides **185** (Scheme 29) <2004IJH151>.



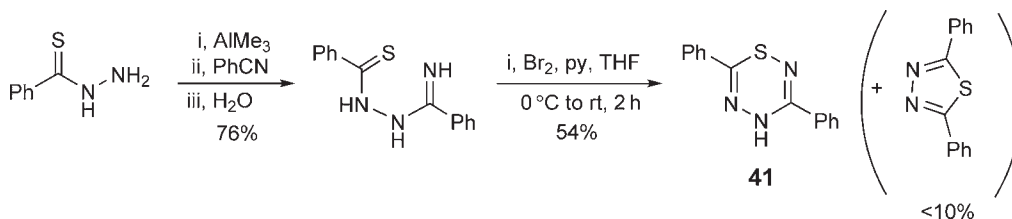
Scheme 29

Another application of this type of methodology is in the synthesis of 1,2,4,5-thiadiazines **188**. *S*-Benzylation of thiosemicarbazides **186** followed by reaction with 4-chlorophenylisocyanate afforded **187**. Oxidative debenzoylation of **187** with bromine in chloroform gave **188** (Scheme 30) <2004IJH135>.



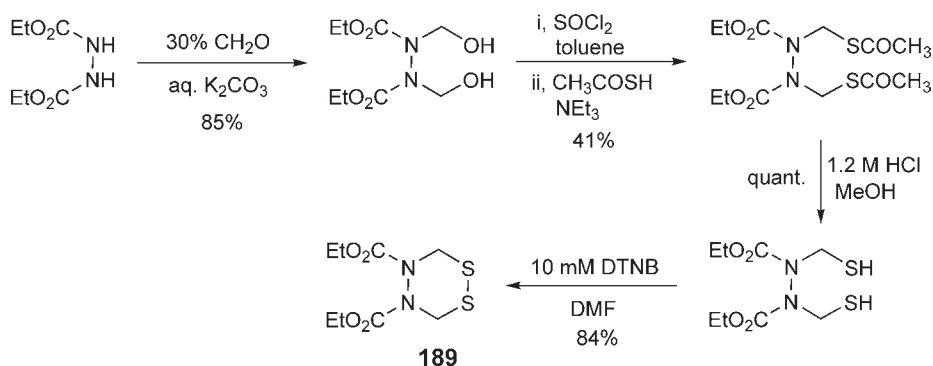
Scheme 30

3,6-Diphenyl-1,2,4,5-thiadiazine **41** was prepared similarly (Scheme 31) <2000JOC931>.



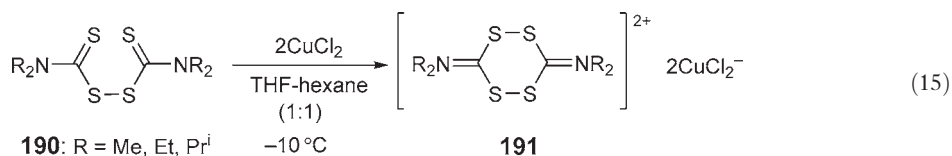
Scheme 31

4,5-Dicarbethoxy-1,2,4,5-dithiadiazine **189** was synthesized in four steps from 1,2-dicarbethoxyhydrazine as outlined in Scheme 32. The oxidative ring closure was effected with Ellman's reagent, 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB) <1993JOC633>.



Scheme 32

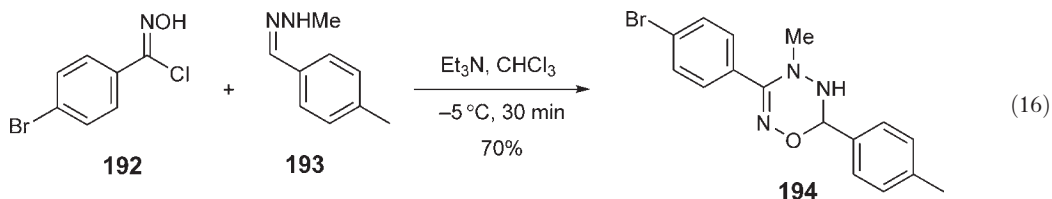
Treatment of thiuram disulfides **190** with CuCl_2 leads to a two-electron oxidation of the ligand, reduction of the Cu(II) to Cu(I) , and formation of a chlorocuprate(I) salt. The resulting Cu(I) complexes **191** are diamagnetic red solids (Equation 15) <1995JCR19>.



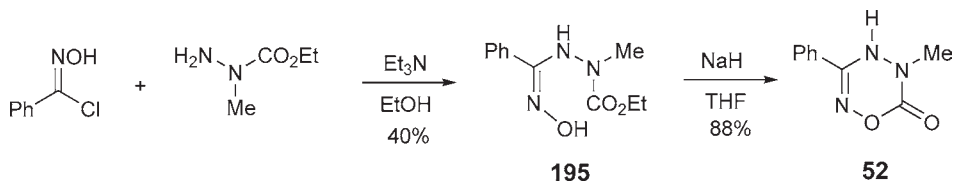
9.14.8.2 Formation of Two Bonds

9.14.8.2.1 From [3+3] atom fragments

1,2,4,5-Oxatriazines can be prepared by reaction of benzonitrile oxides, usually generated *in situ* from the corresponding benzohydroxamoyl chloride and triethylamine, with substituted hydrazines or hydrazones. For example, the nitrile oxide derived from **192** reacts with hydrazone **193** to yield oxatriazine **194** in good yield (Equation 16) <2005SOS(22)489>.

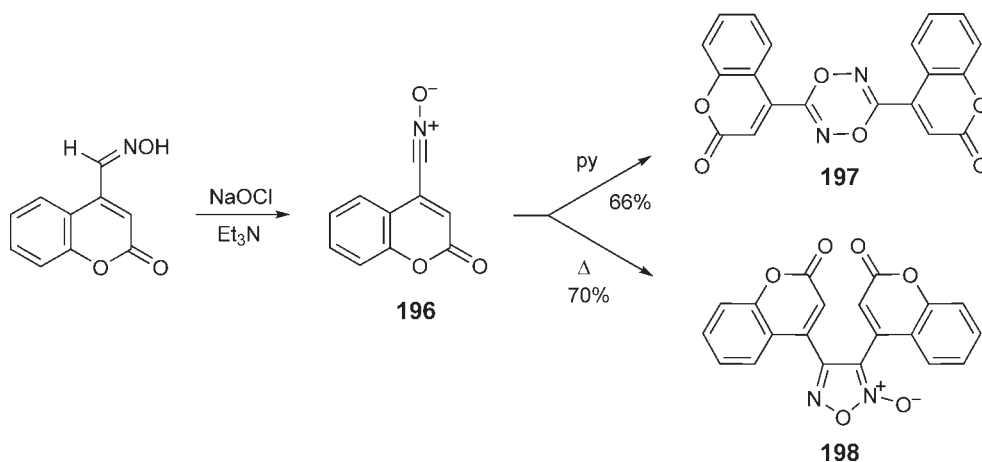


Treatment of benzonitrile oxide with 1-ethoxycarbonyl-1-methylhydrazine affords the hydroxamoylhydrazinecarboxylate **195** which can be cyclized with sodium hydride to the oxatriazinone **52** (Scheme 33) <1998ASJ180>.



Scheme 33

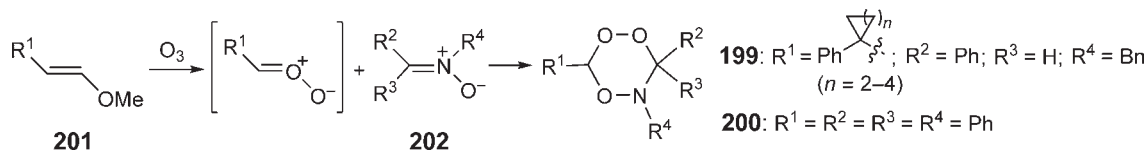
Dimerization of nitrile oxides is one of the most important methods of synthesis of 1,2,5-oxadiazole *N*-oxides (furoxans). However, this process can also lead to formation of symmetrical 1,4,2,5-dioxadiazines. The dipyrindyl dioxadiazine **20** was obtained in 59% yield by treatment of 2-pyridyl hydroximinoyl chloride hydrochloride with triethylamine and pyridine in ethanol <2003EJI405>. The coumarin nitrile oxide **196** was dimerized with pyridine in ethanol to give the dioxadiazine **197** in 66% yield (Scheme 34). When a chloroform solution of the nitrile oxide **196** was heated at reflux in the absence of base, the furoxan **198** was produced in 70% yield (Scheme 34). Attempted purification of **196** by recrystallization caused dimerization into furoxan **198** <1998JHC619>.



Scheme 34

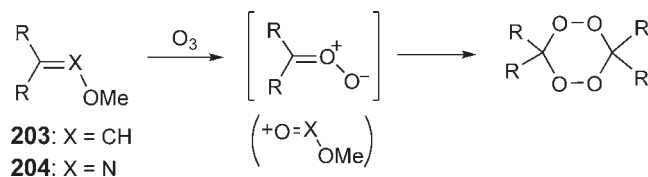
Recent literature is not entirely consistent on this area of chemistry and, in contrast to the above reports, the dioxadiazine **42** was prepared from the corresponding hydroximinoyl chloride at 35 °C in the absence of base, whereas, at 40 °C, in the presence of triethylamine, dimerization afforded the furoxan **43** (see Section 9.14.3.2) <2000ARK683>.

1,2,4,5-Trioxazines **199** and **200** have been prepared by a [3+3] cycloaddition of carbonyl oxides, generated *in situ* from vinyl ethers **201**, ozone, and nitrones **202** (Scheme 35) <1994J(P1)2449, 1995J(P1)41>.



Scheme 35

Similar methodologies have been used to synthesize 1,2,4,5-tetroxanes. Ozonolysis of vinyl ethers **203** efficiently produces the intermediate carbonyl oxide, which dimerizes to the tetroxane (**Scheme 36**) <2002RMC113>.

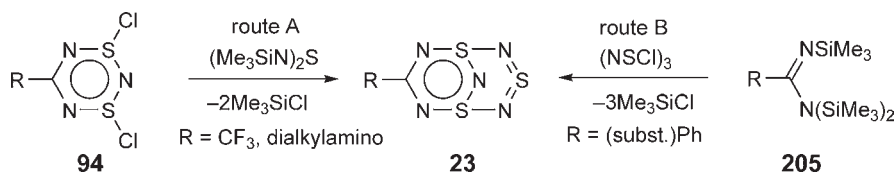


Scheme 36

This ozonolysis method has also been applied to *O*-methyl ketone oximes **204**, in the absence of carbonyl compounds or protic solvents, also affording tetroxanes (**Scheme 36**). The method has been extended to the synthesis of dispirotetroxanes devoid of the usual hexaoxonane by-products often seen in acidic peroxidation reactions (see [Section 9.14.8.3](#)) <2002RMC113>.

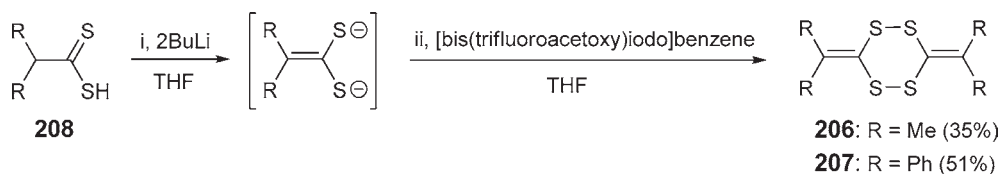
The bridged dithiatriazines **23** are accessible either from the reaction of 1,3-dichlorodithiatriazines **94** with (Me₃SiN)₂S (route A), or from (NSCl)₃ and tris(trimethylsilyl)amidines **205** (route B) (**Scheme 37**) <2003EJI3211>.

For preparation of derivatives of **23** with strongly electron withdrawing aryl groups (e.g., R = C₆F₅, 4-NCC₆H₄), a variation of route B is employed where *N,N'*-bis(trimethylsilyl)amidines are reacted with (NSCl)₃ in diethyl ether. The chloro derivative of **23** (R = Cl) is also accessible via route A, but an analogous preparation of the corresponding fluoro derivative resulted in a very unstable product <2003EJI3211>.



Scheme 37

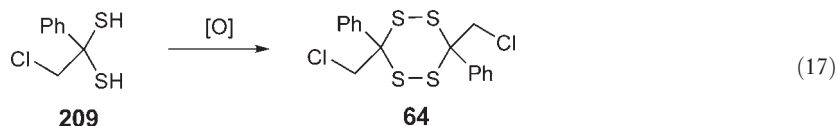
The 1,2,4,5-tetrathianes **206** and **207** were prepared in moderate yield by hypervalent iodine oxidation of the dianions of α,α -disubstituted alkanedithioic acids **208** (**Scheme 38**) <1996CB663>.



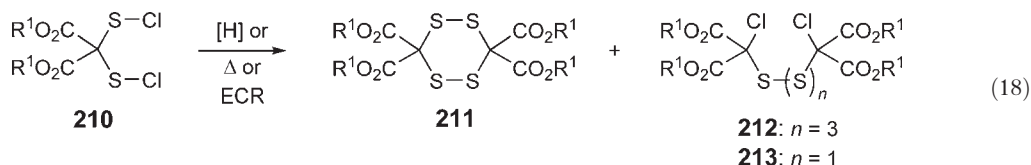
Scheme 38

α -Monosubstituted alkanedithioic acids gave only complex mixtures of decomposition products under the same conditions <1996CB663>.

Oxidation of 2-chloro-1-phenylethane-1,1-dithiol **209** with bromine, iodine, or elemental sulfur, as well as under UV irradiation, leads to formation of the 1,2,4,5-tetrathiane **64** in 50–95% yield ([Equation 17](#)) <2004RJO766>.



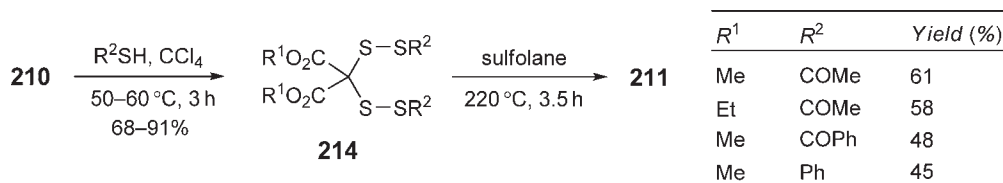
Reduction of the *gem*-disulfonyl dichlorides **210** (obtained from dialkyl malonates and sulfur dichloride) under a variety of conditions, afforded, in varying amounts, the corresponding 1,2,4,5-tetrathianes **211**, sometimes with concomitant formation of the tetrasulfides **212** or the disulfides **213** (Equation 18) <2000EJO2583>.



Pyrolysis of the dichlorides **210** afforded only products **211**, as did electrochemical reduction (ECR) of **210** (Equation 18; Table 2). The reaction of *gem*-disulfonyl dichlorides **210** with various mercapto compounds (thioacids, thiols) gave compounds **214** which, when pyrolyzed, afforded the 1,2,4,5-tetrathianes **211** as the only isolated products (Scheme 39) <2000EJO2583>.

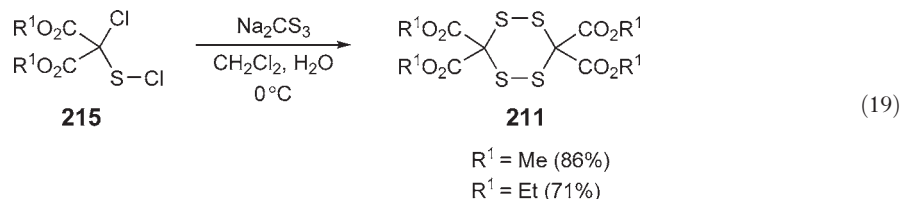
Table 2 Yields of 1,2,4,5-tetrathianes **211** and by-products (Equation 18)

R^1	Method	Yields (%)		
		211	212	213
Me	KI, CH ₃ CN, 20 °C, 2 h	67	28	
Et	KI, CH ₃ CN, 20 °C, 2 h	54		31
Me	KSCN, CHCl ₃ , EtOH, H ₂ O, 20 °C, 1 h	77		
Me	Mg, Et ₂ O	80		
Me	S ₈ , 220 °C, 6 h	76	17	
Et	S ₈ , 220 °C, 6 h	47		34
Me	Sulfolane, 220 °C, 3.5 h	78		
Et	Sulfolane, 220 °C, 3.5 h	63		
Me	ECR	89		
Et	ECR	79		

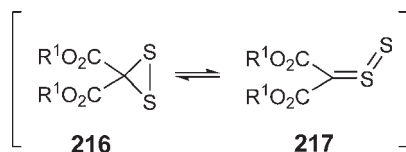


Scheme 39

The same authors also reported that treatment of the α -chloro sulfonyl chlorides **215** (obtained from the pyridine-catalyzed reaction between dialkyl malonates and thionyl chloride) with sodium trithiocarbonate gave 1,2,4,5-tetrathianes **211** in good yield (Equation 19) <2002EJO2039>.

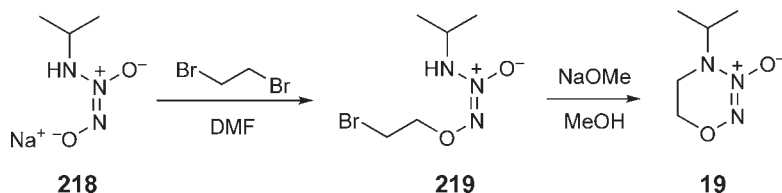


It was proposed that the reactions described in Scheme 38 and Equation (19) and the pyrolysis reactions in Equation (18) proceed via the intermediates **216/217** <2000EJO2583, 2002EJO2039>.



9.14.8.2.2 From [4+2] atom fragments

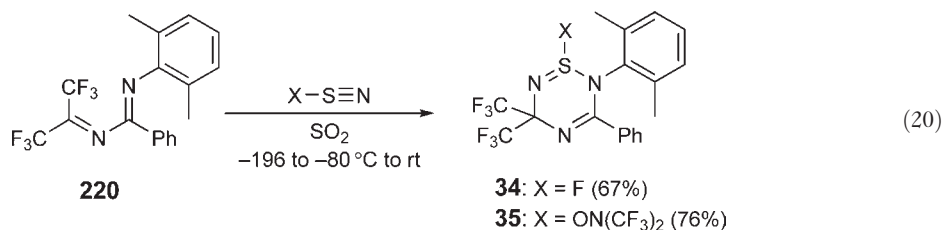
Bromoethylation of the diazenium diolate **218** to give **219** followed by treatment with methanolic sodium methoxide afforded the 1,2,3,4-oxatriazine 3-oxide **19** (Scheme 40) <2005JA5388>.



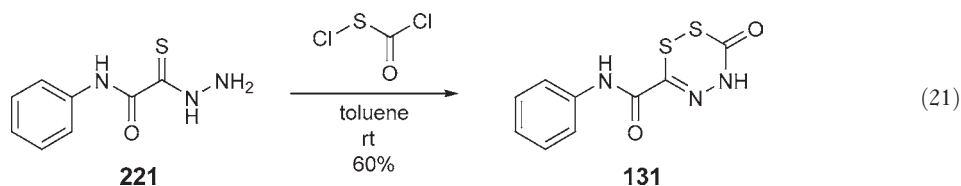
Scheme 40

The 1,3,2,4,6-dithiatriazines **21** were prepared in moderate yields (17–37%) from 2,2,2-trifluoroacetophenone oximes by treatment with tetrasulfur tetranitride in refluxing toluene. The aminosulfenamides **128** and sulfur were also formed as by-products (see Equation 3) <1996JHC295>.

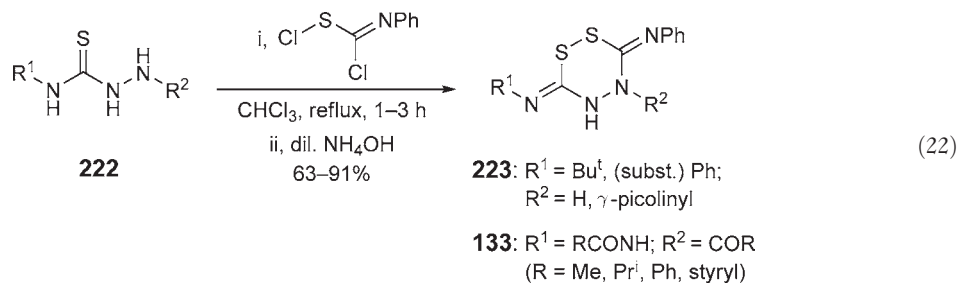
Reaction of the 1,3-diazabutadiene **220** with either thiazylfluoride or $(\text{CF}_3)_2\text{NO-S}\equiv\text{N}$ in SO_2 at low temperature gave the corresponding 2,5-dihydro-1 λ^4 -2,4,6-thiatriazines **34** and **35** (Equation 20) <2000JFC(102)337>.



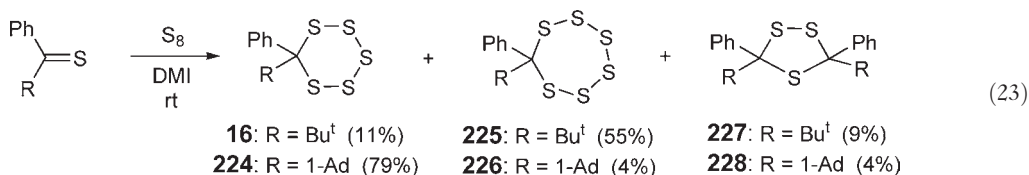
The 1,2,4,5-dithiadiazin-3-one **131** was prepared from thiohydrazide **221** by treatment with chlorocarbonylsulfonyl chloride in toluene at room temperature (Equation 21) <2003PS1283>. On heating, the product can eliminate a sulfur atom (see Section 9.14.6).



The 1,2,4,5-dithiadiazines **223** and **133** have been synthesized in good yield by a one-step condensation reaction of *N*-phenyl-*S*-chloroisoithiocarbamoyl chloride with a range of thiosemicarbazide derivatives **222** (Equation 22) <2002IJH153, 2002ASJ162, 2005ASJ2800>.

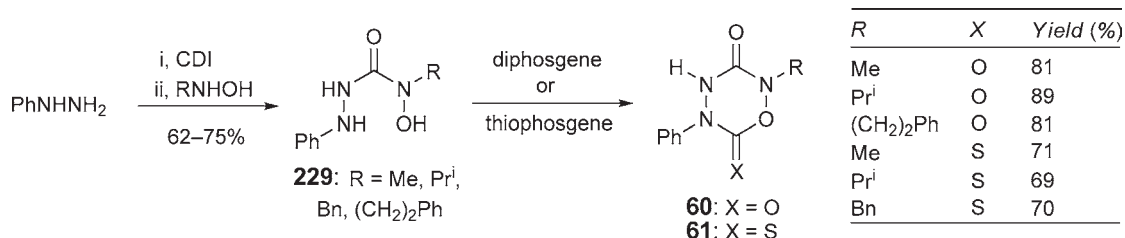


The pentathianes **16** and **224** were prepared by treatment of the corresponding thioketones with elemental sulfur in 1,3-dimethyl-2-imidazolinone (DMI) at room temperature, along with the corresponding hexathiepanes **225** and **226** and 1,2,4-trithiolanes **227** and **228** as by-products (Equation 23) <2002BCJ319>.



9.14.8.2.3 From [5+1] atom fragments

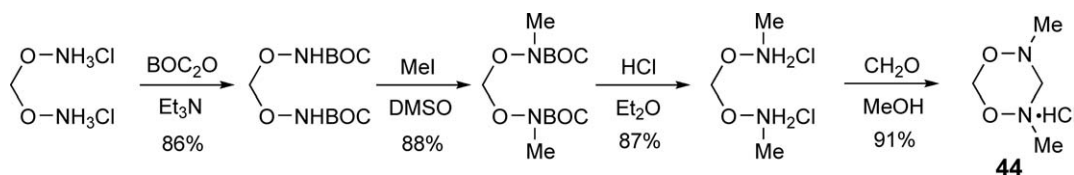
1,2,4,5-Oxatriazin-3,6-diones **60** and 6-thioxo-1,2,4,5-oxatriazin-3-ones **61** have been prepared by cyclic carbonylation of 1,4-disubstituted-4-hydroxysemicarbazides **229** with diphosgene or thiophosgene, respectively (Scheme 41) <2002HCO321>.



Scheme 41

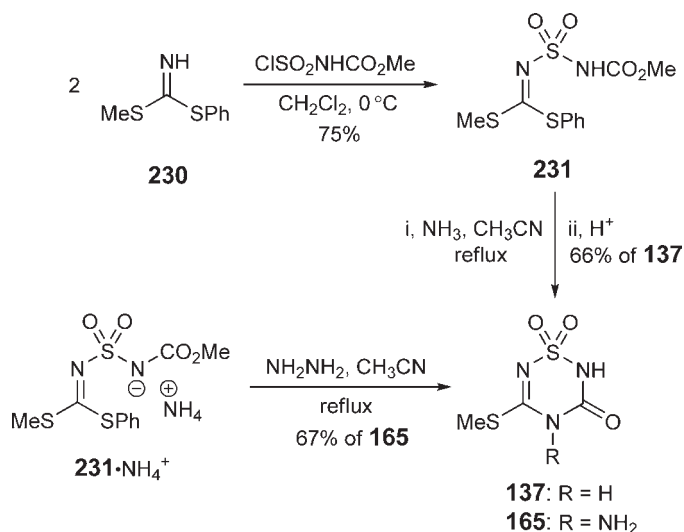
The 1,2,3,5-oxatriazine 2-oxide **117** was an unexpected product from the reaction of 9-fluorenylmethyloxycarbonyl (Fmoc) L-nitroarginine with paraformaldehyde and catalytic camphorsulfonic acid in refluxing benzene (see Section 9.14.6). The proposed structure was evidenced by the usual spectral data and extensive 2-D NMR experiments <2003JOC2652>.

The 1,5,2,4-dioxadiazine **44** was prepared in four steps from bisaminooxymethane dihydrochloride (Scheme 42) <2004RCB1349>.



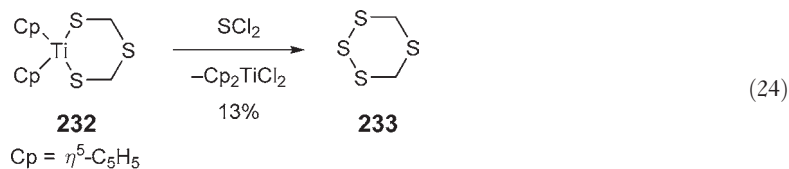
Scheme 42

The synthesis of 4*H*- and *N*⁴-amino-1,2,4,6-thiatriazine 1,1-dioxides **137** and **165** was achieved from the dithioimidocarbonate **230** (Scheme 43). One of the two moles of **230** captured HCl released during formation of **231** and this procedure was higher yielding than with triethylamine as the base. The ammonium salt **231**·NH₄⁺ was prepared from **231** with ammonia in THF or acetonitrile at 0 °C <1996H(43)2199>.



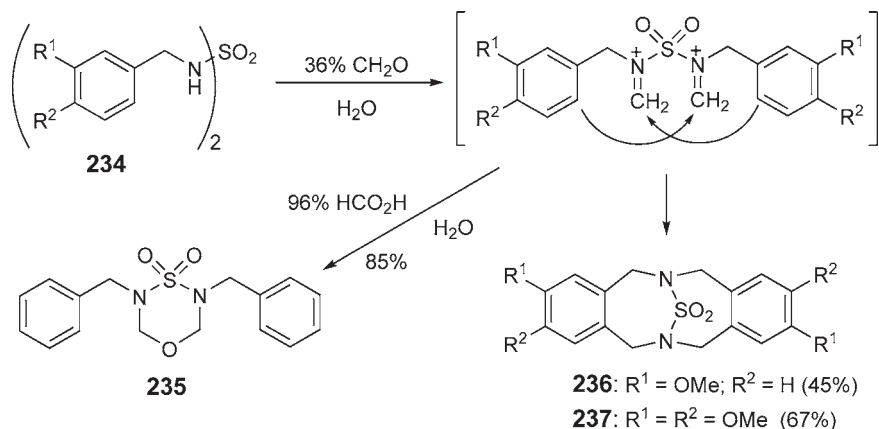
Scheme 43

1,2,3,5-Tetrathiane **233** was obtained in 13% yield from the titanocene thiolato complex **232** by treatment with sulfur dichloride in carbon disulfide solution (Equation 24) <1997CB757>.



9.14.8.3 Formation of Three or More Bonds

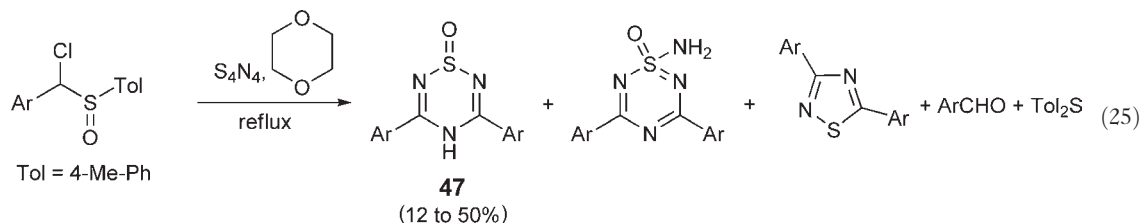
Treatment of *N,N'*-dibenzylsulfamide **234** (R¹ = R² = H) with aqueous formaldehyde and formic acid afforded the 1,4,3,5-oxathiadiazine **235** in high yield (Scheme 44) <2002BKC167>.



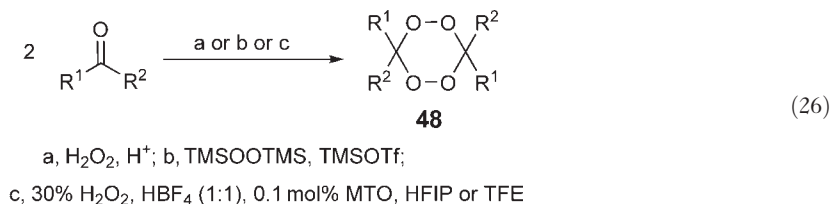
Scheme 44

With the electron-rich methoxy- or dimethoxybenzyl derivatives, a double intramolecular electrophilic substitution reaction occurred to give the alternative products **236** and **237** (Scheme 44) <2002BKC167>.

The reactions of arylchloromethyl *p*-tolyl sulfoxides with S_4N_4 (1 equiv) gave 3,5-diaryl-1,2,4,6-thiatriazine 1-oxides **47** in moderate yields, along with some or all of the by-products shown in Equation (25). A complex reaction mechanism was proposed and discussed <2000T7153>.



Synthetic methods for preparation of 1,2,4,5-tetroxanes have been reviewed recently <2001COR601, 2002RMC113>. The most general method involves acid-catalyzed addition of hydrogen peroxide to carbonyl compounds and subsequent cyclization of the hydroperoxide intermediates. The direct synthesis is carried out normally in the presence of either sulfuric, perchloric, or methanesulfonic acids and affords symmetrically substituted tetroxanes (Equation 26). In many cases, for example, where the carbonyl compound is unsubstituted in the α -position, tetroxanes are contaminated with hexaoxonanes and open-chain hydroperoxides. Selective removal of the more reactive hydroperoxides can be achieved with dimethyl sulfide or potassium iodide. Recrystallization usually removes residual hexaoxonanes but, failing that, heating the mixture with perchloric acid in acetic acid can convert hexaoxonanes to tetroxanes or convert the thermodynamically less stable hexaoxonanes to more water-soluble lactones, which may facilitate the purification process <2002RMC113>.



A related reaction employs bis(trimethylsilyl)peroxide in the presence of trimethylsilyl triflate. This procedure works efficiently with various aldehydes and ketones to give good yields of tetroxanes **48** (Equation 26) <2001COR601, 2002RMC113>. Alternatively, dispirotetroxanes can be prepared unambiguously by ozonolysis of cyclohexanone *O*-methyl oximes (see Section 9.14.8.2.1) <2001COR601>.

A recent improvement to this type of reaction often selects for the formation of tetroxanes over the trimeric hexaoxonane analogs. The use of fluorinated alcohols such as trifluoroethanol (TFE) or, often better, HFIP, as solvent and methyltrioxorhenium (MTO) as catalyst, as well as a substrate concentration of 1 M, are considered important for success (Equation (26); Table 3) <2003TL6309, 2006T1479, 2006BMC7790>.

Examples of symmetrical tetroxanes **48** prepared by this method are shown in Table 3. Aldehydes afforded high yields of tetroxanes **48**, as did cyclohexanone derivatives, but the relatively strained cyclopentanone and larger ring compounds such as cyclooctanone and cyclodecanone gave only trace amounts of tetroxanes. Di-*n*-alkyl ketones provided generally good yields of tetroxanes whereas ketones with branched alkyl chains gave little or no tetroxane product (Table 3).

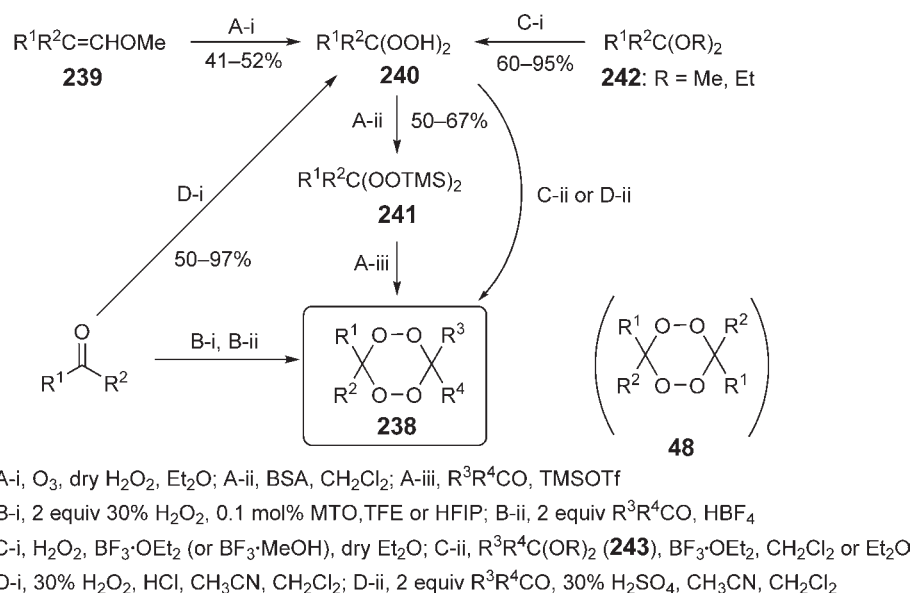
An elegant synthesis of unsymmetrical tetroxanes **238** involves ozonolysis of vinyl ethers **239** in the presence of hydrogen peroxide in diethyl ether. This procedure afforded the 1,1-bishydroperoxides **240**, which on subsequent trimethylsilylation with *N,O*-bis(trimethylsilyl)acetamide (BSA) gave **241**. TMSOTf-catalyzed cyclocondensation of **241** with carbonyl compounds afforded tetroxanes **238** (method A, Scheme 45; Table 4) <1999J(P1)1867>.

An improvement employed the H_2O_2 /MTO/fluorous alcohol system (described earlier) in a one-pot procedure for synthesis of mixed tetroxanes, which did not require isolation of the unstable and potentially explosive *gem*-dihydroperoxide intermediate **240**. The more reactive carbonyl compound was first oxidized to the *gem*-dihydroperoxide **240**, followed by the addition of the less reactive carbonyl compound in the presence of 1 equiv of HBf_4 . This procedure afforded unsymmetrical tetroxanes **238** in good yields (method B, Scheme 45; Table 4) <2003TL6309>.

A variation of the above reaction involves the boron trifluoride etherate-catalyzed condensation of *gem*-dihydroperoxides **240** with dimethyl and diethyl acetals **243** (method C, Scheme 45) <2004S2356>. The *gem*-dihydroperoxides **240** were prepared from cycloalkanone dimethyl or diethyl acetals **242** by treatment with hydrogen peroxide catalyzed by boron trifluoride complexes <2003TL7359> or similarly from appropriate enol ethers <2004RCB681>.

Table 3 Yields of symmetrical tetroxanes **48** from method 'c' (Equation 26)

R^1	R^2	Yield (%)	Reference
Ph	H	77	2003TL6309
C ₇ H ₁₅	H	86	2003TL6309
	-(CH ₂) ₅ -	88	2006BMC7790
	-(CH ₂) ₂ CH(Bu ⁱ)(CH ₂) ₂ -	64	2006T1479
	-(CH ₂) ₂ CH(Ph)(CH ₂) ₂ -	46	2006T1479
	-(CH ₂) ₂ CH(CO ₂ Et)(CH ₂) ₂ -	50	2006T1479
	-(CH ₂) ₂ CH(CF ₃)(CH ₂) ₂ -	86	2006T1479
	-(CH ₂) ₄ or 7 or 9-	<5	2006BMC7790
	-(CH ₂) ₆ -	45	2006BMC7790
	-(CH ₂) ₁₁ -	55	2006BMC7790
Bu ⁿ	Bu ⁿ	44	2006BMC7790
Et	Bu ⁿ	55	2006BMC7790
Me	Hept	72	2006BMC7790
Et	Pr ⁱ	26	2006BMC7790
Pr ⁱ	Pr ⁱ	0	2006BMC7790
Bu ⁱ	Bu ⁱ	0	2006BMC7790
Me	Bu ^t	15	2006BMC7790

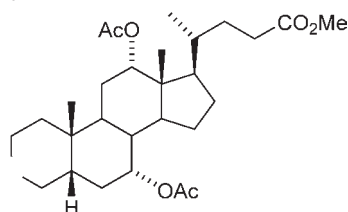
**Scheme 45**

In many of the reactions producing **238** using method C, the symmetrical tetroxane by-product **48** was also formed, in varying minor proportions, from homocyclocondensation of the bishydroperoxides **240**. Use of a larger excess of acetal made only slight improvement in the ratio of **238**:**48**. Dichloromethane as solvent rather than ether resulted in faster reaction and more selective cross-condensation. Omission of BF₃·OEt₂ resulted in no condensation occurring. Reactions involving benzaldehyde or acetophenone acetals were difficult and a larger amount (1.3–1.4 equiv) of BF₃·OEt₂ was required to obtain any of the desired aryl tetroxane **238**. A selection of the many analogs prepared is included in Table 4 <2004S2356>.

A further, convenient variation of this type of reaction, using more readily accessible and inexpensive starting materials, involves the acid-catalyzed condensation of crude *gem*-dihydroperoxides **240**, derived from cyclohexanone or a cholic acid derivative, with various cycloalkanones (method D, Scheme 45; Table 4) <2002JME3331, 2003JSC291, 2004JSC919>.

Table 4 Synthesis of tetroxanes **238** (Scheme 45)

R^1	R^2	R^3	R^4	Method	Yield ^a (%)	Reference
Ph	H	Me	Me	A-iii	26	1999J(P1)1867
Ph	H	-(CH ₂) ₅ -		A-iii	33	1999J(P1)1867
Cyclohexyl	H	Ph	H	A-iii	73	1999J(P1)1867
Cyclohexyl	H	PhCO(CH ₂) ₃	H	A-iii	48	1999J(P1)1867
Heptyl	H	-(CH ₂) ₂ CH(Bu ^t)(CH ₂) ₂ -		A-iii	44	1999J(P1)1867
Heptyl	H	Bu ⁿ	Bu ⁿ	B	51	2003TL6309
-(CH ₂) ₂ CH(Me)(CH ₂) ₂ -		Bu ⁿ	Bu ⁿ	B	64	2003TL6309
-(CH ₂) ₂ CH(Me)(CH ₂) ₂ -		heptyl	H	B	45	2003TL6309
-(CH ₂) ₂ CH(Me)(CH ₂) ₂ -		-(CH ₂) ₂ CH(Bu ^t)(CH ₂) ₂ -		B	62	2003TL6309
-(CH ₂) ₂ CH(Me)(CH ₂) ₂ -		Ph	H	B	54	2003TL6309
-(CH ₂) ₅ -		-(CH ₂) ₇ -		C-ii	50 (16)	2004S2356
-(CH ₂) ₅ -		<i>n</i> -C ₈ H ₁₇	H	C-ii	52 (18)	2004S2356
-(CH ₂) ₅ -		Ph	H	C-ii	22 (20)	2004S2356
-(CH ₂) ₅ -		Bu ⁿ	Bu ⁿ	C-ii	77 (6)	2004S2356
-(CH ₂) ₆ -		Me ₂ CHCH ₂	Me	C-ii	61 (10)	2004S2356
-(CH ₂) ₇ -		adamantyl		C-ii	32 (10)	2004S2356
-(CH ₂) ₁₁ -		-(CH ₂) ₆ -		C-ii	90	2004S2356
-(CH ₂) ₁₁ -		-(CH ₂) ₁₁ -		C-ii	46	2004S2356
-(CH ₂) ₁₁ -		-CH(Me)(CH ₂) ₄ -		C-ii	46 (2)	2004S2356
adamantyl		-(CH ₂) ₅ -		C-ii	61	2004S2356
-(CH ₂) ₅ -		-(CH ₂) ₂ CH(CO ₂ Me)(CH ₂) ₂ -		D-ii	28	2004JSC919
(Methyl diacetylcholate)-3-yl ^b		-(CH ₂) ₂ CH(Ph)(CH ₂) ₂ -		D-ii	15 + 12 ^c	2003JSC291
(Methyl diacetylcholate)-3-yl ^b		-(CH ₂) ₄ -		D-ii	26	2002JME3331
(Methyl diacetylcholate)-3-yl ^b		-(CH ₂) ₇ -		D-ii	34	2002JME3331
(Methyl diacetylcholate)-3-yl ^b		-CH ₂ CH(Me)(CH ₂) ₂ CH(Pr ⁱ)-		D-ii	19	2002JME3331

^aNumber in brackets refers to yield of symmetrical tetroxane by-product **48**.^b^cYields of separated diastereomers.

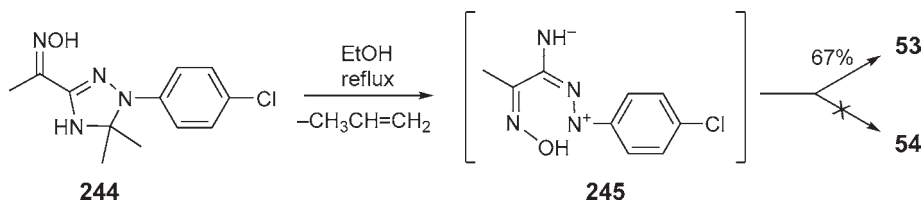
Elemental sulfur and a catalytic amount of sodium thiophenoxide in acetone at room temperature convert thioketones $R_2C=S$ to the corresponding 1,2,4,5-tetrathiane derivatives **55**, **56**, and **57** in yields of 95%, 80% and 60%, respectively. An attack of the oligothiolate ($R-S_x^-$) on the thione C-atom is proposed as initiating step. Thione *S*-sulfides cannot be intermediates, since they combine rapidly with thiones, affording 1,2,4-trithiolanes <1997H(45)507, 1997LA1517>.

Treatment of benzofuran-3(2*H*)-one with S_2Cl_2 in xylene afforded the bis-spiro-1,2,4,5-tetrathiane **92** (82%) (see Section 9.14.4.5) <1996T1961>.

UV irradiation ($\lambda > 350$ nm) of a CS_2 solution of phenylchlorodiazirine at 238 K results in the formation of an intense red solution, from which the yellow *trans*-3,6-bis(chlorophenylmethylene)-1,2,4,5-tetrathiane **91** was isolated in 15% yield (see Section 9.14.4.5). The proposed mechanism involved trapping of an intermediate carbene with CS_2 to give a methylenedithiirane, followed by photochemical ring opening to a biradical which dimerized to give the product <2002AXEo555>.

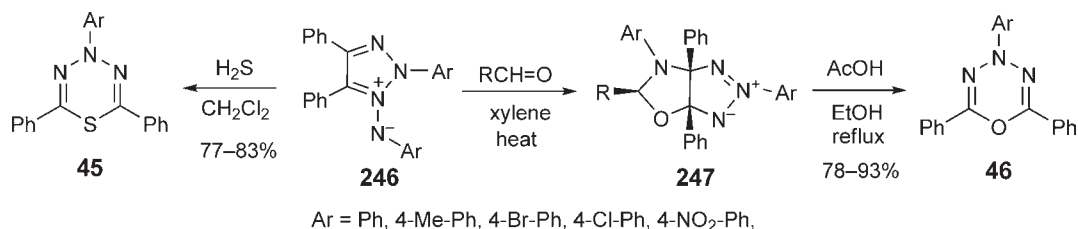
9.14.9 Ring Syntheses by Transformation of Another Ring

The 1,2,3,6-oxatriazine **53** (see Section 9.14.3.3) has been synthesized by ring transformation of triazoline oxime **244**, probably via elimination of propene and recyclization of the intermediate **245** as shown in Scheme 46 <2005ICA(358)4511>.



Scheme 46

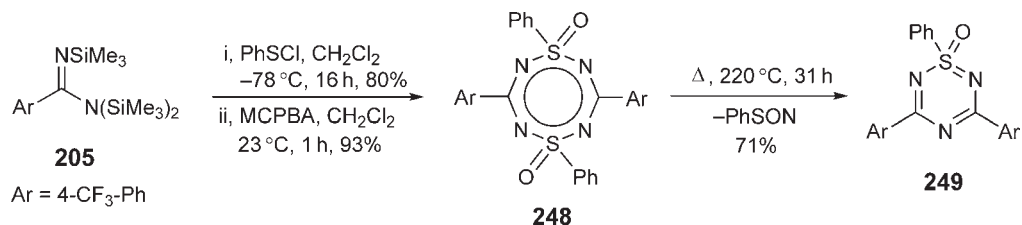
The rare 2,4,6-triaryl-1,3,4,5-oxatriazines **46** have been obtained in high yield from 1,2,3-triazolium-*N*¹-arylimides **246** via oxazolo[4,5-*d*]-1,2,3-triazoles **247** by a ring transformation effected by acetic acid in refluxing ethanol (Scheme 47) <1994J(P1)2797>. The mechanism of this reaction was discussed in CHEC-II(1996) <1996CHEC-II(6)967>.



Scheme 47

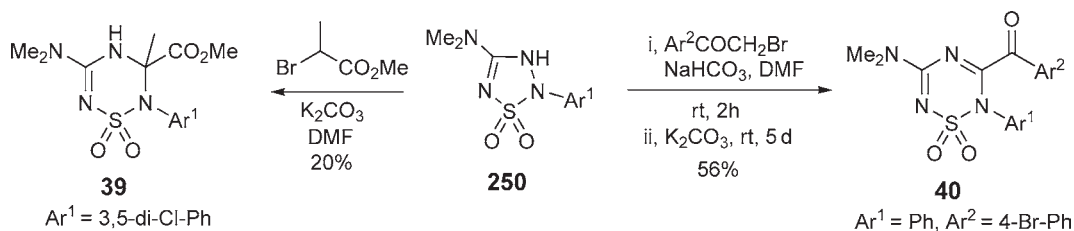
Treatment of the triazolium *N*¹-imide 1,3-dipoles **246** with dry hydrogen sulfide in dichloromethane gave high yields of the 2,4,6-triaryl-1,3,4,5-thiatriazines **45** (Scheme 47) <1994JCM350>.

Thermolysis of the eight-membered heterocycle **248** (prepared from trisilylated benzamidine **205** and phenyl sulfonyl chloride, followed by S-oxidation) resulted in ring contraction and formation of the 1,2,4,6-thiatriazine **249** (Scheme 48). Photolysis (254 nm) of **248** in toluene at 25 °C also afforded **249**, but the thermolysis procedure was cleaner <2000IC1697>.



Scheme 48

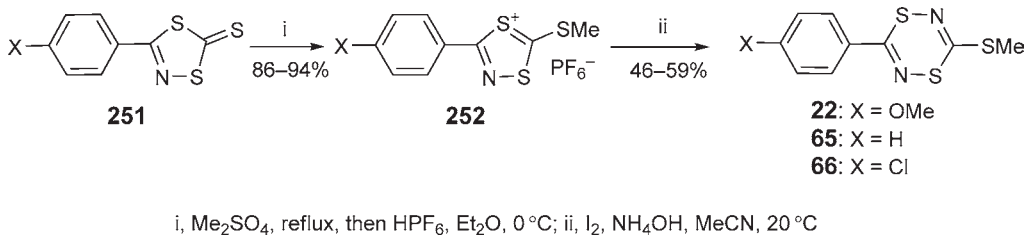
The 1,2,4,6-thiatriazine 1,1-dioxides **39** and **40** were obtained from a novel base-promoted ring expansion reaction of the 1,2,3,5-thiatriazole 1,1-dioxides **250** (Scheme 49). Treatment of **250** with methyl 2-bromopropanoate and



Scheme 49

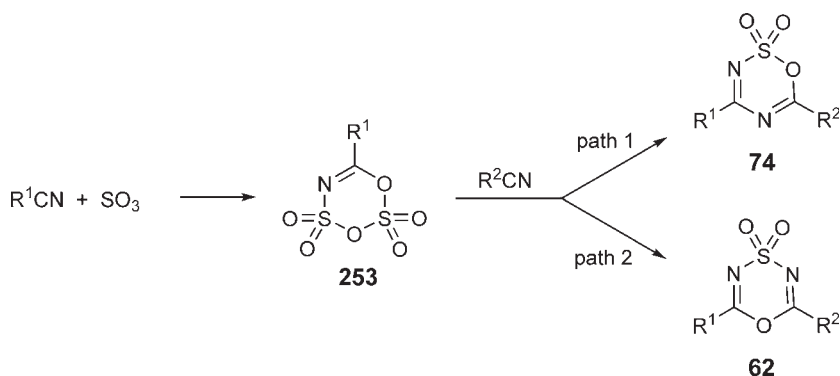
potassium carbonate initially gave the N^3 -alkylated product, which underwent ring expansion to **39** <2005AX(E)o2694>. Similar alkylation of **250** with a phenacyl bromide followed by ring expansion and aerial oxidation afforded **40** <2006AX(E)o3794>.

The 1,4,2,5-dithiadiazines **22**, **65**, and **66** were synthesized according to Scheme 50 <1997J(P1)1157>. The 3-aryl-1,4,2-dithiazole-5-thiones **251** (prepared from the corresponding thiobenzamides and trichloromethanesulfonyl chloride) were S-methylated with dimethyl sulfate and isolated as the hexafluorophosphate salts **252** which then furnished the dithiadiazines **22**, **65**, and **66** <1997J(P1)1157>.



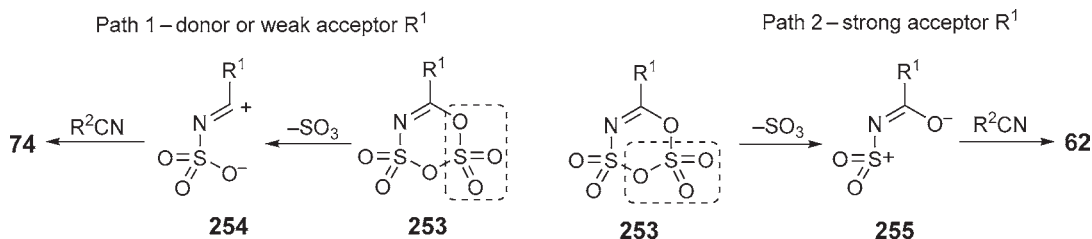
Scheme 50

Syntheses of 4,6-disubstituted-1,2,3,5-oxathiadiazine 2,2-dioxides **74** and 2,6-disubstituted-1,4,3,5-oxathiadiazine 4,4-dioxides **62** are based on reaction of nitriles and other cyano-containing compounds (cyanamides, cyanates) with SO_3 and its bound forms (complexes, adducts) (Scheme 51) <1997CHE1028>.



Scheme 51

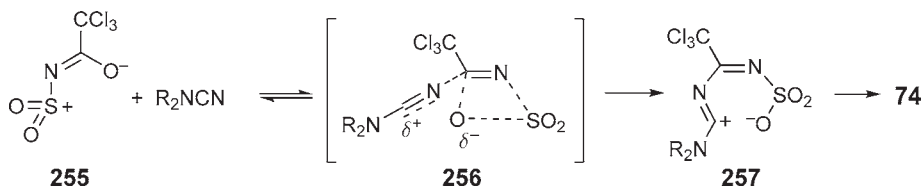
Reactions of cyano compounds (R^2CN) with the intermediate cyclic adduct **253** can occur with retention of the C–O bond or its cleavage. Ultimately, this is associated with cleavage of SO_3 from different positions in the ring of **253** as shown in Scheme 52.



Scheme 52

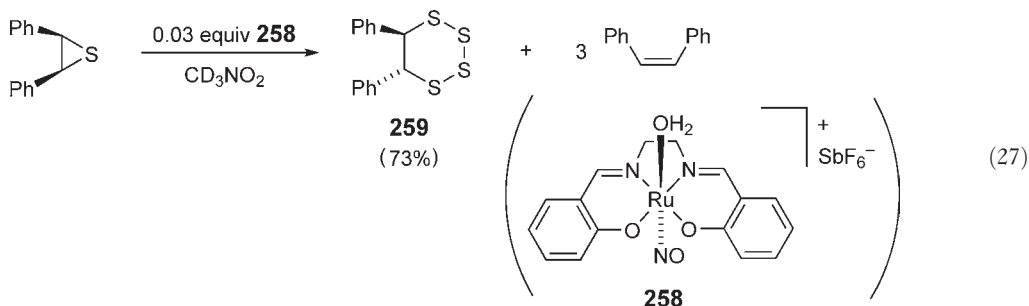
The course of the reaction depends upon the electronic properties of the substituent R^1 . Path 1 is typical for heterocycles **253** with donor or relatively weak acceptor substituents (e.g., $R^1 = \text{Me}$, Et, tolyl, chlorophenyl) and path 2 is typical for dioxadithiazines **253** having strong acceptor substituents (e.g., $R^1 = \text{CCl}_3$, CBr_3 , 3,5-dinitrophenyl) <1997CHE1028>. Syntheses of 1,4,3,5-oxathiadiazine 4,4-dioxides **62** ($R^1 = \text{C}_6\text{F}_5$; $R^2 = \text{C}_6\text{F}_5$, Me) using the above methodology have been reported recently <2002RJO889>. Unsaturated groups in the nitrile (e.g., (meth)acrylonitrile, crotonitrile) significantly complicate formation of the oxathiadiazine ring, since the alkene moiety can also react with SO_3 , giving mixed oligomers as by-products <1997CHE1028>.

A simple method for synthesis of 1,2,3,5-oxathiadiazine 2,2-dioxides **74** bearing strong acceptor ($R^1 = \text{CCl}_3$) and donor ($R^2 = \text{NR}_2$) groups involves reaction of dialkylcyanamides with **253** ($R^1 = \text{CCl}_3$). On the basis of Scheme 52 one would not expect to obtain products **74** from these reactions since the intermediate 1,4-dipole **254** ($R^1 = \text{CCl}_3$) is unlikely; however, the observed outcome of the reaction has been rationalized by proposing that zwitterionic intermediate **255** ($R^1 = \text{CCl}_3$) is probably converted to 1,2,3,5-oxathiadiazines **74** by nucleophilic attack by the cyano group on the electron-deficient carbon atom of **255** with formation of intermediate **257** through the transition state **256** (Scheme 53) <1997CHE1028>.

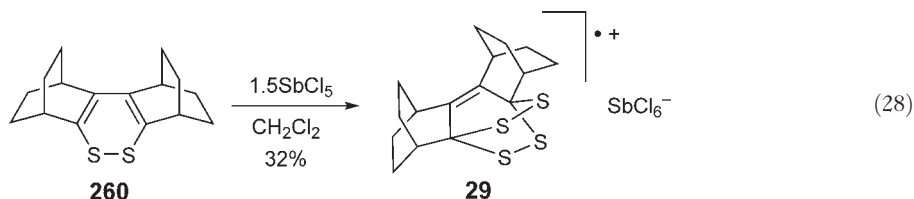


Scheme 53

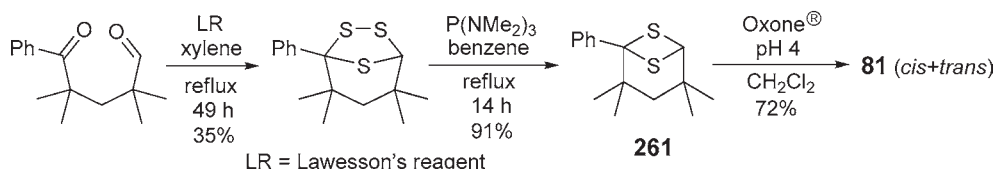
trans-5,6-Diphenyl-1,2,3,4-tetrathiane **259** was produced from a disproportionation reaction of *cis*-stilbene sulfide, catalyzed by the ruthenium *N,N'*-bis(salicylaldehyde)ethylenediamine (salen) nitrosyl complex **258** (Equation 27). Monosubstituted thiiranes did not give the analogous monosubstituted tetrathianes; instead, the corresponding trithiolane was produced <2002JA4770>.



Treating a 0.06 M CH_2Cl_2 solution of the 1,2-dithiine **260** with 1.5 equiv of SbCl_5 caused a one-electron oxidation to form the radical cation of **260** which underwent a disproportionation reaction giving an SbCl_5 salt of the remarkably stable radical cation **29** (Equation 28) <2002JA15038> (see Section 9.14.3.1).



A 1:1 mixture of *cis*- and *trans*-isomers of 1,2,4,5-tetrathiane **81** (see Section 9.14.4.5) was produced by treatment of the 1,3-dithietane **261** with Oxone[®] ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) (Scheme 54). The isomers were separated and their structures confirmed by X-ray crystallography (Section 9.14.3.1). A proposed mechanism involving oxidative hydrolysis of **261** was supported by intermediate-trapping experiments <2000BCJ729>.



Scheme 54

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

Over the last decade or so, synthetic methods for 21 different parent heterocycles within the scope of this chapter have been reported and the spectrum of methods described is as diverse as the range of ring systems themselves. A list of the synthetic methods reported in the last decade for each of the ring systems appears below. The most important factors which determine the overall efficacy and generality of a route are (1) availability/ease of preparation of precursors, (2) how readily substituents can be varied, and (3) yield. Comparisons drawn along these lines are included below for the more common heterocycles in this chapter. For 13 of these 21 heterocycles, only one synthetic method has been reported, so critical comparison is obviously not possible. Also, with many of the synthetic methods in this chapter, only a single example was reported and these are marked with an asterisk (*). For those interested in the preparation of a particular heterocycle, the survey of known systems (Tables 6 to 10, Chapter 2.28 of CHEC(1984), parts of Section 2.26.4.2.3 of CHEC(1984), and Section 6.23.4 of CHEC-II(1996)) will also be useful for this purpose and should be considered in addition to the information below.

1,2,3,4-Oxatriazines. Reaction of an amino-substituted diazenium diolate with 1,2-ethylenedibromide (Scheme 40).*

1,2,3,6-Oxatriazines. Thermal ring transformation of a 3-acetyl-1,2,4-triazole oxime (Scheme 46).*

1,3,4,5-Oxatriazines. Acid-catalyzed ring transformation of 4,5-diaryl-1,2,3-triazolium-*N*¹-aryl imides (Scheme 47) – good yields of 2,4,6-triarylsubstituted products only.

1,2,4,5-Oxatriazines. (1) Reaction of benzonitrile oxides with hydrazones (Equation 16) – this method gives 3-aryl derivatives; (2) reaction of benzonitrile oxides with hydrazine carboxylates and cyclization (Scheme 33)*; (3) cyclic carbonylation of 1,4-disubstituted-4-hydroxy-semicarbazides with (thio)phosgene (Scheme 41) – this method gives 3,6-dione-type derivatives. Methods (1) and (3) both appear quite general and high yielding, with precursors readily available.

1,4,2,5-Dioxadiazines. Dimerization of aryl nitrile oxides (Scheme 34) – currently unclear how conditions (e.g., inclusion/exclusion of added base) influence which product (1,4,2,5-dioxadiazine or 1,2,5-oxadiazole *N*-oxide (furan)) is favored.

1,5,2,4-Dioxadiazines. Reaction of a bisaminooxymethane with formaldehyde (Scheme 42).*

1,2,4,5-Oxathiadiazines. Oxidative cyclization of 1,5-bisacylated thiocarbohydrazides (Scheme 29) – good yields, several examples, readily available precursors.

1,4,3,5-Oxathiadiazines. (1) Reaction of *N,N'*-dibenzylsulfamide with aqueous formaldehyde and formic acid (Scheme 44)* – with electron-rich phenyl moieties, different bicyclic products are formed; (2) reaction of cyano-containing compounds with 1,3,2,4,5-dioxadithiazine 2,2,4,4-tetraoxides bearing a strong acceptor substituent (e.g., CCl₃ or dinitrophenyl); with donor or weak acceptor substituents, the isomeric 1,2,3,5-oxathiadiazines are formed (Schemes 51 and 52). This is the best method available at present.

1,2,3,5-Oxathiadiazines. Reaction of cyano-containing compounds with 1,3,2,4,5-dioxadithiazine 2,2,4,4-tetraoxides bearing a donor or weak acceptor substituent (e.g., alkyl, tolyl); with a strong acceptor substituent, the isomeric 1,4,3,5-oxathiadiazines are formed (Schemes 51 and 52).

1,2,4,5-Trioxazines. Condensation of carbonyl oxides (from ozonolysis of vinyl ethers or *O*-methyl oximes) with nitrones (Scheme 35).

1,3,2,4,6-Dithiatrazines. (1) Reaction of 2,2,2-trifluoroacetophenone oximes with S₄N₄ (Section 9.14.8.2.2) – moderate yields, limited range of products, and significant aminosulfenamide by-product; (2) reaction of tris(trimethylsilyl)amidines and (NSCl)₃ (Scheme 37) only provides derivatives with sulfur diimide bridge.

1,2,4,5-Thiatrazines. Oxidative cyclization of product from thiosemicarbazides + (aryl isocyanates (Scheme 30) or benzonitriles (Scheme 31)).

1,3,4,5-Thiatrazines. Ring transformation of 4,5-diaryl-1,2,3-triazolium-*N*¹-aryl imides with H₂S (Scheme 47) – good yields of 2,4,6-triaryl derivatives only.

1λ⁴-1,2,4,6-Thiatrazines. (See Section 6.23.4 of CHEC-II(1996) and <2000JHC583> for older syntheses of this relatively common heterocycle.) Recently reported methods include (1) reaction of a 1,3-diazabutadiene with X-S≡N

(Equation 20) – only two examples ($X = \text{F}$, $(\text{CF}_3)_2\text{NO}$); (2) reaction of arylchloromethyl tolyl sulfoxides with S_4N_4 (Equation 25) – only 3,5-diaryl 1-oxide products, moderate yields, and many by-products; (3) displacement of the chloro atoms of 1,3,5-trichloro- $1\lambda^4$ -1,2,4,6-thiatriazine (Equation (13); Schemes 22 and 25–28). Method (3) is the best and most general recent method, though (to date) restricted to heteroatom-linked substituents at C-3 and C-5.

1 λ^6 -1,2,4,6-Thiatriazines. (See Section 6.23.4 of CHEC-II(1996) for older syntheses of this relatively common heterocycle.) Recently reported methods include (1) reaction of a dithioimidocarbonate with methyl chlorosulfonylcarbamate then cyclization with ammonia* or hydrazine* (Scheme 43); (2) thermal ring contraction of a 1,3,5,7-tetraaryl-1,5,2,4,6,8-dithiatetrazocine 1,5-dioxide* (Scheme 48); (3) ring expansion of 1,2,3,5-thiatriazole 1,1-dioxides (Scheme 49) – to date only a few examples have been published, but the method is potentially quite general, though restricted to 3-amino derivatives; (4) chlorination of $1\lambda^6$ -1,2,4,6-thiatriazine 1-oxides and displacement of the chloro atom(s) of the resulting 1-chloro- $1\lambda^6$ -1,2,4,6-thiatriazine 1-oxide derivatives (Equation (12); Scheme 23) – restricted (to date) to heteroatom-linked S-substituents. Of these recent methods, (3) is quite convenient and potentially the most general.

1,4,2,5-Dithiadiazines. Ring expansion of 3-aryl-1,4,2-dithiazole-5-thiones (Scheme 50) – only 3-aryl-5-methylthio derivatives reported.

1,2,4,5-Dithiadiazines. (1) Oxidative cyclization of 1,6-diphenyl-2,5-dithiobiurea (Equation 14)*; (2) oxidative cyclization of *N,N'*-dicarbethoxy-*N,N'*-bis(mercaptomethyl)hydrazine (Scheme 32)*; (3) condensation of an oxamic acid thiocarbazine with chlorocarbonylsulfonyl chloride (Equation 21)*; (4) condensation of thiosemicarbazide derivatives with *N*-phenyl-*S*-chloroisothiocarbamoyl chloride (Equation 22). Method (4) is the most general of these, provides good yields, and precursors are reasonably accessible.

1,2,4,5-Tetroxanes. (1) Dimerization of carbonyl oxides (Scheme 36); (2) acid-catalyzed cyclization of carbonyl compound bishydroperoxides (Equation 26) – a variety of conditions are available but the HBF_4 -mediated, MTO-catalyzed reaction in fluorinated alcohols gives the highest ratios of tetroxane to hexaoxonane by-product; (3) acid-catalyzed reaction of 1,1-bishydroperoxides with carbonyl compounds or their di(m)ethyl acetals (Scheme 45) – again a variety of conditions are available and the acid-mediated MTO/ H_2O_2 /fluorinated alcohol system seems best in terms of yield, selectivity for desired product, and, unlike the other variants, obviates the need to isolate unstable intermediates. Methods (1) and (2) give symmetrical products only, whereas (3) affords unsymmetrical products; however, all of these methods lack stereocontrol.

1,2,3,4-Tetrathianes. Ru-catalyzed disproportionation reaction of a disubstituted thiirane (Equation 27)* (monosubstituted thiiranes give trithiolanes).

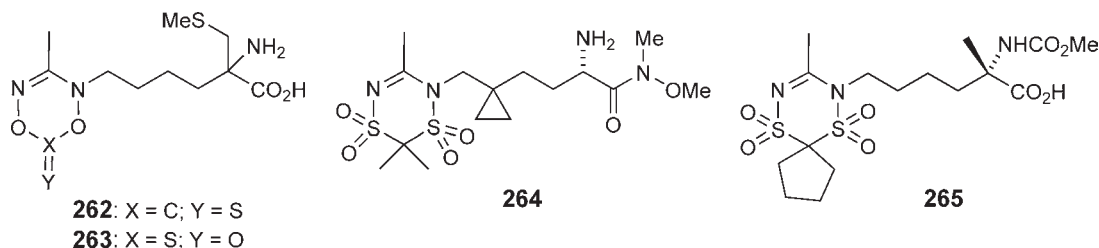
1,2,3,5-Tetrathianes. Reaction of a 1,3,5-trithia-2-titanacyclohexane with sulfur dichloride (Equation 24)*.

1,2,4,5-Tetrathianes. (1) Oxidative dimerization of α,α -disubstituted alkanedithioic acid dianions (Scheme 38) or 1,1-dithiols (Equation 17) – very limited examples and α -monosubstituted alkanedithioic acids decompose; (2) reductive or pyrolytic dimerization of *gem*-disulfonyl dichlorides (Equation 18) – only malonate-derived examples; (3) reaction of α -chloro sulfonyl chlorides with sodium trithiocarbonate (Equation 19) – only malonate-derived examples; (4) sodium thiophenoxide-catalyzed reaction of thioketones with elemental sulfur; (5) reaction of benzofuran-3(2*H*)-one with S_2Cl_2 *; (6) UV irradiation of a CS_2 solution of a diazirine*; (7) reaction of a 2,2,4-trisubstituted-1,3-dithietane with Oxone® (Scheme 54)*. Method (4) is the most convenient and general of these.

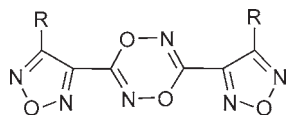
Pentathianes. Reaction of thioketones with elemental sulfur (Equation 23) – only two examples with thiophenones recently reported; yields variable, significant by-products.

9.14.11 Important Compounds and Applications

The 1,5,2,4-dioxadiazine 262, the 1,3,2,4,6-dioxathiadiazine 263, 1,5,2,4-dithiadiazine tetraoxides 264 and 265, and a selection of further derivatives have been patented as nitric oxide synthase inhibitors with potential use as agents for treatment of arthritis, pain, some neurodegenerative conditions, and other disorders involving NO production <2000WO0063195>.



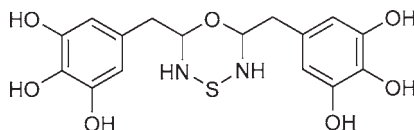
The 1,4,2,5-dioxadiazines **67** and **157** have been patented in Russia as activators of the soluble form of guanylate cyclase, which plays a major regulatory role in the relaxation and contraction of blood vessel muscles and aggregation of thrombocytes <2003RUP2208438, 2003RUP2212409>.



67: R = NH₂

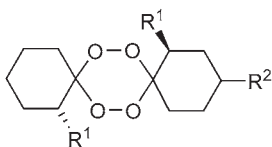
157: R = N₃

The 1,4,3,5-oxathiadiazine **266** has been patented as an agent for reducing food intake and reducing endocrine levels <2001WO0160319>.



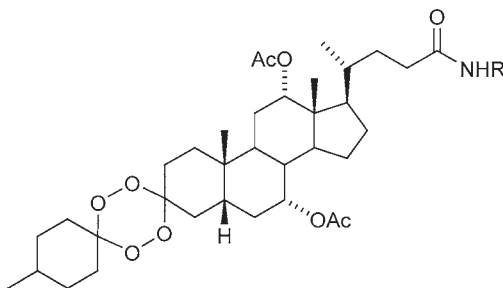
266

Over the past decade or so, 1,2,4,5-tetroxanes have attracted growing attention due to the impressive antimalarial activity of some derivatives. The antimalarial mode of action of tetroxanes is believed to parallel that of artemisinin, a potent 1,2,4-trioxane antimalarial compound of natural origin. In each case, the reaction with intraparasitic heme results in peroxide bond scission to generate cytotoxic carbon radicals, causing cell death and killing the parasite by alkylation. Good antimalarial activity (comparable with artemisinin) has been found with 3,6-dispiro compounds **267**; the monocyclic and monospiro tetroxanes examined so far are generally poor antimalarials. An overview of reported antimalarial activities for this class of compounds was published in 2002 <2002RMC113>. At present, the most active tetroxane compounds are those of structure **268** <2003WO03/068736> which have activities generally significantly higher than those of nonsteroidal mixed tetroxanes, bis-steroidal tetroxanes, and simple cyclohexane-based tetroxanes. The *in vitro* IC₅₀ values against *Plasmodium falciparum* W2 clone (chloroquine resistant, mefloquine sensitive) and *P. falciparum* D6 clone (chloroquine sensitive, mefloquine resistant) of the most active compounds are in the ranges of 0.58–3.93 and 1.17–5.96 nM, respectively (artemisinin 7.3 and 8.4 nM) <2002JME3331>. Interestingly, the corresponding *in vitro* IC₅₀ values for the highly active nonsteroidal amide **269**, possessing an *N,N*-dimethylamino group, are 9.72 and 11.24 nM, which is attributed to protonation of the basic nitrogen <2004JSC919>.



267: R¹ = H, alkyl, CH₂CH=CH₂,
H₂C≡, CH₂O-alkyl; R² = H

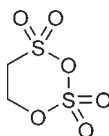
269: R¹ = H; R² = CONHCH₂CH₂NMe₂



268

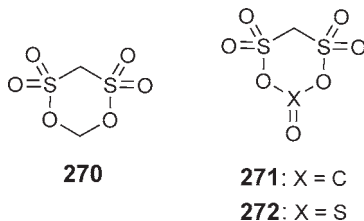
The tetroxanes **268** were assessed as antimycobacterials also and activity was established (minimum inhibitory concentration (MIC) 3.13–6.26 µg ml⁻¹) <2002JME3331>.

Carbonyl sulfate **68** is a useful reagent in various patented industrial processes, including the production of nitroethionate <2001WO0160787>, an intermediate in the production of dyes and a synthesis of 1-(2-sulfoethyl)pyridinium betaine <1999WO9941236>, important as a secondary brightener in the electrolytic deposition of nickel.

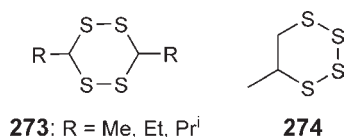


68

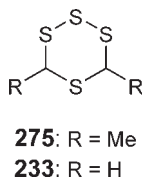
The dioxadithianes **270** and **271** and the dioxatrithiane **272** as well as related derivatives have been patented as components of electrolyte solutions for secondary batteries which have attracted attention as power sources for cell phones and notebook computers <2004EUP1394888>.



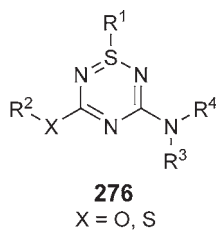
The 3,6-dialkyl-1,2,4,5-tetrathianes **273** are key components of flavoring mixtures that impart the flavor of onion, leek, garlic, or shiitake to food <2006WO2006/027352>. Gas chromatography–mass spectrometry (GC–MS) studies have shown 5-methyl-1,2,3,4-tetrathiane **274** to be a component of the essential oil from fresh garlic (*Allium sativum*) <2006USO54> and a thermal degradation product of alliin (*S*-allyl-L-cysteine sulfoxide), deoxyalliin (*S*-allyl-L-cysteine) <1997JFA3580>, and allyl isothiocyanate (a flavor compound in mustard and Wasabi) <1998JFA220>.



Similar studies have shown 4,6-dimethyl-1,2,3,5-tetrathiane **275** to be a volatile component of meat from the popularly consumed edible crab, *Charybdis feriatius* <1999JFA2280>, and 1,2,3,5-tetrathiane **233** to be a volatile component of shiitake mushrooms *Lentinus edodes* <1997CB757>. GC–MS studies also showed **275** and 3,6-dimethyl-1,2,4,5-tetrathiane (**273**: R = Me) as minor products when cysteic acid or cysteinesulfinic acid were heated with D-glucose in an aqueous system of pH 6 at 160 °C for 2 h <1997JFA3586>. Such studies have also revealed that the 1,2,4,5-tetrathiane **273** (R = Me) is a component of durian fruit (*Durio zibethinus* Murr.) <1996FFJ295>, onions <2001MI1011>, and extracts of cooked spinach leaves (*Spinacia oleracea* L.) <2000FFJ329>.

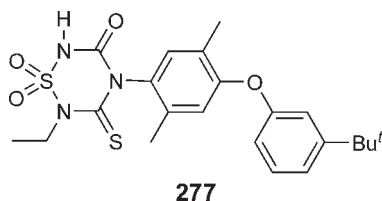


The 1λ⁴-1,2,4,6-thiatriazines **276** act as very potent inhibitors of the biosynthesis of cellulose and as such have been extensively investigated as a novel class of herbicides <2003C725, 1996WO9601814, 1997WO9725318, 1997WO9725319, 1998WO9808845>.



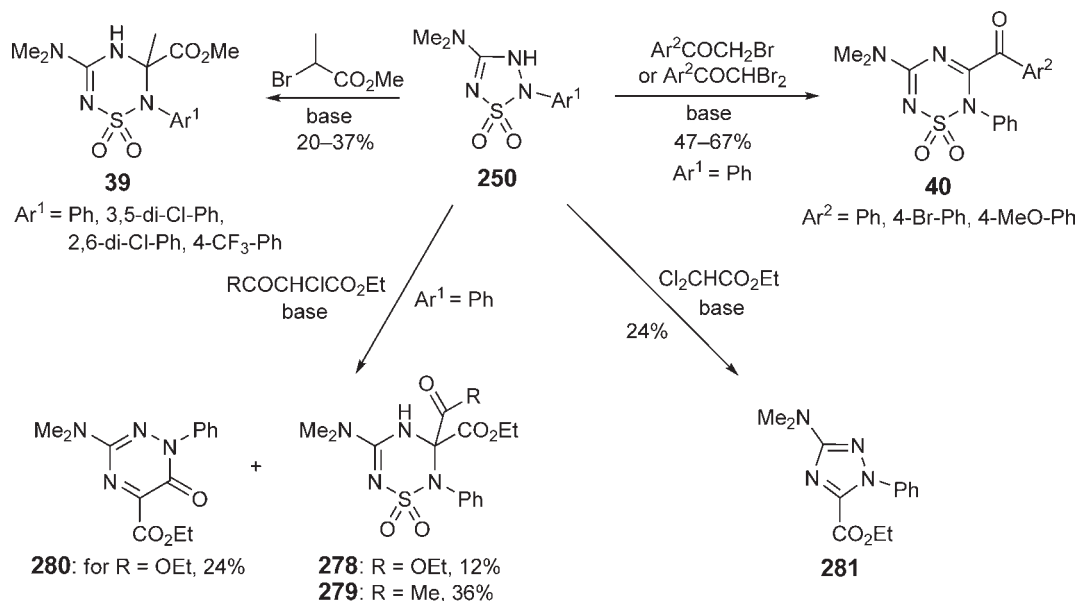
R¹ = alkyl, alkenyl, alkynyl, (het)aryl
R² = alkyl, aryl; R³, R⁴ = H, alkyl, aryl, acyl

The 1λ⁶-1,2,4,6-thiatriazine **277** has been patented for its fungicidal activity against phytopathogenic fungi of crops <2004USP6696487>.



9.14.12 Further Developments

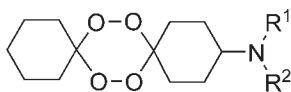
The scope of the novel base-promoted ring expansion reaction of 1,2,3,5-thiadiazole-1,1-dioxides **250** to afford 1,2,4,6-thiadiazine-1,1-dioxides **39** and **40** (see [Scheme 49](#), [Section 9.14.9](#)) has been investigated. Additional examples of **39** with differently substituted N²-phenyl groups were prepared ([Scheme 55](#)) and a reaction mechanism was proposed. Diethyl chloromalonate and ethyl 2-chloroacetoacetate also produced the ring expanded products **278** and **279**; the chloromalonate reaction also gave the triazinone **280**. A plausible mechanism for formation of the triazinone, involving initial alkylation at N⁵ and SO₂ expulsion was offered [<2007OBC472>](#).



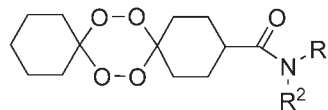
Scheme 55

Further examples of the alkylation of **250** with phenacyl bromides followed by ring expansion and aerial oxidation to afford **40** were reported. Reaction of **250** with 2,2-dibromo-4-methoxyacetophenone afforded the ring-expanded product **40** directly in 67% yield ([Scheme 55](#)), whereas the reaction with ethyl dichloroacetate gave the triazole **281**. Related electrophiles, including 2-chloroamides, 2-chlorosulfonamides, and bromomethyl phenylsulfone, did not react [<2007OBC472>](#).

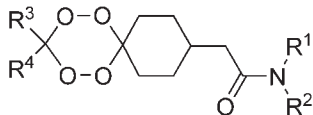
A report in late 2006 described a small array of unsymmetrical dispiro- and spiro-tetroxanes **282**, **283**, **284**, and **285**, synthesized *via* acid-catalyzed cyclocondensation of *bis*(hydroperoxides) with ketones (see [Scheme 45](#), [Section 9.14.8.3](#)). Incorporation of water-soluble and polar functionalities resulted in some analogs with unprecedented levels of oral antimalarial activity for this class of compound [<2006OBC4431>](#).



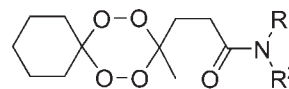
282: $R^1 = H$; $R^2 = CH(CH_2)_2$, $(CH_2)_2NEt_2$, $(CH_2)_2N(CH_2)_4$ or 5 , $(CH_2)_2N(CH_2)_4O$; $R^1R^2 = (CH_2)_4O$



283: $R^1 = H$; $R^2 = CH(CH_2)_2$, $(CH_2)_2NEt_2$, $(CH_2)_2N(CH_2)_4O$; $R^1R^2 = (CH_2)_4O$



284: R^1 , R^2 as for **282**;
 $R^3R^4 = (CH_2)_5$ or 11 , adamantylidene



285: R^1 , R^2 as for **283**

The compounds most active against *P. falciparum* (3D7 strain), **283** ($R^1 = H$; $R^2 = (CH_2)_2NEt_2$), **284** ($R^1 = H$; $R^2 = (CH_2)_2NEt_2$; $R^3R^4 = (CH_2)_5$), **284** ($R^1 = H$; $R^2 = CH(CH_2)_2$; $R^3R^4 = \text{adamantylidene}$), and **284** ($R^1R^2 = (CH_2)_4O$; $R^3R^4 = \text{adamantylidene}$), had *in vitro* IC_{50} values of 1.5, 5.15, 2.3, and 5.2 nM, respectively (artemisinin 9.5 nM, artemether 3.4 nM, and chloroquine 8.5 nM). The two adamantanone derived analogs **284** (described above) showed 100% inhibition by oral administration at a dose of 30 mg kg⁻¹ in a 4-day Peter's suppressive test *vs.* *P. berghei* (ANKA strain) in mice. In the 4-day Peter's test to determine oral *in vivo* ED₅₀ and ED₉₀ values, the morpholino derivative demonstrated outstanding oral activity, superior to the control, artemether <2006OBC4431>.

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Biographical Sketch



Dr. Craig Francis was born in 1966 in Adelaide, Australia. He obtained his B.Sc. (First Class Honors) in 1987 at The University of Adelaide and qualified for his Ph.D. (1991) under the supervision of Dr. David Ward while studying electrophile-initiated cyclization methodology for the synthesis of reduced quinolines related to virantmycin. As a postdoctoral research fellow at the University of Cambridge with Professor Andrew Holmes (1991–1992), he studied the asymmetric synthesis of the marine natural product obtusenyne. Dr. Francis then returned to Australia to join the Commonwealth Scientific and Industrial Research Organization (CSIRO) as a postdoctoral research fellow with Dr. Andy Liepa in 1993. Over the following decade, he rose through the ranks and is presently a principal research scientist.

Dr. Francis' research at CSIRO has been devoted largely to the application of synthetic organic chemistry, in particular heterocyclic chemistry, to the field of bioactive molecule discovery and development. These projects have involved extensive national and international collaborations with partners in the pharmaceutical, animal health, and crop protection sectors.

His abiding interest is in the development of synthetic methods for the preparation of novel or uncommon heterocyclic ring systems.

9.15

Six-membered Rings with Two or More Heteroatoms with at least One Selenium or Tellurium

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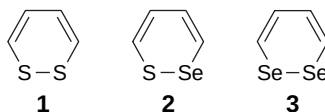
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9.15.1 Introduction

The chemistry of six-membered heterocycles containing two or more heteroatoms with at least one selenium or tellurium atom initially was covered in CHEC-II(1996), 6.24. This topic was not discussed specifically in CHEC(1984). Although the organization of this chapter follows the general format, the individual heterocyclic ring systems are arranged as in CHEC-II(1996), 6.24. A number of novel ring systems have been reported in this area since CHEC-II(1996). Some quite simple ring systems, including many tellurium-based structures (e.g., ditelluranes), have not appeared in the literature since the publication of CHEC-II(1996). Structures of heterocyclic systems discussed in this chapter are included in [Figure 1](#). One major review of tellurium-containing heterocycles has appeared [<1994M1>](#).

9.15.2 Theoretical Methods

Theoretical studies of six-membered ring molecules with two or more heteroatoms containing at least one selenium or tellurium have been relatively limited since CHEC-II(1996). One such study deals with determining the optimum geometries of 1,2-dichalcogenins **1–3**. These compounds are predicted to be nonplanar with puckered structures [<2000JA5065>](#). These results are consistent with ^{77}Se NMR shift data.



The dimerization of α,β -unsaturated selenoaldehydes (selenals) and selenoketones (selones) is known to proceed in a ‘head-to-head’ fashion (see [Schemes 21 and 22](#)). This transformation has been studied at the density functional theory (DFT) level using selenoacrolein **4** as a model ([Scheme 1](#)) [<1999JOC1565>](#). These calculations indicate that even though both types of dimerization have very low energy barriers (0.9–2.8 kcal mol^{−1}), ‘head-to-head’ dimerization is thermodynamically favored over ‘head-to tail’ addition by about 14 kcal mol^{−1}. The optimized geometries of the product diselenanes **5** and **6** have also been determined. The *cis*-compounds prefer the half-chair conformation while the *trans*-isomers prefer boat-like conformations.

Ab initio molecular orbital calculations at the MP2 level have been carried out on halogen addition to R₂Se models to understand the factors determining whether selenium-containing heterocyclic compounds including selenanthrene **7** form trigonal bipyramidal adducts such as **8** or molecular complexes such as **9** [<1999JOC2630>](#) ([Scheme 2](#)). These results were compared with nuclear magnetic resonance (NMR) studies (see [Section 9.15.3.2](#)). Structural information – bond lengths

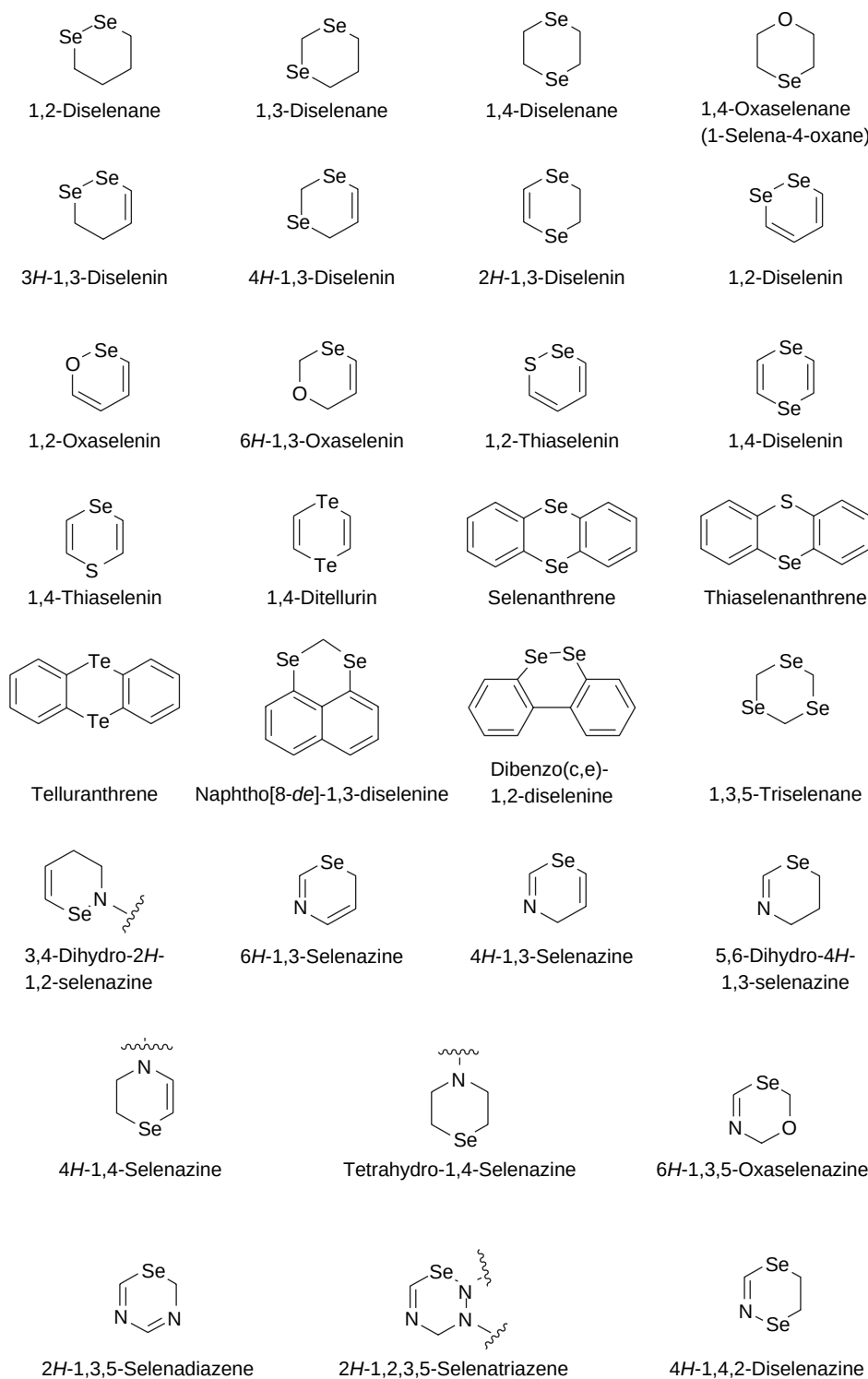
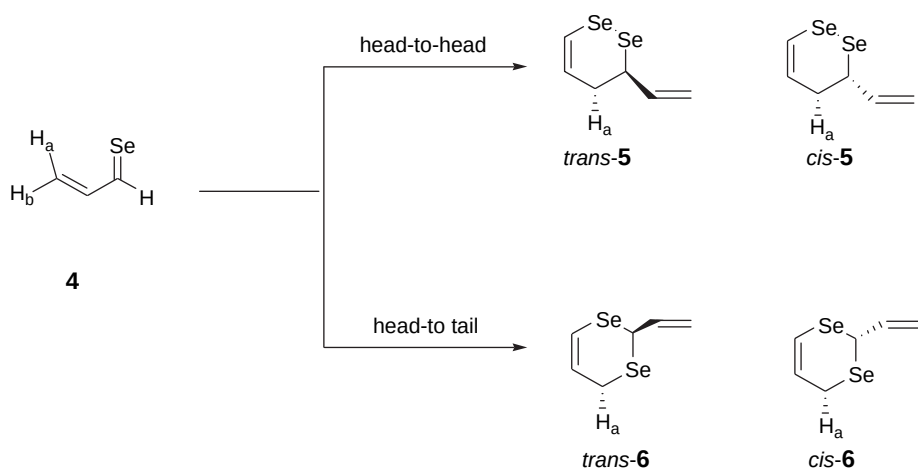
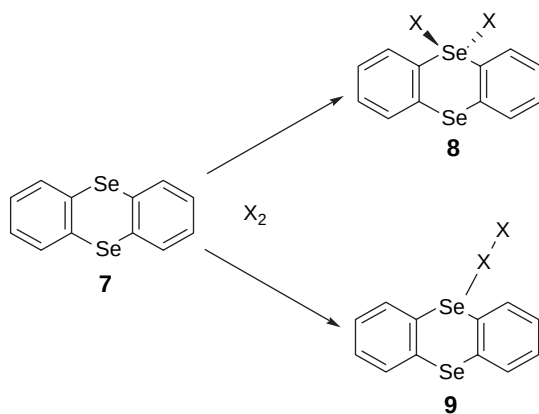


Figure 1 Structures and nomenclature of heterocyclic ring systems discussed in this chapter.

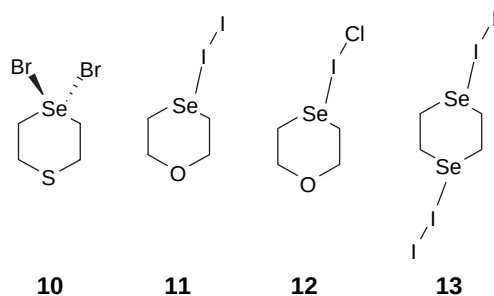
and bond orders – dealing with a related trigonal bipyramidal adduct **10** and variety of charge transfer complexes **11–13** were also reported. Another report, also at the MP2 level, deals with elucidating bonding in structures of crystals formed when selenanthrene reacts with bromine in a ratio of (7:Br₂) = (4:5) [<2004CC140>](#) (see Structure **24**, Section 9.15.3.1).



Scheme 1



Scheme 2

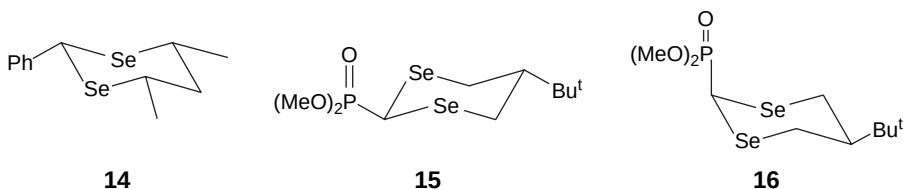


9.15.3 Experimental Structural Methods

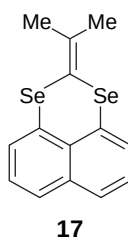
9.15.3.1 X-Ray Structures

The crystal structure of *cis*-4,6-dimethyl-2-phenyl-1,3-diselenane **14** has been published <1998AXC1505> and two other crystal structures of 1,3-diselenanes **15** and **16** have been reported previously <1991TL4189>; however, the

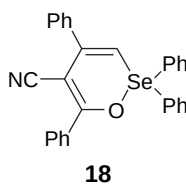
structures of these molecules were thought to be strongly affected by the phosphoryl substituent (cf. CHEC-II(1996), 6.24.21.1). As expected, introduction of Se atoms into a cyclohexane ring results in an increased C–Se bond length relative to the C–C bond length in cyclohexane. The C–Se–C bond angle is also smaller than that in cyclohexane.



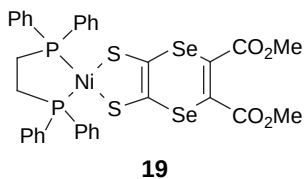
The X-ray structure of naphtho[8-*de*]-1,3-diseleninylidene **17** has been reported and shows an Se–Se distance of 3.216(1) Å which is significantly shorter than twice the van der Waals radius of selenium (4.00 Å).



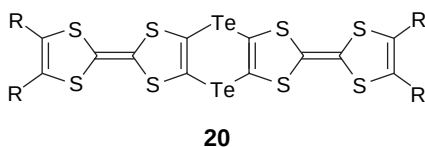
An X-ray crystal structure determination of **18**, the first member of the 1,2-oxaselenin ring system to be isolated, has been published <1998JOC6382>. These heterocycles are also known as [10-Se-4(C3O)] oxyselenuranes. This X-ray confirmed the covalent bond between oxygen and selenium in this molecule (see Section 9.15.6.1). The O–Se–C bond angle of 173.5° in this molecule is approximately collinear, indicating a very distorted six-membered ring.



The X-ray structure of a metal complex containing a 1,4-selenine moiety **19** has been reported <1997CC2293>. The diselenine structure is folded, with the plane containing the ester substituents inclined by about 50° to the plane containing the sulfur atoms.



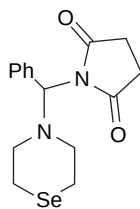
X-Ray structure determinations of **20a** and **20b** have been carried out in which the 1,4-ditellurin molecule in the crystal displays ‘sombbrero-like’ nonplanar conformations <1994TL8489, 1994CC2115>.



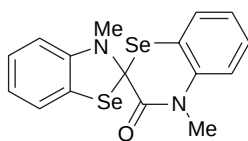
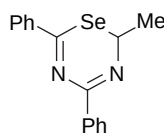
a: R = MeS (26%)

b: R = Me (63%)

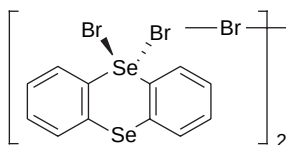
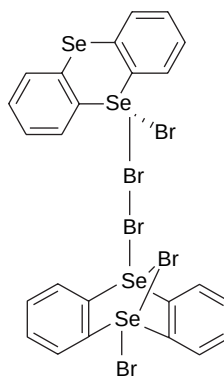
Preliminary X-ray crystal structure data of a 1,4-selenazine, *N*-[α -(*N*-succinidyl)-benzyl]selenamorpholine **21** have been published <1998AXCii>. In this molecule the selenazine adopts a chair conformation.

**21**

The structure of the spiro 1,4-benzoselenazin-2-one **22** was confirmed by an X-ray crystal determination (see Equation 42) <2001CC1336>. The crystal structure of 2,4-diphenyl-6-methyl-1,3,5-selenadiazene **23** was used to distinguish between possible isomeric structures for the molecule <2001BCJ511>.

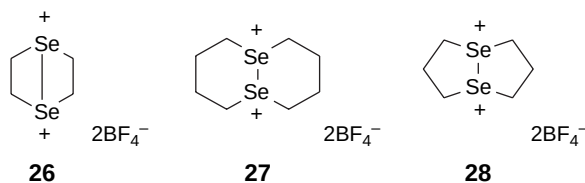
**22****23**

Two crystalline molecular complexes of selenanthrene with bromine with a ratio of selenanthrene to bromine of 4:5 have been isolated <2004CC140, 2000JOM178>. A key feature of these 'partial structures' **24** and **25** is the linear nature of the bromine atoms in these nonionic complexes.

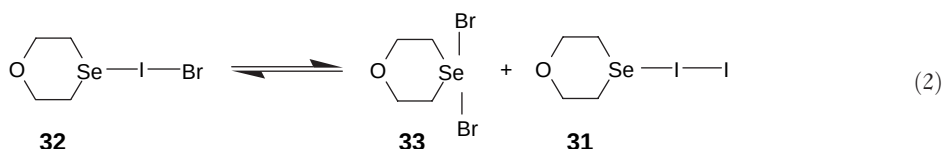
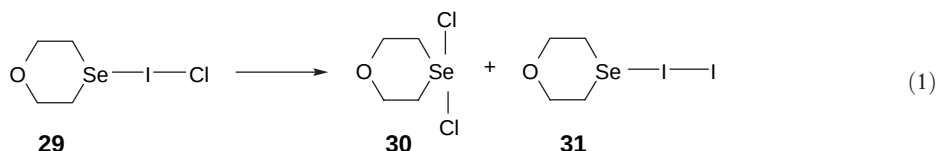
**24****25**

9.15.3.2 NMR Spectroscopy

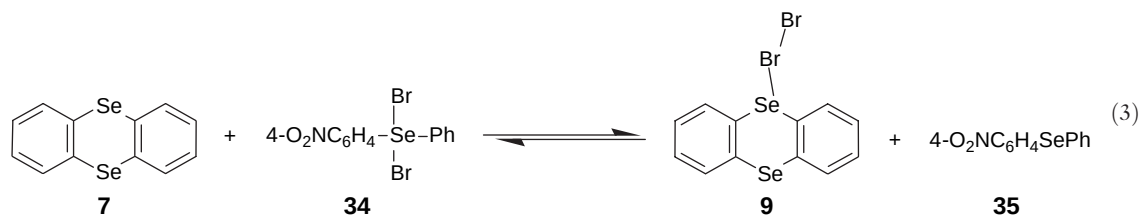
A number of NMR studies on unusual six-membered ring molecules containing two or more heteroatoms with at least one selenium or tellurium atom have appeared since CHEC-II(1996) was published. 1,4-Diselenoniabicyclo[2.2.0]hexane bis-(tetrafluoroborate) **26** was characterized spectroscopically, particularly by ^1H , ^{13}C , and ^{77}Se NMR. The ^{77}Se NMR shifts are remarkably downfield, δ 1202, relative to other selenium dications **27** and **28** (δ 439, 807, respectively).



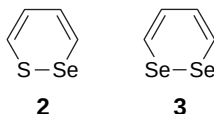
Detailed ^{13}C NMR studies have been carried out on 1-selena-4-oxane and the adducts formed in the presence of iodine monochloride, iodine monobromide, chlorine, bromine, and iodine [<1999JOC2630>](#). In deuterated chloroform solution the 1-selena-4-oxane molecular complex **29** affords equimolar amounts of bipyramidal adduct **30** and the molecular complex **31** (Equation 1). No such mixture was observed in the solid state. When NMR studies were carried out on the corresponding bromine complex **32**, an equilibrium between the complex **32** and adducts **33** and **31** was observed (Equation 2).



The relative stabilities of the molecular complex **9** compared to the trigonal bipyramidal adduct **34** were determined by ^1H NMR studies (Equation 3) [<1999JOC2630>](#). When an equimolar amount of **7** was added to a solution of **34** in CDCl_3 , the molar ratios of **7**:**34**:**9**:**35** were shown to be 0.36:0.36:0.64:0.64. When an additional equivalent of **7** was added to the mixture, the ratios became 1.18:0.19:0.82:0.81. These results indicate that the molecular complex **9** is more stable than the trigonal bipyramidal adduct **34**.



Detailed spectroscopic information including ^{77}Se data has been described for 1,2-dichalcogenins **2** and **3**. The ^{77}Se NMR shift of 1,2-diselenin **3** appears at high field relative to open chain diselenides [<2000JA5052>](#). The ^{77}Se chemical shifts were calculated also using the gauge-independent atomic orbital (GIAO) method.

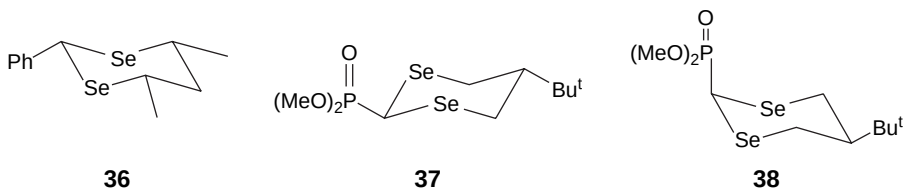


9.15.4 Thermodynamic Aspects

9.15.4.1 Conformational Analysis

Conformations of a variety of 1,3-diselenanes were discussed in detail in CHEC-II(1996), 6.24.2.1.1. The structure of *cis*-4,6-dimethyl-2-phenyl-1,3-diselenane **36** has been determined by X-ray crystallography [<1998AXC1505>](#)

(see Section 9.15.3.1). The conformation is predominately chair (94%) with only a small contribution from the boat conformation. The observed structure actually corresponds well to the structures of the previously reported phosphoryl derivatives **37** and **38** <1991TL4189>.



Conformational effects seem to be important in deprotonation of 1,3-diselenanes <1996TL2667> (see Table 1).

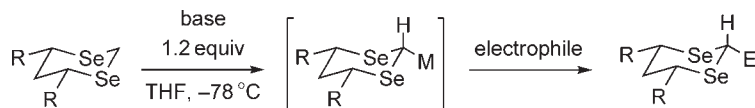
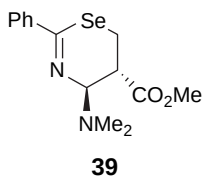


Table 1 Metallation of diselenanes

No.	R	Base	Electrophile	E	Yield (%)	(cis/trans)	Reference
i	H	LDA, 2 h	MeI	Me	85		1996TL2667
ii	H	LDA, 2 h	PhCHO	PhCHOH	76		1996TL2667
iii	Me	LDA, 2 h	MeI	Me	50	(100:0)	1996TL2667
iv	Me	KDA, 2 h	MeI	Me	70	(100:0)	1996TL2667
v	Me	KDA, 2 h	MeOD	D	87	(100:0)	1996TL2667
vi	Me	KDA, 2 h	1. CO ₂ , 2. CH ₂ N ₂	CO ₂ Me	45	(95:5)	1996TL2667
vii	Me	KDA, 2 h	PhSeSePh	PhSe	90	(98:2)	1996TL2667
viii	H	BuLi	MeSeSeMe	MeSe	81	(100:0)	1996TL8015

NMR studies indicate that the 5,6-dihydro-4*H*-1,3-selenadiazine **39** adopts a half-chair conformation in solution <1998T2545>.



9.15.5 Diselenanes and Ditelluranes

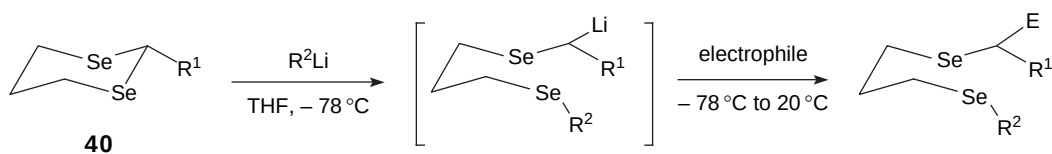
9.15.5.1 1,3-Diselenanes

9.15.5.1.1 Structural studies

X-Ray structures and conformational studies of 1,3-diselenanes were discussed in Sections 9.15.3.3 and 9.15.4.1.

9.15.5.1.2 Reactions

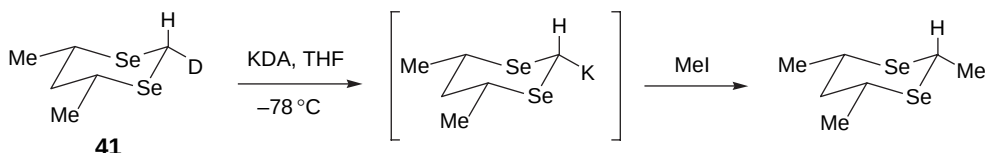
Attempts at direct metallation of 1,3-diselenanes have been unsuccessful until recently (cf. CHEC-II(1996), 6.24.2.2.2). While alkylolithium reagents readily metallate cyclic thioacetals, the corresponding reaction of selenoacetals **40** leads to ring cleavage at a C–Se bond affording α-selenoalkyl lithium compounds (Scheme 3) <1996TL2667, 1996TL8011>. These compounds can be trapped by electrophiles.



Scheme 3

Detailed investigations of conditions for metallations of 1,3-diselenanes by Krief and co-workers have led to useful procedures for these transformations [<1996TL2667, 1996TL8011, 1996TL8015>](#). 1,3-Diselenanes are metallated by lithium diisopropylamide (LDA) or potassium diisopropylamide (KDA) in tetrahydrofuran (THF) at low temperature. The latter reagent appears to be more efficient, particularly in conformationally rigid systems (see [Table 1](#), entries iii and iv).

The stereochemistry of the metallation reactions of 2-substituted 1,3-diselenanes has also been investigated [<1996TL2667>](#). An experiment using the deuterated substrate **41** showed that KDA stereoselectively removes the equatorial deuterium despite an unfavorable isotope effect. This has been explained by the strong preference of an unshared pair of electrons to take the equatorial position in cyclohexanes. Methylation of this carbanion introduces the new methyl substituent into an equatorial position ([Scheme 4](#)).



Scheme 4

Similar equatorial preferences have been noted in metallation reactions of other substituted 1,3-diselenanes ([Table 2](#)).

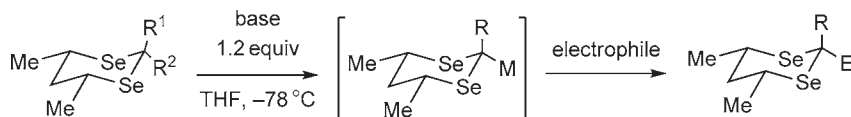


Table 2 Metallation of 2-substituted diselenanes

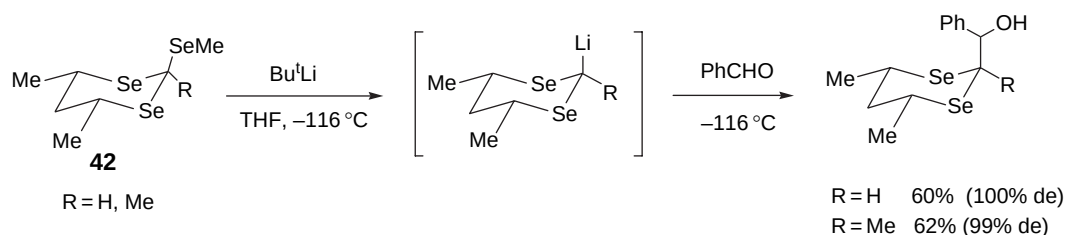
No.	R^1	R^2	Base	Electrophile	E	R	Yield (%)	(cis/trans)	Reference
i	H	Me	BuLi	PhCHO	PhCHOH		nr		1996TL8011
ii	H	Me	Bu ^t Li	PhCHO	PhCHOH		nr		1996TL8011
iii	H	Me	Bu ^s Li (2 h)	PhCHO	PhCHOH	Me	47	(99:1)	1996TL8011
iv	H	Me	Bu ^s Li (6 h)	PhCHO	PhCHOH	Me	78	(99:1)	1996TL8011
v	H	Ph	PhLi, HMPA	MeI	Me	Ph	70	(100:0)	1996TL8011
vi	H	Ph	MeLi, HMPA	MeI	Me	Ph	60	(100:0)	1996TL8011
vii	Ph	H	PhLi	MeI	Me	Ph	68	(100:0)	1996TL8011
viii	Ph	H	MeLi	MeI	Me	Ph	65	(100:0)	1996TL8011
ix	H	SeMe	LDA	MeOH	H	SeMe	95	(100:0)	1996TL8015
x	H	SeMe	LDA	MeI	Me	SeMe	93	(100:0)	1996TL8015
xi	H	Ph	LDA	PhCHO	PhCHOH	Ph	nr		1996TL2667
xii	H	Ph	KDA	PhCHO	PhCHOH	Ph	75	(100:0)	1996TL2667
xiii	H	Ph	KDA	MeOH	H	Ph	98	(99:1)	1996TL2667
xiv	H	Ph	KDA	MeI	Me	Ph	100	(100:0)	1996TL2667

(Continued)

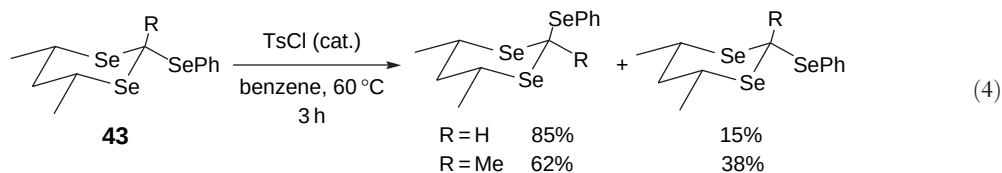
Table 2 (Continued)

No.	R ¹	R ²	Base	Electrophile	E	R	Yield (%)	(cis/trans)	Reference
xv	Ph	H	LDA	MeI	Me	Ph	95	(98:2)	1996TL2667
xvi	H	Me	LDA	MeOD	D	Me	nr		1996TL2667
xvii	H	Me	KDA	MeOD	D	Me	75	(100:0)	1996TL2667
xviii	H	Me	KDA	MeOH	H	Me	95	(98:2)	1996TL2667
xix	Me	H	KDA	MeOD	D	Me	75	(100:0)	1996TL2667
xx	SeMe	H	Bu ^t Li (−130 °C)	MeOD	H	D	85	(98:2)	1996TL8015
xxi	SeMe	H	Bu ^t Li (−98 °C)	MeOD	H	D	90	(95:5)	1996TL8015

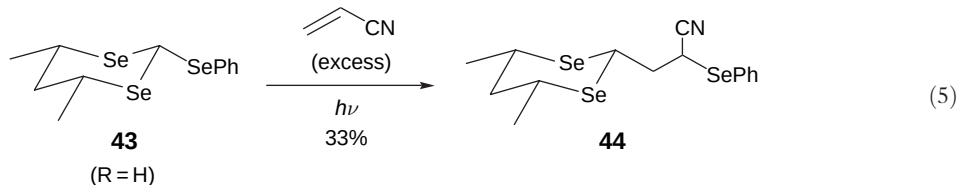
Axial organolithium compounds can be prepared by metallation of the axial 2-selenomethyl-1,3-diselenane **42** (Scheme 5) <1996TL8015>. The intermediate organolithium compound can be trapped by benzaldehyde with almost complete stereocontrol but does not react with less reactive electrophiles such as chlorotrimethylsilane.

**Scheme 5**

A rapid acid-catalyzed ‘contrathermodynamic’ isomerization of the 2-phenylseleno-1,3-selenanes **43** has been reported (Equation 4) <1996TL8015>.

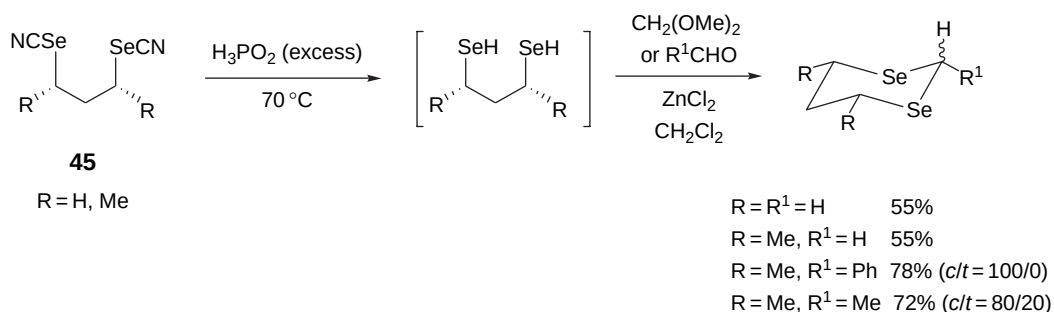


Irradiation of 2-phenylseleno-4,6-dimethyl-1,3-diselenane **43** (R = H) in the presence of acrylonitrile leads to insertion of an acrylonitrile unit into the molecule affording **44** in modest yield (Equation 5) <1996TL8015>.



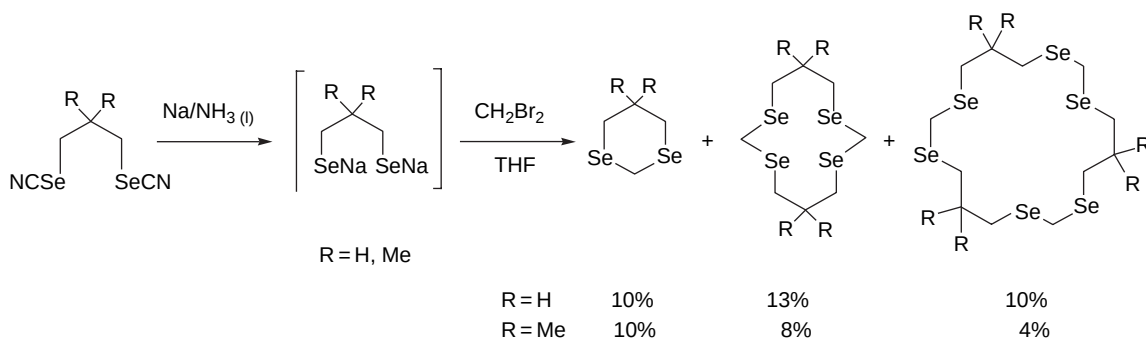
9.15.5.1.3 Synthesis

Alkylation reactions affording substituted 1,3-diselenanes have been discussed in the previous section. The desired precursor 1,3-diselenanes can be prepared by modifications of standard synthetic procedures (see CHEC-II(1996), 6.24.2.3.2). Treatment of bis-selenocyanates **45** with excess H₃PO₂ in the presence of aldehydes (or aldehyde equivalents) and ZnCl₂ provides a convenient route to the target compounds (Scheme 6) <1996TL2667>.



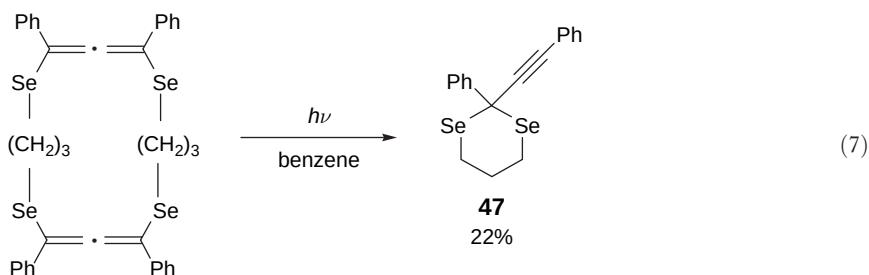
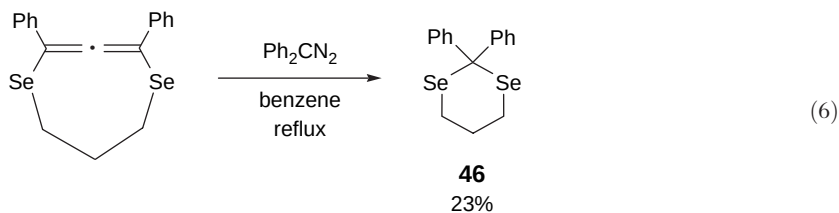
Scheme 6

1,3-Diselenanes have been isolated as by-products in the attempted formation of selenium corrands by reaction of 1,3-diselenolates with dibromomethane (Scheme 7) <1989JA6582>.



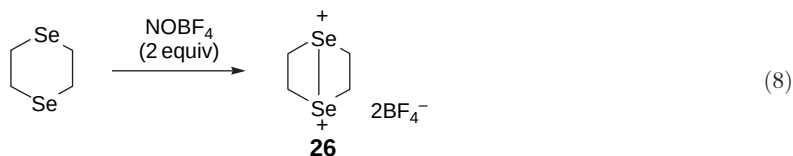
Scheme 7

Treatment of the diselenocyclic allene shown with diphenyldiazomethane in refluxing benzene affords 2,2-diphenyl-1,3-selenane **46** in modest yield (Equation 6) <2001JOC7202>. Presumably, the reaction involves a complex series of diphenyldiazomethane additions, losses of nitrogen, and rearrangements. Irradiation of the diallene shown affords the acetylenic diselenane **47**, again in modest yield (Equation 7) <2001JOC1787>.



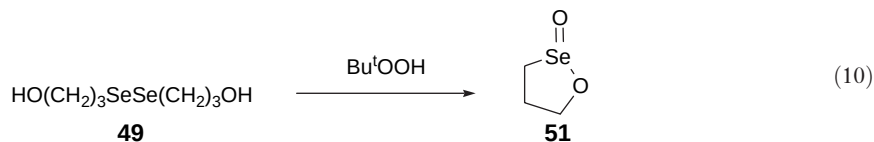
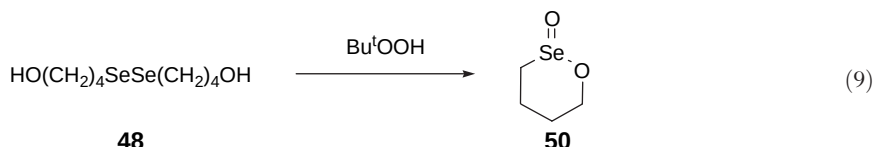
9.15.5.2 1,4-Diselenanes

1,4-Diselenane has been oxidized with 2 equiv of nitrosonium tetrafluoroborate to afford the stable diselenide dication, 1,4-diselenoniabicyclo[2.2.0]hexane bis-(tetrafluoroborate) (**26**) (Equation 8) <1993T1605>. This dication ditetrafluoroborate salt was characterized spectroscopically, particularly by ^1H , ^{13}C , and ^{77}Se NMR (see Section 9.15.3.2).



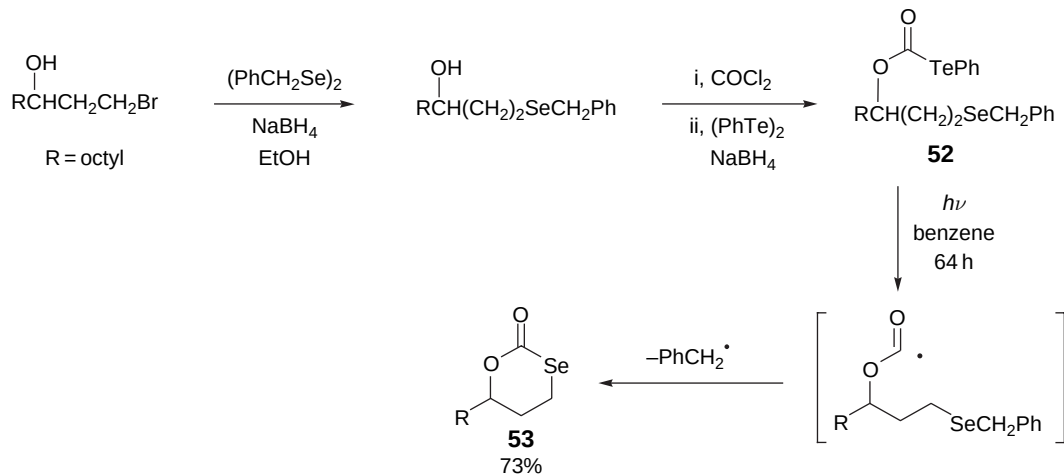
9.15.5.3 1,2-Oxaselenanes

Cyclic seleninate esters have been implicated in catalytic cycles in which diselenides act as glutathione peroxidase mimetics <2003JA13455> (see Section 9.15.11). Treatment of the diselenides **48** and **49** with excess *tert*-butylhydroperoxide leads to the formation of the first unsubstituted isolable cyclic seleninates **50** and **51** (Equations 9 and 10). The six-membered ring compound **50** proved to be a less effective catalyst than **51** in the former reactions.



9.15.5.4 1,3-Oxaselenanes

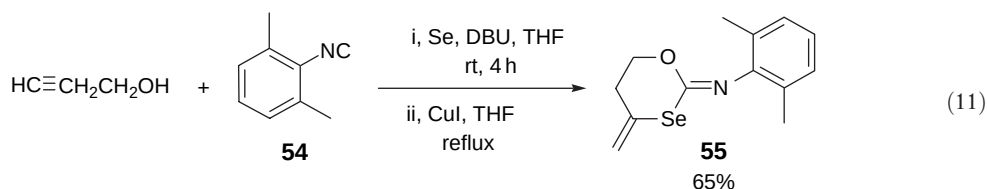
The previously unknown 1,3-oxaselenan-2-one ring system **53** can be prepared in high yield by a tellurium radical-promoted fragmentation and ring closure of the telluroformate **52** (Scheme 8) <1998JOC3032>. Formation of the



Scheme 8

six-membered ring appears to be favored over the corresponding cyclization to a seven-membered ring. This intramolecular homolytic substitution reaction at selenium is also about three orders of magnitude faster than for the corresponding sulfur system. This reaction can also proceed thermally. Treatment of **52** at 160 °C in the dark for 79 h afforded **53** with a 56% conversion <1998JOC3032>.

The 2-imino-1,3-oxaselenenane ring system **55** can be prepared by the reaction of the sterically hindered isonitrile **54** with an acetylenic alcohol in the presence of selenium, cuprous iodide, and a base (Equation 11) <2004JOC4845>. This reaction probably occurs via the formation of an intermediate isoselenocyanate. The product was not formed in the absence of CuI.

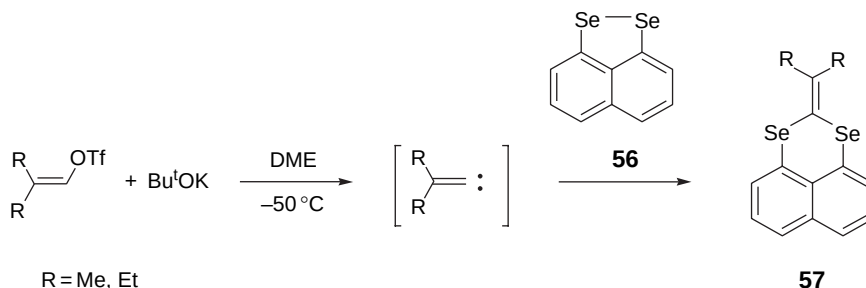


9.15.5.5 1,4-Oxaselenanes

NMR studies of halogen adducts of 1,4-oxaselenin (1-selena-4-oxanes) have been described previously (see Section 9.15.2, Structures **11,12** and Section 9.15.3, structures **29–33**).

9.15.5.6 Related Structures

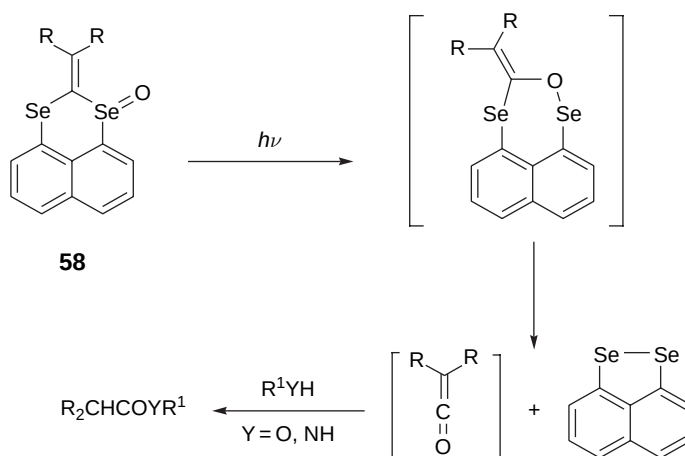
Naphtho[8-*de*]-1,3-diseleninylienes **57** can be prepared by the addition of unsaturated carbenes to naphtho[8-*de*]-1,3-diselenole (Scheme 9) <1999TL5211>. These carbenes can be prepared and are known to insert into Se–Se and Te–Te bonds <1984JOC1653>. The structure of the dimethyl derivative has been described previously (see Section 9.15.3.1) and exhibits a particularly short Se–Se distance, less than the twice the van der Waals radius of selenium.



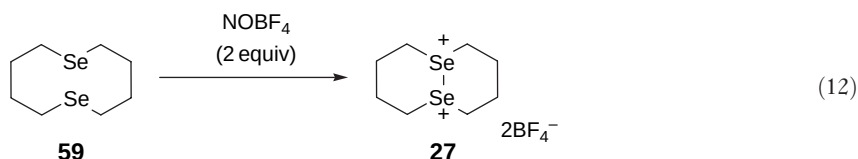
Scheme 9

Photolysis of naphtho[8-*de*]-1,3-diseleninylidene 1-oxides **58** provides an efficient method for generating ketenes which can be trapped by various nucleophiles (Scheme 10) <1999TL5211>. The proximity of the selenium atoms in **58** may allow for a ready rearrangement of the excited selenoxide to the corresponding selenenic ester. Based on the previously mentioned short Se–Se distance in **57** and on structural studies of the analogous sulfur species, the corresponding Se–Se distance in the selenoxide would be predicted to be even shorter, favoring the observed, ready ketene extrusion.

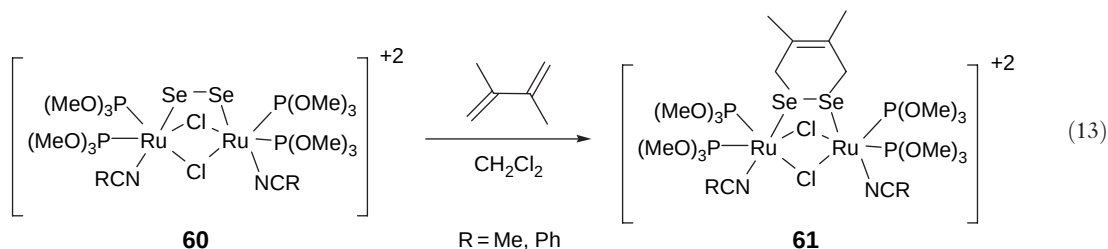
Treatment of the cyclic bis-selenide, 1,6-diselenacyclodecane **59**, with nitrosonium tetrafluoroborate affords the ring-fused diselenide dication **27** (Equation 12) <1993T1605>. The dication ditetrafluoroborate salt was characterized spectroscopically using ¹H, ¹³C, and ⁷⁷Se NMR and gave a correct elemental analysis for the structure described (cf. Section 9.15.3).



Scheme 10



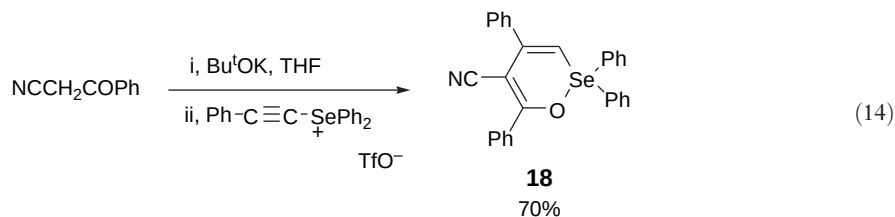
Cycloaddition of 2,3-dimethylbutadiene with the dicationic diselenido-bridged dinuclear ruthenium complex **60** affords the dicationic complex containing a diselenin structure **61** (Equation 13) <2001CL306>.

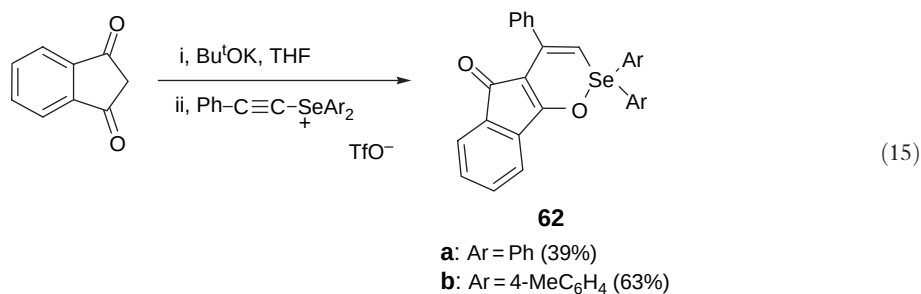


9.15.6 Oxaselenins, Oxatellurins, Diselenins, and Ditellurins

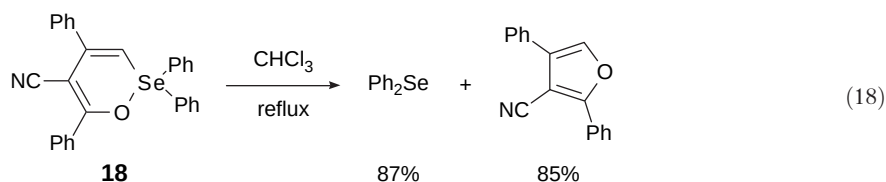
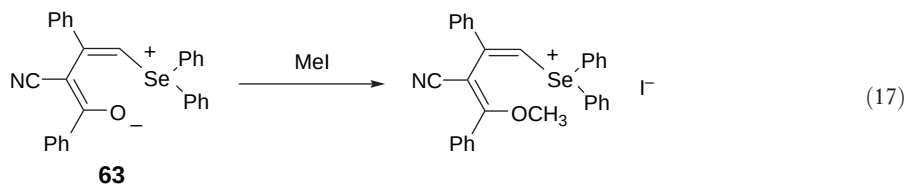
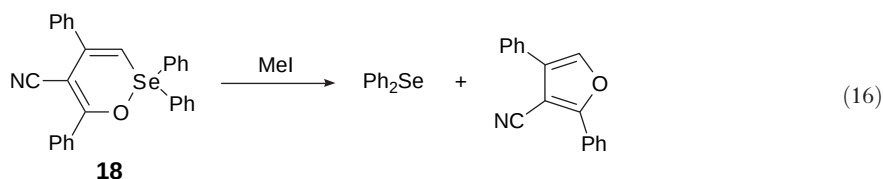
9.15.6.1 1,2-Oxaselenins

Treatment of diaryl(phenylethynyl)selenonium triflates with active methylene compounds provides the first reported syntheses of 1,2-oxaselenins **18** and **62** (Equations 14 and 15) <1998JOC6382>. These heterocycles are also known as [10-Se-4(C3O)] oxyselenuranes.



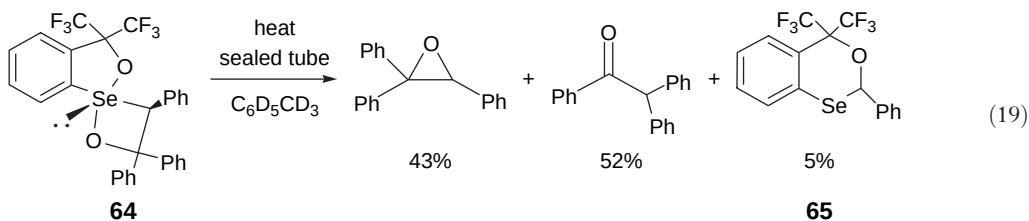


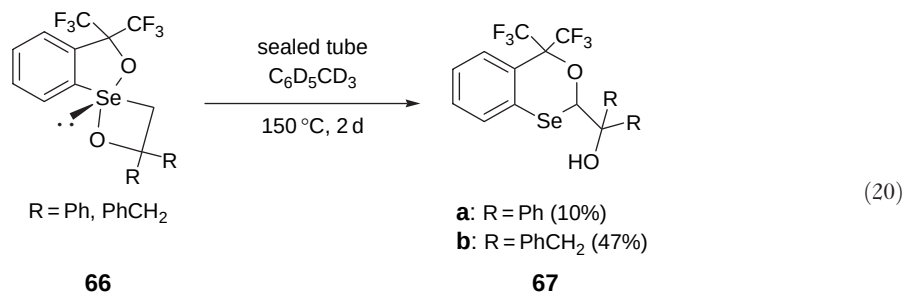
Complete determination of the structure of these compounds required evaluation of both chemical and physical data. The observed chemical reactivity favors the indicated cyclic structure. Oxaselenin **18** is transformed into the corresponding furan and diphenylselenide upon treatment with methyl iodide (Equation 16). The alternative betaine structure **63** would be expected to afford the methoxyselenonium salt under these conditions (Equation 17). Refluxing **18** in chloroform, or allowing the chloroform solution of **18** to stand at room temperature, also led to the formation of the selenide and corresponding furan (Equation 18). The structure of **18** was confirmed ultimately by X-ray crystallography (see Section 9.15.3.1).



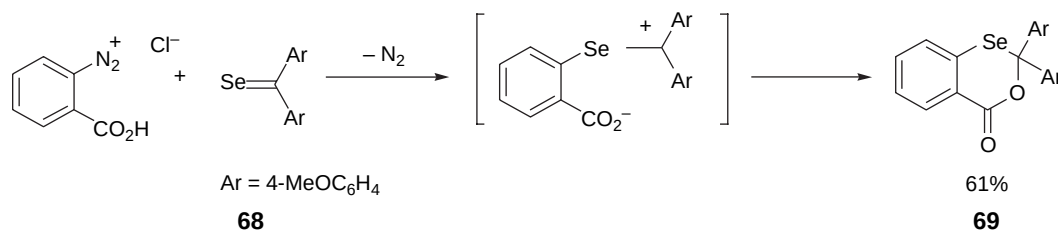
9.15.6.2 3,1-Oxaselenins

The ring-expanded 4*H*-3,1-benzoxaselenin **65** is formed as a minor by-product in the thermolysis of 1,2-λ⁴-oxaselenetane **64** (Equation 19) <1997CL1671>. The 4*H*-3,1-benzoxaselenin **67** is the major product in the thermolysis of the related spiro-1,2-oxaselenetane **66** (Equation 20) <1993JA10434>.





Treatment of benzenediazonium-2-carboxylate with 4,4'-dimethoxybenzophenone selone **68** affords 2,2-bis(4-methoxyphenyl)-4*H*-3,1-benzoxaseleninone **69** in good yield (Scheme 11) <1994J(P1)2151>. The reaction occurs using diphenyliodonium-2-carboxylate as a precursor, although the yield is lower (25%). These reactions do not occur via typical benzyne-like mechanisms, but rather via initial displacement followed by cyclization to the benzoxaseleninone.

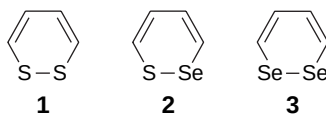


Scheme 11

9.15.6.3 1,2-Diselenins and 1,2-Thiaselenins

9.15.6.3.1 Structural and theoretical studies

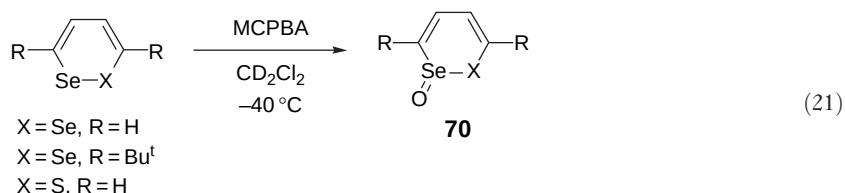
Preparations of the parent 1,2-dichalcogenins, 1,2-dithiin **1**, 1,2-thiaselenin **2**, and 1,2-diselenin **3**, and simple derivatives have been reported <1999AGE1604, 2000JA5052>. Complete ^1H , ^{13}C , ^{77}Se NMR data on these compounds have been described, as well as UV-Vis characterization <2000JA5052> (see Section 9.15.3.2). Although 1,2-dichalcogenins lack a normal chromophore, they are highly colored molecules. Photoelectron spectroscopy was used to probe their ionization energies and orbital assignments <2000JA5065>. These compounds exhibit a sharp ionization corresponding to removal of an electron from the weak chalcogen–chalcogen σ -bond. These results were compared with theoretical calculations (see Section 9.15.2). The geometries of the radical cations of **1–3** are predicted to be planar. The intense color of these compounds arises due to a low-energy highest occupied molecular orbital (HOMO) to lowest unoccupied molecular orbital (LUMO) transition described as a $\pi/\text{lone pair}$ to σ^* transition.



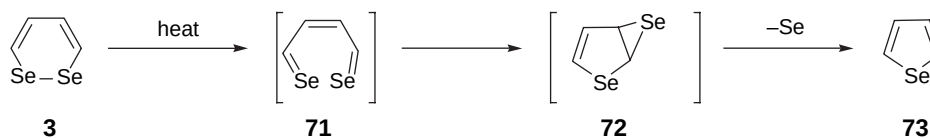
9.15.6.3.2 Reactions

1,2-Diselenins and 1,2-thiaselenin could be oxidized at the selenium atom by *m*-chloroperbenzoic acid (MCPBA) at low temperature to the corresponding thermally unstable 1,2-diselenin-1-oxides (selenoselenates) and 2-thiaselenin-2-oxide **70** which were characterized spectroscopically (Equation 21) <2000JA5052>. Electrochemical oxidations of **1**

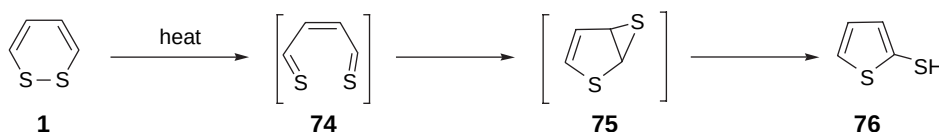
and **3** were studied by cyclic voltammetry. These compounds undergo an initial, reversible, one-electron oxidation to the radical cation followed by an irreversible oxidation at higher potential.



Heating of the 1,2-diselenin **3** at 200–300 °C in a GC–MS inlet led to a ring contraction affording selenophene **73** (Scheme 12) while the corresponding reaction of 1,2-dithiin **1** gave 2-thiophenethiol **76** (Scheme 13) <2000JA5052>. The mechanisms of these transformations presumably involve formation of the diselenal **71** and dithial **74**, which recyclize to the selenirane **72** and the corresponding thiirane **75**. Thermally, these intermediates behave differently with the selenirane directly extruding selenium to afford the aromatic system. The thiirane simply rearranges to 2-thiophenethiol **76**.

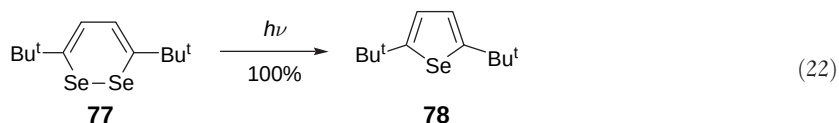


Scheme 12



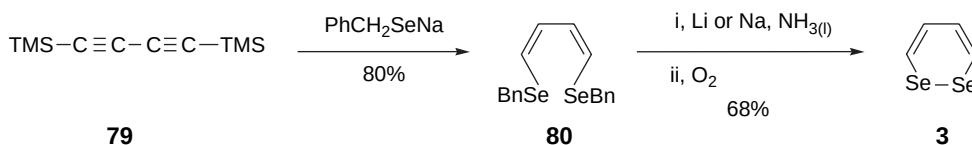
Scheme 13

Irradiation of the di-*tert*-butyl diselenine **77** leads to extrusion of selenium, affording 2,4-di-*tert*-butylselenophene **78** quantitatively (Equation 22) <2000JA5052>.



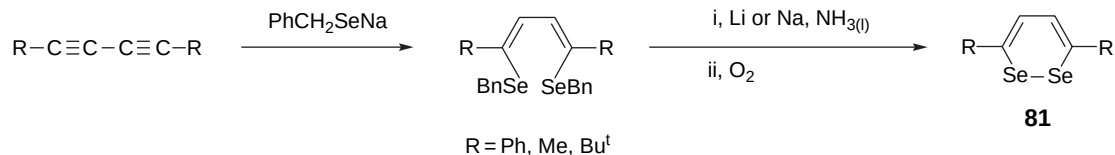
9.15.6.3.3 Synthesis

1,2-Diselenin and simple substituted derivatives have been prepared using a variety of strategies <1999AGE1604, 2000JA5052>. Treatment of the protected 1,3-butadiyne **79** in refluxing ethanol with sodium benzyl selenide (generated *in situ* by sodium borohydride reduction of the corresponding diselenide) afforded the (*Z,Z*)-1,4-bis(benzylseleno)-1,3-butadiene **80** in good yield. Dissolving metal reduction, followed by oxidation with molecular oxygen, afforded 1,2-diselenin **3** in 54% overall yield (Scheme 14).

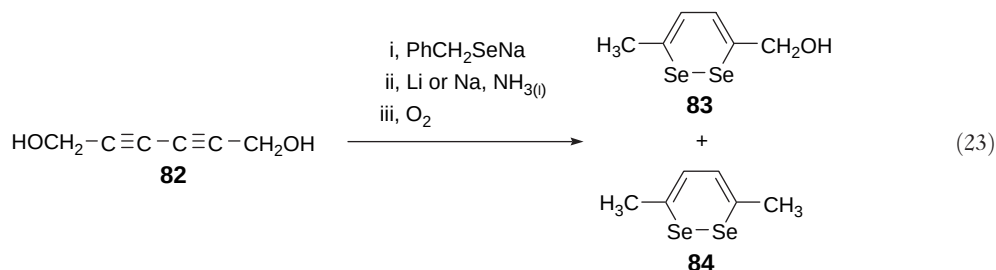


Scheme 14

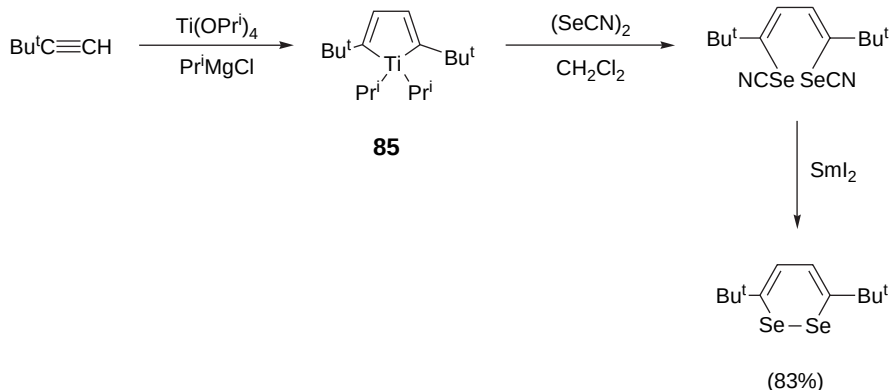
Substituted 1,2-diselenins **81** could be prepared similarly using substituted butadiynes (Scheme 15) <2000JA5052>. Reaction of the bis-hydroxymethyl derivative **82** led to a mixture of the readily separated hydroxymethyldiselenin **83** and dimethyldiselenin **84** by reductive cleavage of the allylic hydroxyl groups (Equation 23).



Scheme 15

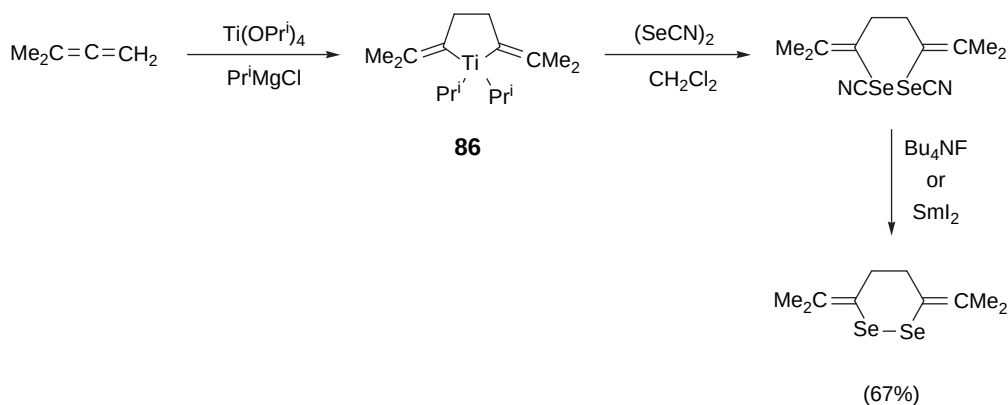


An alternative route to 1,2-diselenines involved titanium-mediated cyclizations of terminal alkynes or allenes, followed by trapping with selenocyanogen and then treatment with tetrabutylammonium fluoride or samarium(II) iodide (Schemes 16 and 17) <2000JA5052>. Mixed alkyne–allene reactions are also successful using this procedure (Scheme 18). Titanacycles **85–87** are key synthetic intermediates in these reactions.

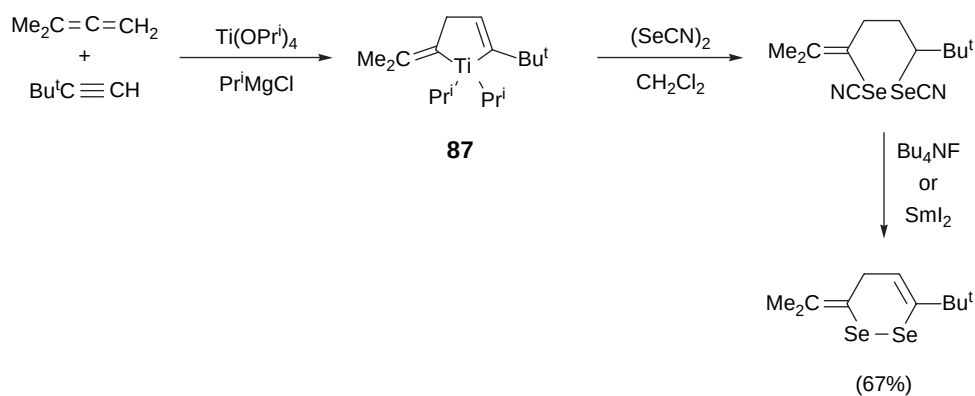


Scheme 16

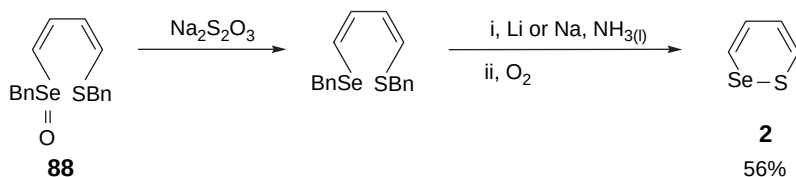
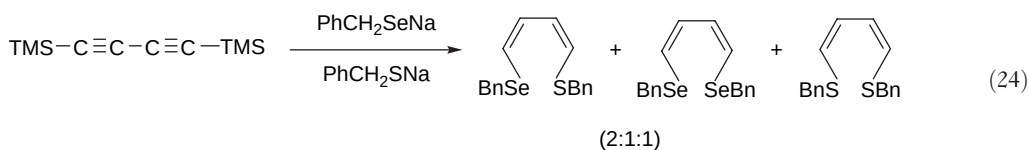
1,2-Thiaselenin **2** could be prepared using a method similar to that used for 1,2-diselenin <2000JA5052>. The diyne was treated with a mixture of the benzyl selenium and sulfur sodium salts to afford a mixture of thiobenzyl- and selenobenzyl-substituted dienes (Equation 24). Oxidation of this mixture with hydrogen peroxide removed the bis-benzylselenide as the Se,Se-bis oxide. Under these conditions the dithiin is not oxidized. The desired sulfide selenoxide **88** could be isolated by chromatography and reduced, first using sodium thiosulfate and then sodium in liquid ammonia. Oxidation with oxygen afforded the desired 1,2-thiaselenin (Scheme 19).



Scheme 17

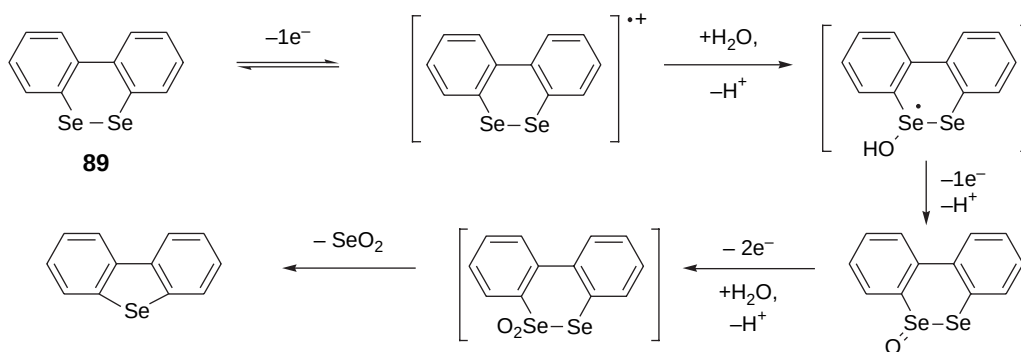


Scheme 18



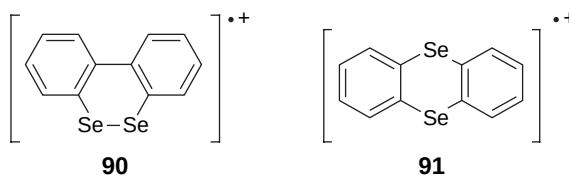
Scheme 19

The electrochemical oxidation of dibenzo(c,e)-1,2-diselenine **89** to its radical cation and further transformations have been described (Scheme 20) <1996JEC183>. In wet acetonitrile the oxidation has been shown to take place in two steps, the first an oxidation to the selenoxide followed by a further oxidation with extrusion of selenium dioxide to afford the corresponding selenophene <1992MI2077>.



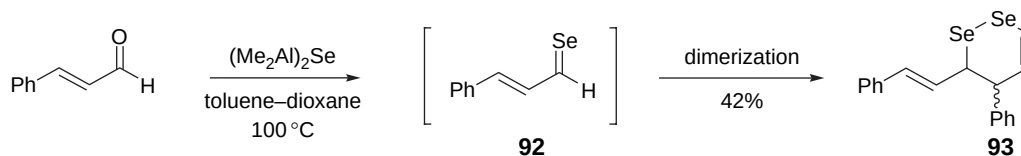
Scheme 20

The oxidation of **89** has been studied in dry acetonitrile using both conventional and microelectrode techniques [<1996JEC183>](#) and the results compared with those for its isomer selenanthrene. This study confirmed that radical cation reactivity in the case of the 1,2-dibenzo diselenins is greater than that of the 1,4-dibenzodiselenins. This difference in reactivity has been explained by the existence of a ‘three-electron’ selenium–selenium bond in the case of the radical cation of the 1,2-dibenzodiselenine, **90**. This bond is a $\sigma(p-p)$ bond with the additional electron promoted into the corresponding σ^* orbital. This bonding is not possible in the case of the radical cation of 1,4-dibenzodiselenine, **91**.

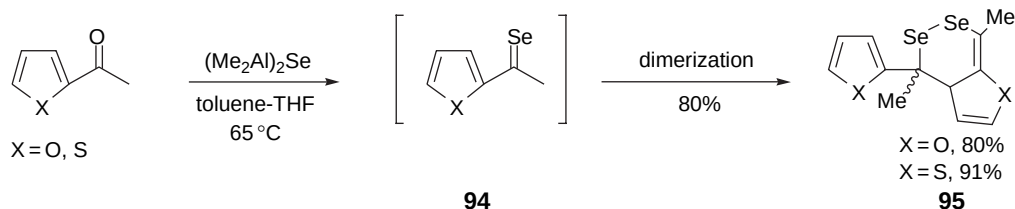


9.15.6.4 3H-1,2-Diselenines

Until relatively recently 3H-1,2-diselenines were not well represented in the chemical literature. Dimerization of *in situ* generated α,β -unsaturated selenals (selenoaldehydes) **92** or selones (selenoketones) **94** affords 3,4-dihydro-1,2-diselenines **93** and **95** (Schemes 21 and 22) [<1992TL3515, 1999JOC1565>](#). These [4+2] cyclization reactions are



Scheme 21



Scheme 22

regioselective, occurring in a 'head-to-head' fashion. Alternative methods of preparing selenals and selones, which may prove useful in the syntheses of other 3*H*-1,2-diselenines, have been reviewed <2005COFGT-II>.

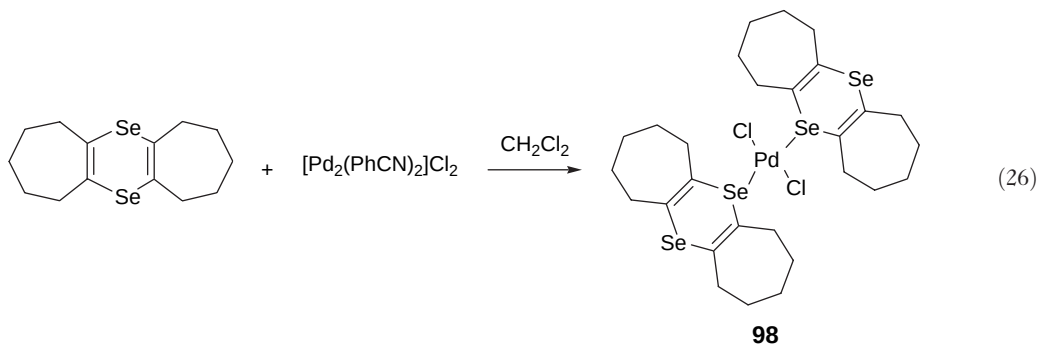
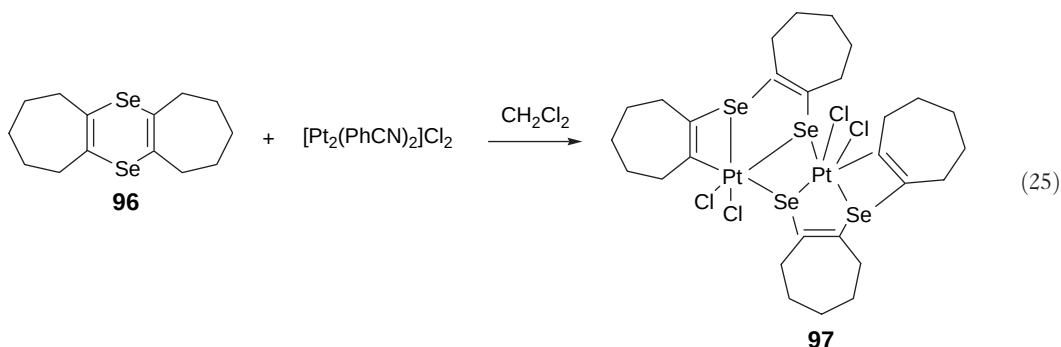
9.15.6.5 1,4-Diselenines

9.15.6.5.1 Structural studies

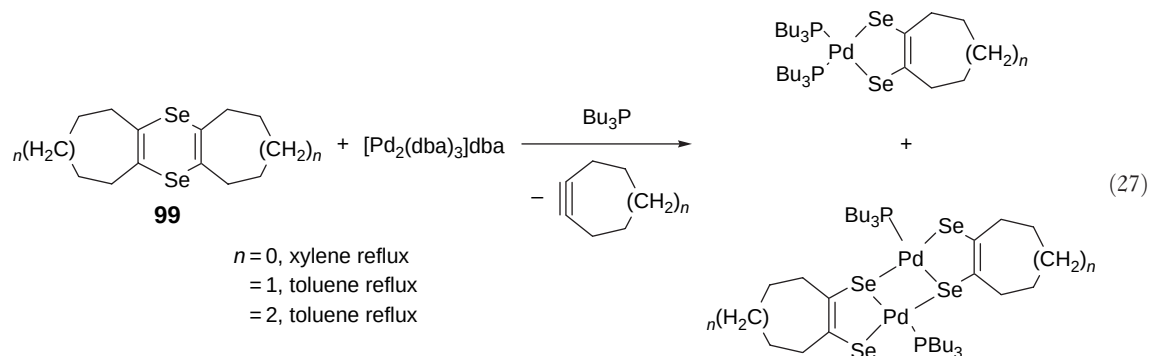
The X-ray structure of a metal complex containing a 1,4-selenine moiety, viz. **19**, has been described earlier <1997CC2293> (see Section 9.15.3.1).

9.15.6.5.2 Reactions

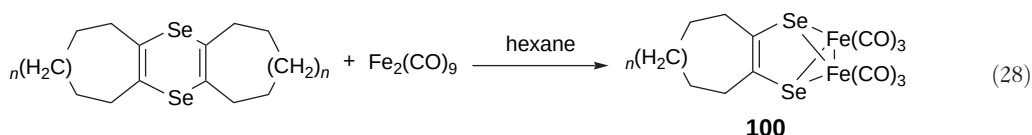
The cyclohepteno-1,4-diselenin **96** reacts with a platinum complex to afford a dimeric platinum(IV) product **97** via an unprecedented oxidative addition of platinum to a C–Se bond (Equation 25) <1997CC913>. A very different *trans*-complex **98** is formed from the corresponding palladium complex (Equation 26).



Other reactions of diselenines with metal complexes lead to ring cleavage. Ring-fused 1,4-diselenines **99** react with palladium complexes in the presence of tributylphosphine at elevated temperature to afford mixtures of mononuclear and dinuclear palladium complexes via expulsion of a cycloalkyne (Equation 27) <1999NJC811, 2004IC7101>.

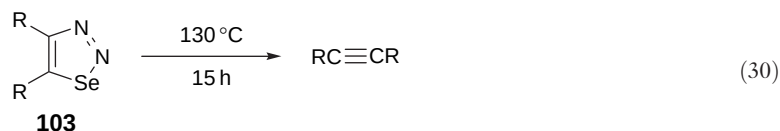
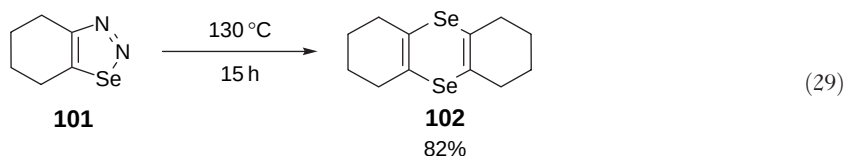


The same ring-fused selenines also react with diiron nonacarbonyl to afford diiron selenolates **100** (Equation 28) <1999JCD791>.

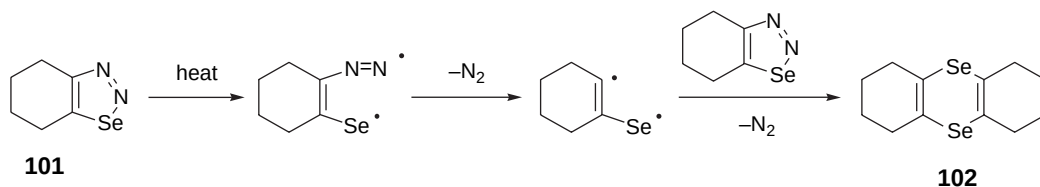


9.15.6.5.3 Synthesis

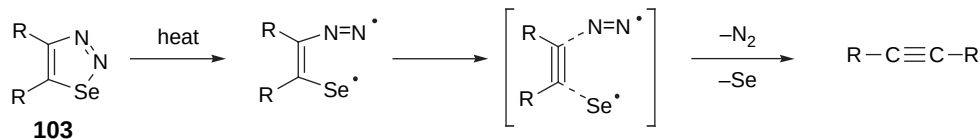
1,4-Diselenine **102** could be prepared in good yield by thermolysis of the 1,2,3-selenadiazole **101** (Equation 29) <2000JOM488>. The ring-fused 1,4-diselenines **99** mentioned previously were prepared in the same way <1999JCD791>. This reaction is unusual in the fact that pyrolysis of 1,2,3-selenadiazoles, **103**, derived from acyclic and aromatic ketones leads to the formation of alkynes generated as the sole isolable organic products in good yields (Equation 30).



The change in the relative courses of these reactions has been explained in terms of significantly different transition state geometries leading to these products (Schemes 23 and 24). The ring-fused derivative **101** cannot approach linearity in the transition state, preventing simultaneous extrusion of nitrogen and selenium as is observed in nonfused derivatives such as **103**.



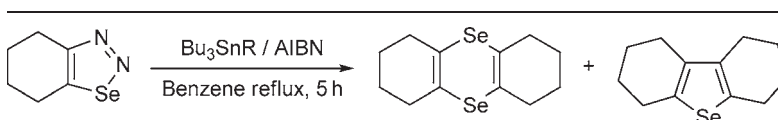
Scheme 23



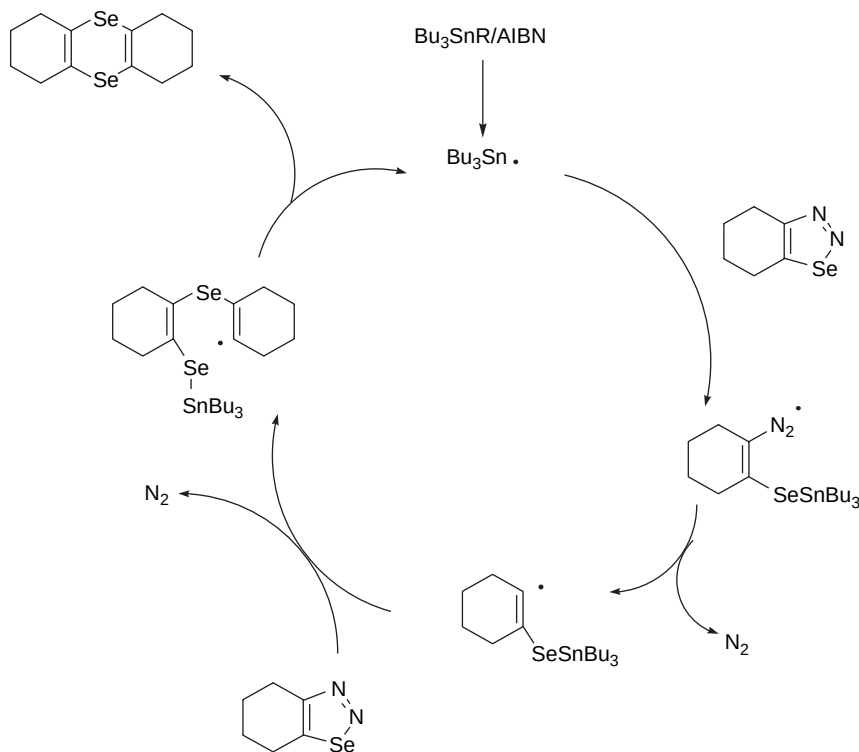
Scheme 24

Treatment of the 1,2,3-selenadiazole **101** with a catalytic amount of tri-*n*-butyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in refluxing benzene also affords 1,4-diselenine **102**, along with a small amount of the corresponding selenophene. When allyltributyltin/AIBN was used the diselenine yield was increased while the selenophene yield dropped. Under identical conditions without addition of the tin reagent and radical initiator only small amounts of the diselenine and the selenophene are formed (Table 3) <1999TL6293>.

Table 3 Reactions of selenadiazole **101** under radical conditions

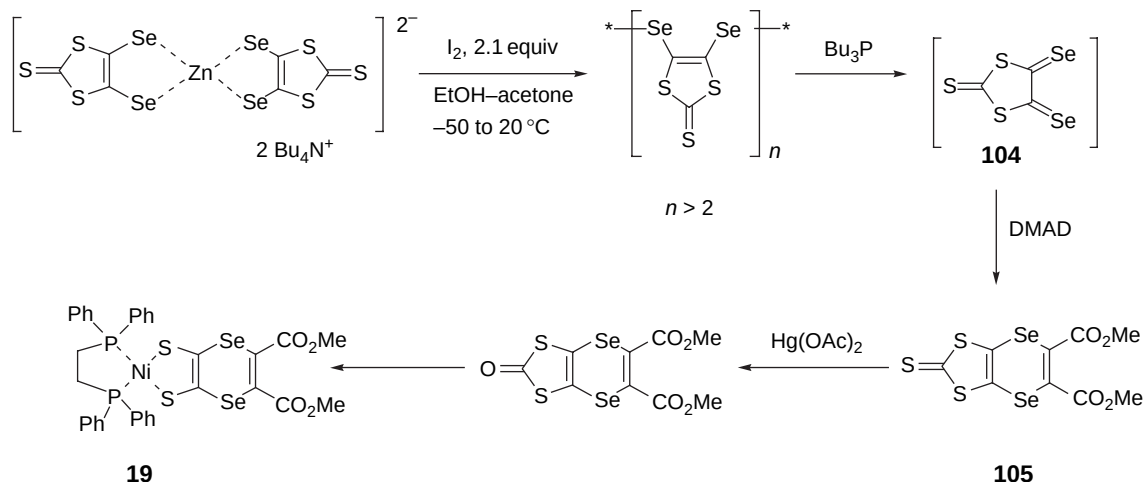
		
101	102	<i>Yield (%)</i>
$\text{Bu}_3\text{SnH/AIBN}$	77	15
$\text{SnBu}_3/\text{AIBN}$	81	7
No added reagents	17	2

These results have been explained by the catalytic process outlined in [Scheme 25](#) <2002JOC1520>.

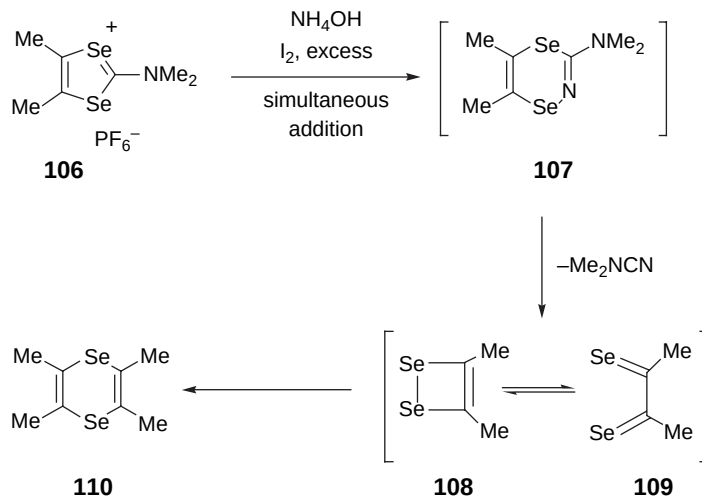
**Scheme 25**

A diselenine fused to the dithiolthione ring system **105** has been prepared using a multistep sequence involving trapping of an intermediate diselone **104** with dimethylacetylene dicarboxylate ([Scheme 26](#)) <1997CC2293>. The previously mentioned diselenine **19**, which was studied by crystallographic analysis, was prepared using this sequence.

Selenine **110** can be prepared through a multistep sequence, which also traps a possible diselone intermediate **109** ([Scheme 27](#)) <1996CC2375>. Simultaneous treatment of a 1,3-diselenolium salt **106** in acetonitrile with ammonium hydroxide and excess iodine affords the symmetrical diselenine, presumably through an intermediate 1,4,2-diselenazine **107** and 1,2-diselenete **108**. The diselenete **108** was presumed to be of lower energy than the tautomeric diselone **109**. Addition of dimethylacetylene dicarboxylate to a solution of isolated **107** at 20 °C gave the 1,4-diselenine diester in low yield, providing mechanistic evidence for the presumed selenete/diselone intermediates in the reaction (see [Section 9.15.7.2](#)).

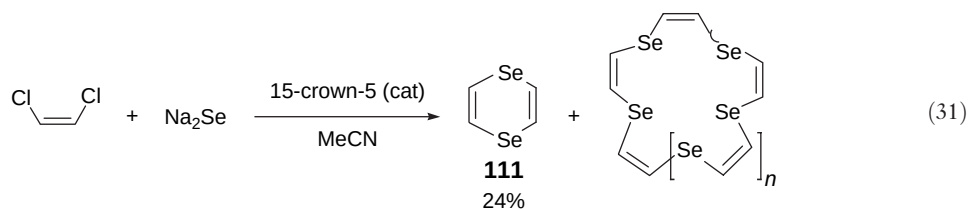


Scheme 26



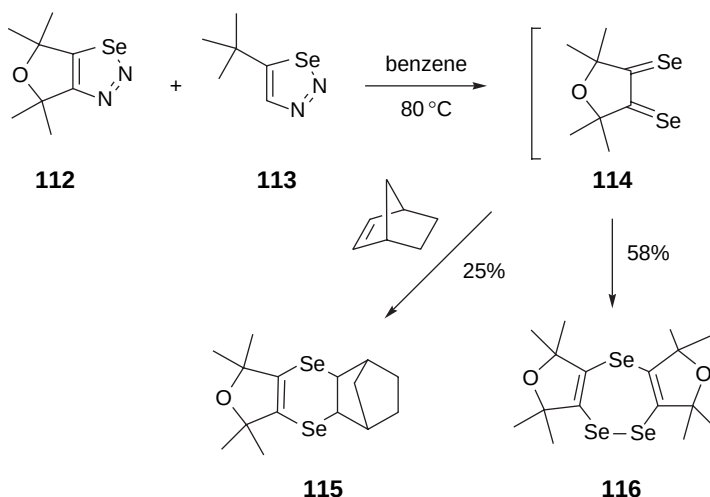
Scheme 27

The unsubstituted diselenene **111** could be prepared in up to 24% yield by direct reaction of *cis*-1,2-chloroethene with sodium selenide in acetonitrile in the presence of a crown ether (Equation 31) <2005JOC5036>. Although many congeners form, under certain circumstances **111** predominates. It is interesting to note that the sodium selenide used in this preparation could be prepared at room temperature by reaction of selenium with sodium hydroxide and Rongalit (sodium hydroxymethanesulfinate).



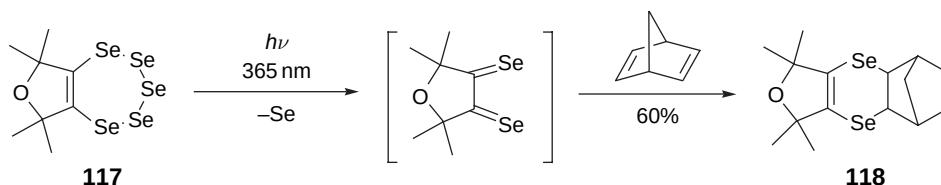
9.15.6.6 5*H*-1,4-Diseleninins

Treatment of the 1,2,3-selenadiazole **112** in refluxing benzene with 5-*tert*-butyl-1,2,3-selenadiazole **113** as a selenium atom source afforded an intermediate diselone **114** which could be trapped by norbornene to afford the dihydro-1,4-diseleninin **115** (Scheme 28) <1987TL5699>. If the reaction is run without a trapping agent, the main product is the 1,2,5-triselenepin **116**.



Scheme 28

Irradiation of the 1,2,3,4,5-pentaselenepin **117** in the presence of norbornadiene affords a 5*H*-1,4-diseleninin **118**, again presumably through a diselone intermediate (Scheme 29) <1987TL5699>.



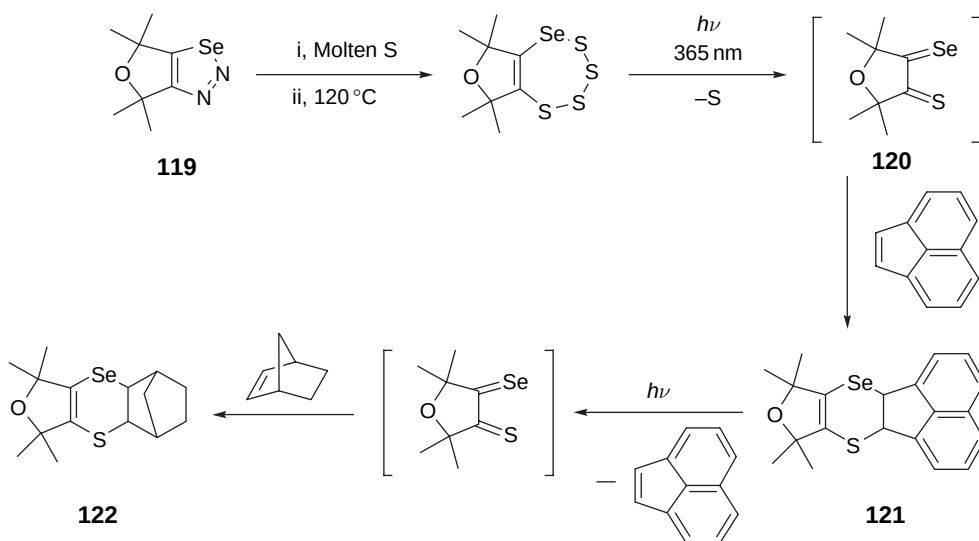
Scheme 29

9.15.6.7 5*H*-1,4-Thiaseleninins

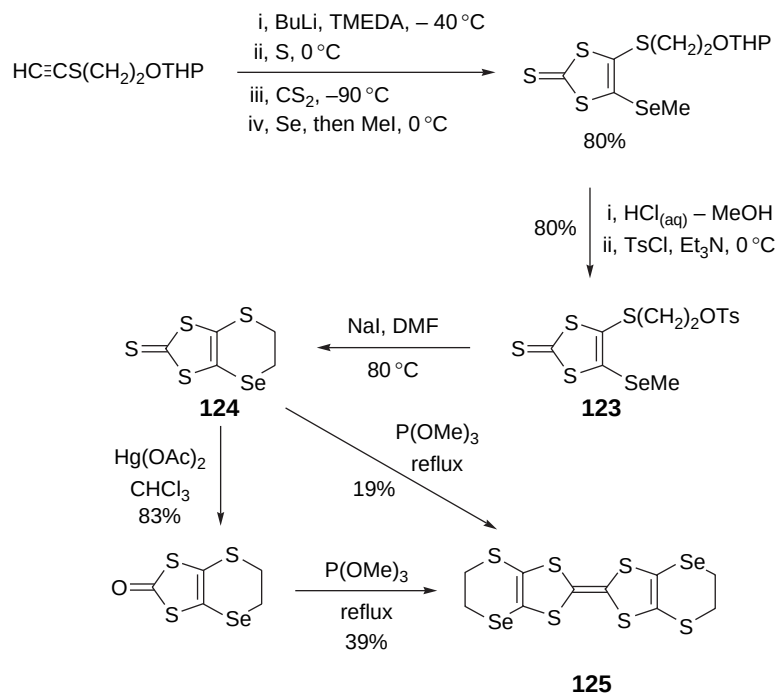
5*H*-1,4-Thiaseleninins **121** and **122** have been prepared using procedures analogous to those used for the preparations of 5*H*-1,4-diseleninins (see Scheme 29). Thiaselenin **121** can be prepared photochemically by extrusion of sulfur and by trapping of the intermediate 1-selone-2-thione **120** with acenaphthene. Thiaselenin **122** can be prepared by photochemical extrusion of acenaphthene from **121** and trapping by norbornene (Scheme 30) <1987TL4833>.

1,4-Thiaselenin rings fused to tetrathiafulvalenes such as **125** have been prepared by a multistep sequence (Scheme 31) <2002JOC4218>. The key step in the reaction scheme involves an intramolecular transalkylation reaction (Scheme 32). In this reaction the tosylate group in **123** is displaced by iodide allowing an intramolecular displacement by selenium. Cyclization leads to an intermediate selenonium salt **126**, which is dealkylated by iodide affording **124**. Standard reactions forming the tetrathiafulvalene complete the synthesis.

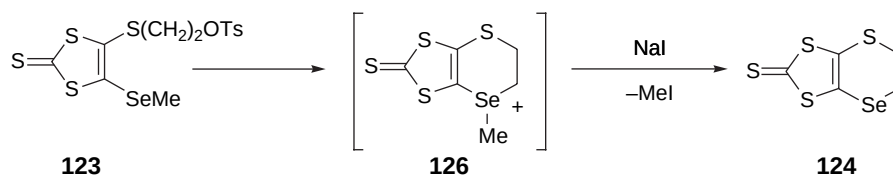
Although, in theory, this sequence should be amenable to the preparation of the corresponding 1,4-diselenin-fused tetrathiafulvalenes such as **128**, the key cyclization reaction fails in the diselenium case <2002JOC4218>. It appears that formation of a seleniranium salt **127** is favored over the desired transalkylation reaction leading to decomposition (Scheme 33).



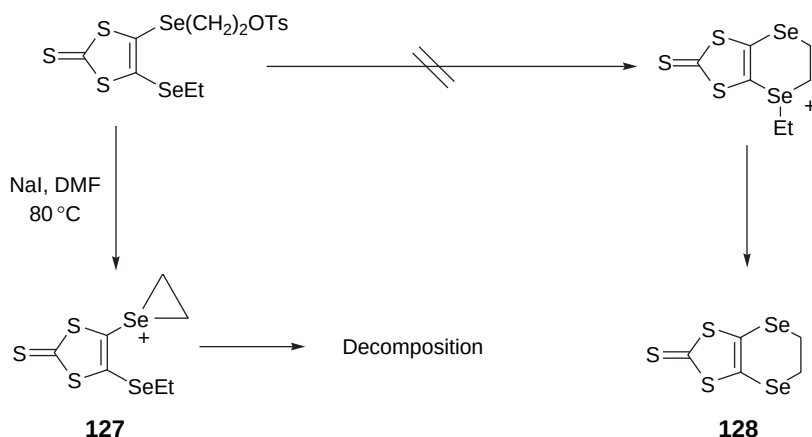
Scheme 30



Scheme 31



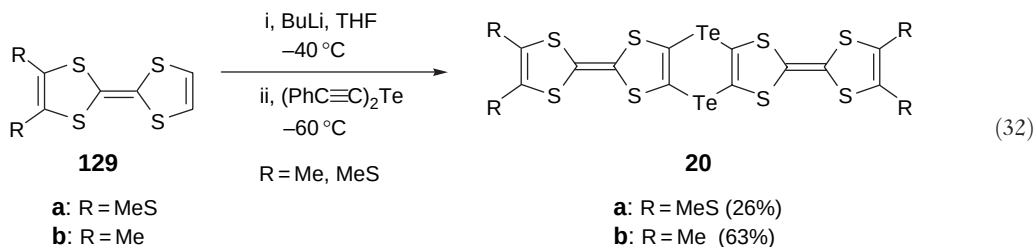
Scheme 32



Scheme 33

9.15.6.8 1,4-Ditellurins

The 1,4-ditellurin ring system fused to two tetrathiafulvalene units, as in **20**, has been prepared by a novel metallation sequence starting from the parent tetrathiafulvalenes **129a** and **129b** (Equation 32) <1994TL8489, 1994CC2115>. Treatment of **129a** and **129b** with butyllithium in THF followed by addition of bis(phenylacetylene)telluride affords the desired 1,4-ditellurins **20a** and **20b**. X-ray structure determinations of **20a** and **20b** have been described previously (see Section 9.15.3.1). Although **20b** proved to be too insoluble for electrochemical studies, these investigations have been carried out on **20a** using cyclic voltammetry. This molecule exhibits two reversible two-electron oxidation waves but undergoes no further electrochemical oxidations. This is presumably due to the 1,4-ditellurin ring system acting as an ‘electronic insulator’, dividing the molecule into two nearly independent tetrathiafulvalene units.

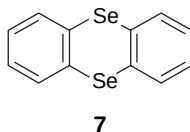


9.15.7 Selenanthrenes, Thiaselenanthrenes, Telluranthrenes, and Related Structures

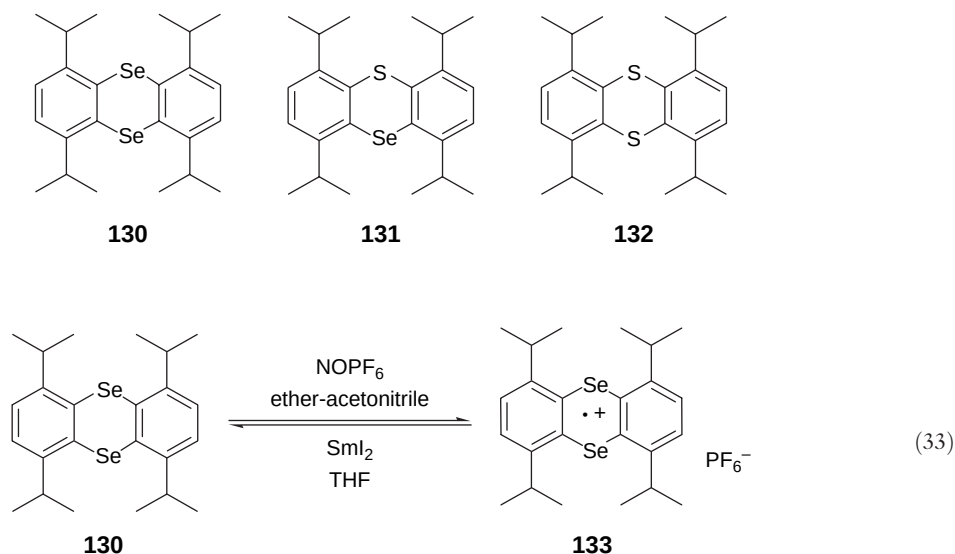
9.15.7.1 Selenanthrenes, Thiaselenanthrenes, and Related Structures

9.15.7.1.1 Reactions

Selenanthrene **7** and related molecules react with halogens to form hypervalent selenium compounds (CHEC-II(1996), 6.24.4.2.1) and numerous unusual structures of this type have been reported recently (see Section 9.15.3.1). Theoretical investigations of these reactions have also been described in Section 9.15.2. Comparison of the electrochemistry of **7** with dibenzo(ce)-1,2-diselenine **89** has been discussed in Section 9.15.3.3.

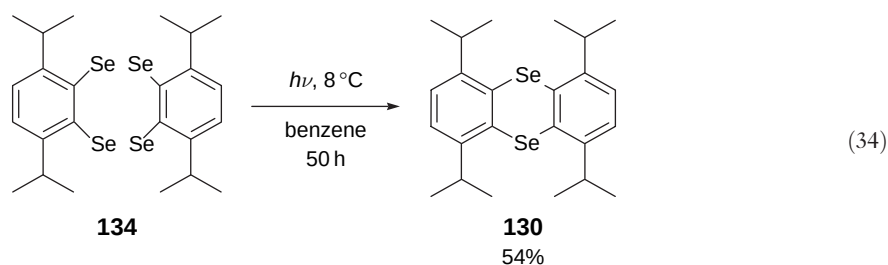


The electrochemistry of the tetrasubstituted selenanthrene **130**, thiaselenanthrene **131**, and the disulfur analog **132** was studied using cyclic voltammetry, indicating a reversible anodic oxidation step <1999TL9101>. Lowered oxidation peaks and less reversibility were observed with increasing selenium substitution, and this was attributed to a higher localization of electron deficiency on selenium rather than sulfur. This explains the higher reactivity of the radical cations containing selenium. The radical cation of **130** can be prepared by oxidation with nitrosonium hexafluorophosphate and isolated as a purple crystalline solid (Equation 33). The structure of the radical cation **133** was characterized by esr spectroscopy and the latter could be reduced to the starting selenanthrene using samarium(II) iodide.



9.15.7.1.2 Synthesis

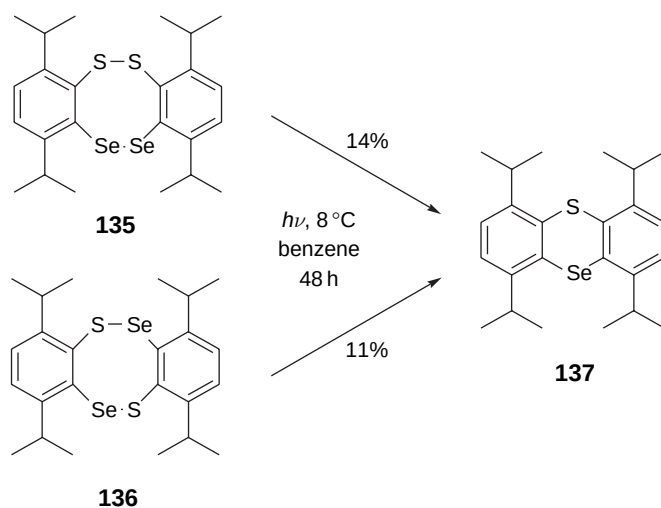
Photochemical extrusion of selenium from the tetraisopropylselenocin **134** affords the selenanthrene **130** in good yield (Equation 34) <1999TL9101>. The corresponding thiaselenanthrene **137** can be prepared from the mixed precursors **135** or **136** (Scheme 34). The required precursors for these extrusions, viz. **135** and **136**, can be prepared readily from the corresponding diselenostannole **138** (Scheme 35).



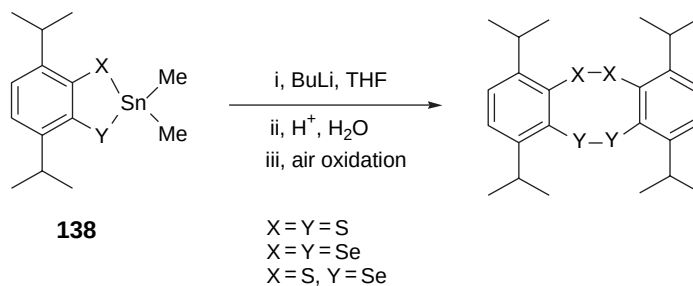
Upon treatment of 2,3-dichloro-1,4-naphthoquinone with an equimolar amount of selenobenzamide in ethanol, dibenzo[*b,i*]selenanthrene-5,7,12,14-tetraone **139** can be isolated in good yield (Scheme 36) <1995JOM19>. Presumably, the reaction occurs by formation of the intermediate selenol, which dimerizes under the reaction conditions.

9.15.7.2 Telluranthrenes

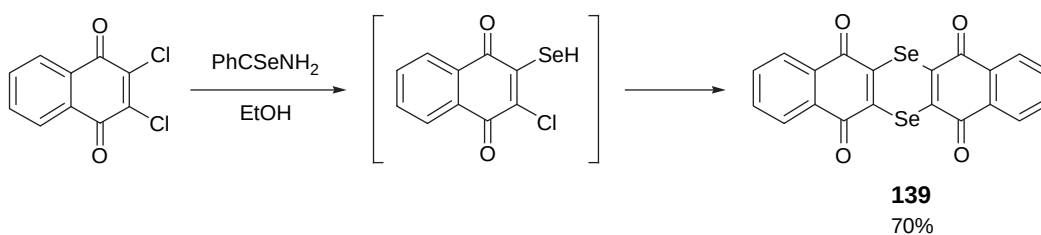
2,7-Dinitrotelluranthrene **140** has been prepared by treatment of 1,2-diiodo-4-nitrobenzene with a tellurium-copper slurry obtained *in situ* from disodium telluride and copper(I) iodide in *N*-methylpyrrolidine (NMP) (Equation 35)



Scheme 34

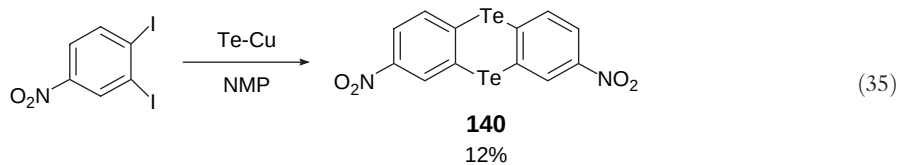


Scheme 35



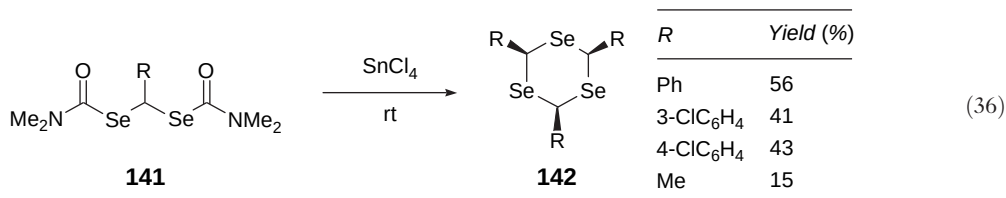
Scheme 36

<1995JOC5274>. Although the product was formed in low yield, no attempts at optimization of this reaction were carried out. The reaction conditions reported are milder than most methods used for the preparation of telluranthrenes (CHEC-II(1996), 6.25.4).



9.15.8 Triselenanes

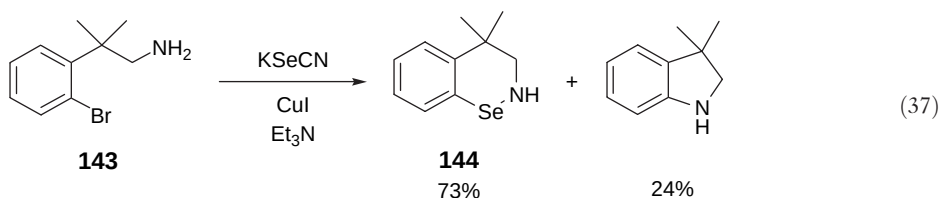
1,3,5-Triselenanes **142** can be prepared by reaction of the bis(*N,N*-dimethylcarbamoylseleno)methanes **141** with tin tetrachloride (Equation 36) <2005TL3775>. Single β -isomers of the triselenanes were obtained using this method. The reaction presumably involves *in situ* generation of selenals, whose trimerization has been well documented (CHEC-II(1996), 6.24.5.2). No reaction occurred using boron trifluoride etherate and attempts to carry out the corresponding reactions with the tellurium analog of **141** were under investigation.



9.15.9 Selenazines

9.15.9.1 1,2-Selenazines

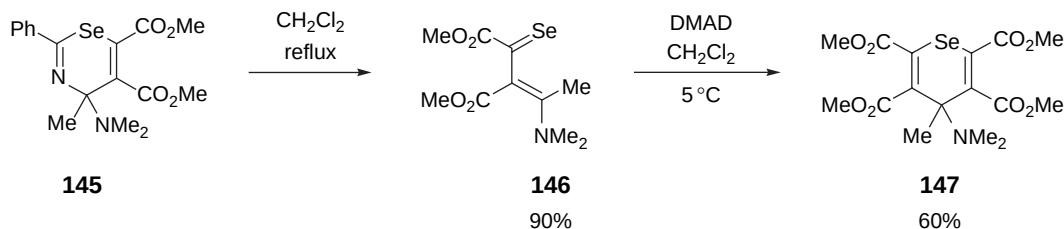
The benzo-1,2-selenazine (benzisoselenazine) ring system **144** can be prepared by copper(I)-promoted reaction of amine **143** with potassium selenocyanate in the presence of triethylamine (Equation 37) <2000JOC8152>. The ring closure also affords 3,3-dimethylindoline as a by-product, but a twofold excess of selenocyanate and acetonitrile as a solvent led to optimum formation of the desired selenazine.



9.15.9.2 4*H*-1,3-Selenazines and 5,6-Dihydro-4*H*-1,3-Selenadiazines

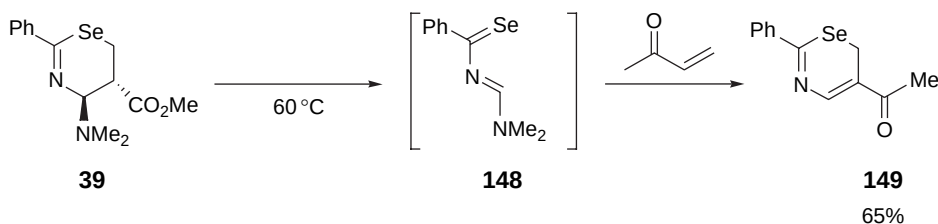
9.15.9.2.1 Structure and reactions

Retrocyclization of the 4*H*-1,3-selenazine **145** can be carried out in refluxing dichloromethane to afford the vinylogous selenoamide **146** (Scheme 37) <1995TL237, 1998T2545>. Further reaction with dimethyl acetylenedicarboxylate (DMAD) affords the 4*H*-selenin **147**.



Scheme 37

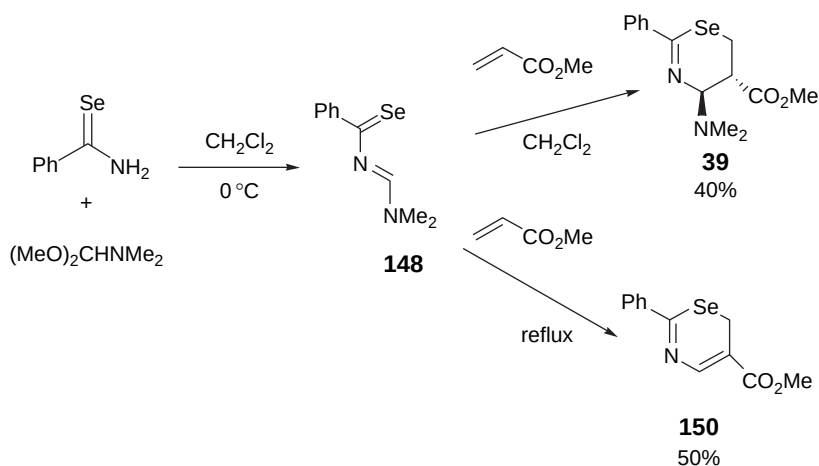
The conformation of 5,6-dihydro-4*H*-1,3-selenadiazine **39** has been described (see Section 9.15.4). This selenadiazine can be converted to the 6*H*-1,3-selenazine **149** by treatment with methyl vinyl ketone at elevated temperature (Scheme 38) <1998T2545>. The *N*-selenoacylamidine **148** is an intermediate in this reaction (see following section).



Scheme 38

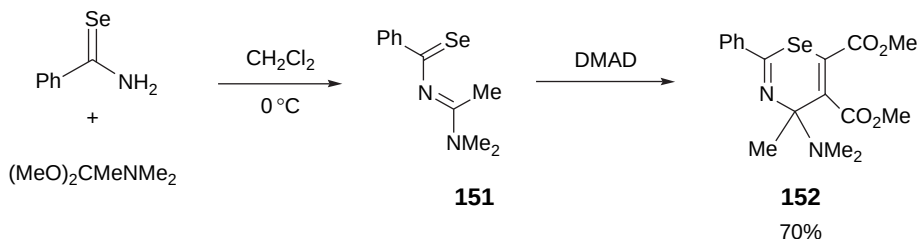
9.15.9.2.2 Synthesis

Treatment of selenobenzamide with *N,N*-dimethylformamide dimethyl acetal leads to the isolation of the previously mentioned *N*-selenoacylamidine **148** (Scheme 39). This compound reacts with methyl acrylate to afford the 5,6-dihydro-4*H*-1,3-selenazine **39** or the 6*H*-1,3-selenazine **150** depending on the temperature of the reaction <1995TL237, 1998T2545>.



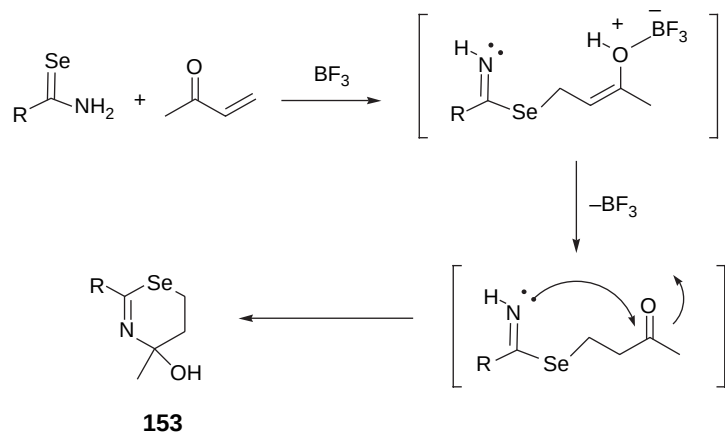
Scheme 39

Selenobenzamide reacts with *N,N*-dimethylacetamide dimethyl acetal to afford the *N*-selenoacylamidine **151**. The latter reacts with dimethylacetylene dicarboxylate to afford the 4*H*-1,3-selenazine **152** (Scheme 40) <1998T2545>.



Scheme 40

The reaction of aromatic and aliphatic primary selenoamides with α,β -unsaturated ketones in the presence of boron trifluoride affords a variety of 4*H*-1,3-selenazines in high yields (Scheme 41, and Tables 4 and 5) <1999J(P1)453>. The reaction proceeds by conjugate addition of the selenium to the β -position of the unsaturated system followed by cyclization. In cases where diastereomeric compounds are formed, the *cis*-isomer predominates.

**Scheme 41****Table 4** Preparation of 1,3-selenazines from aliphatic primary selenoamides and α,β -unsaturated ketones

No.	Selenoamide	α,β -Unsaturated ketone	Product	Yield (%) (<i>cis/trans</i>)
i.				100
ii.				93
iii.				91 (84/16)
iv.				86 (90/10)
v.				100
vi.				32

Table 5 Preparation of 1,3-selenazines from an aryl selenoamide and α,β -unsaturated ketones

No.	Selenoamide	α,β -Unsaturated Ketone	Product	Yield (%) (<i>cis/trans</i>)
i.				73
ii.				88
iii.				93
iv.				85
v.				71 (89/11)
vi.				85
vii.				100 (74/26)
viii.				81

A number of the 1,3-selenazines shown above exhibit interesting biological properties (see [Section 9.15.11](#)).

4*H*-1,3-Selenazines **156** can be prepared from 6*H*-1,3,5-oxaselenazines **154** by thermal reaction with excess acetylenic dienophiles ([Table 6](#) <1997CL701>. The reaction proceeds through a 1,3-selenaza-1,3-butadiene intermediate **155** (cf. [Scheme 39](#)).

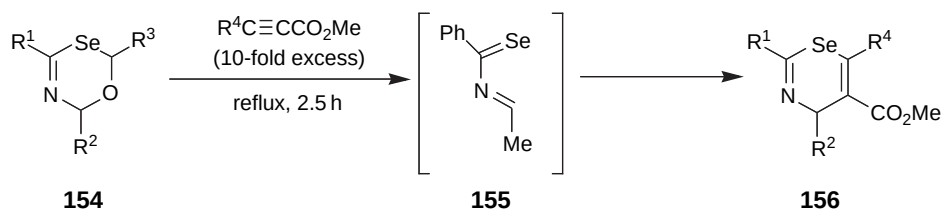
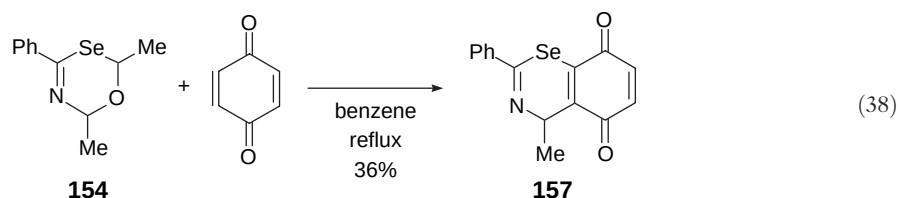


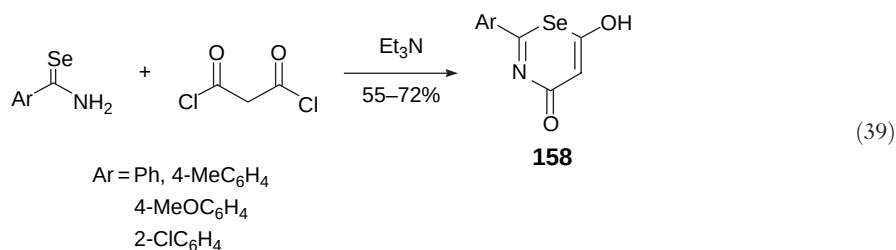
Table 6 Preparation of 4*H*-1,3-selenazines from 6*H*-1,3,5-oxaselenazines

No.	R^1	R^2	R^3	R^4	Solvent	Yield (%)
i.	Ph	Me	Me	CO ₂ Me	Benzene	78
ii.	Ph	Me	Me	H	Benzene	76
iii.	Ph	Bu ^t	Bu ^t	CO ₂ Me	Benzene	53
iv.	4-ClC ₆ H ₄	Me	Me	CO ₂ Me	Benzene	14
v.	4-ClC ₆ H ₄	Me	Me	H	Toluene	33

Similar treatment of the oxaselenazine **154** ($R^1 = \text{Ph}$, $R^2 = R^3 = \text{Me}$) with benzoquinone afforded the corresponding benzoquinone-fused selenazine **157** (Equation 38) <1997CL701>.

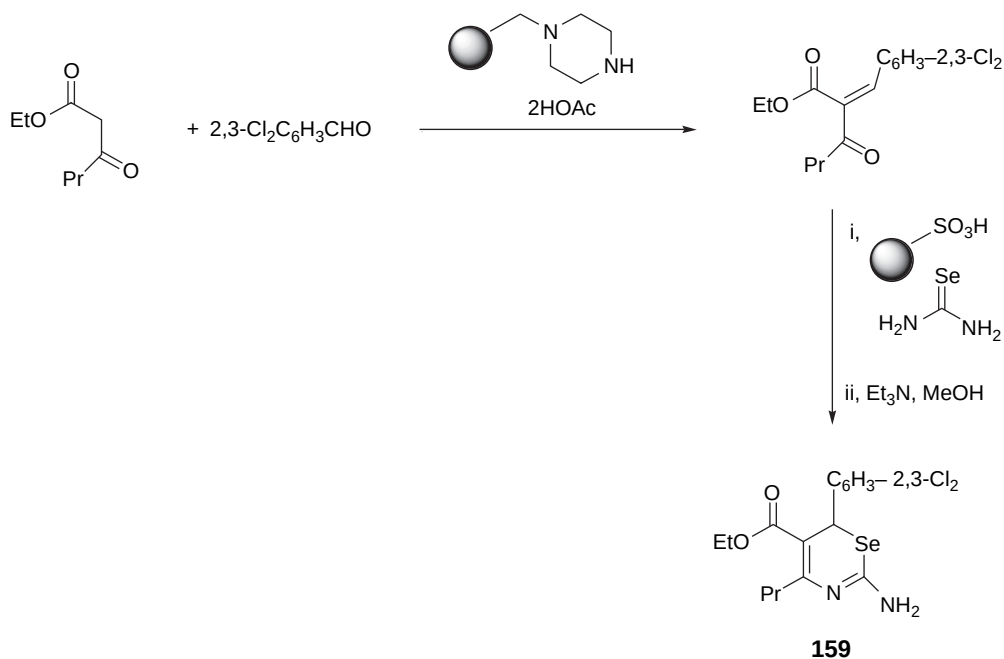


Reaction of an aromatic primary selenoamide with malonyl dichloride in the presence of triethylamine affords 6-hydroxy-1,3-selenazin-4-ones **158** (Equation 39) <1999CL485>. Significantly lowered yields of products result if no triethylamine is used in the reaction.

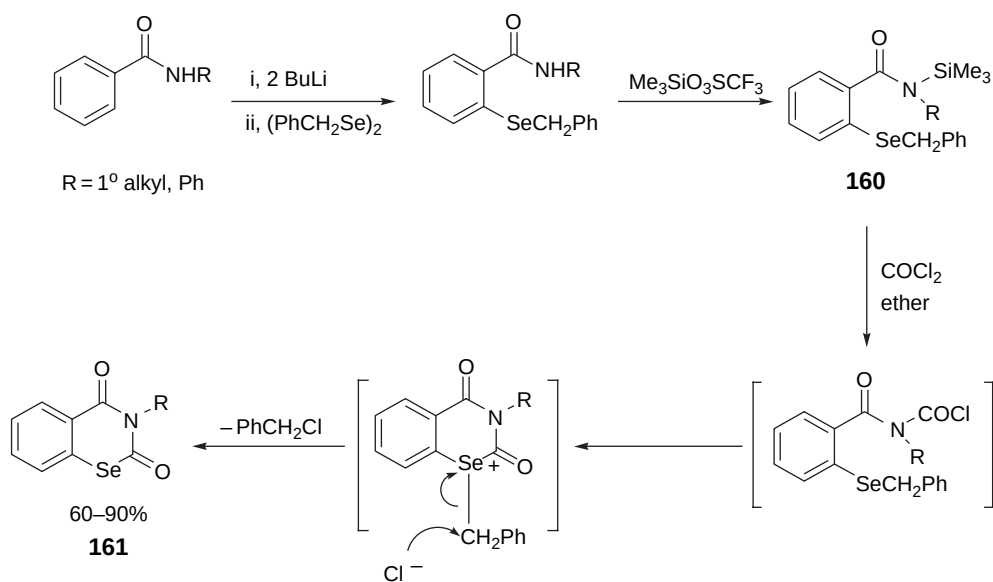


A 2-amino-1,3-selenazine **159** was prepared as part of a combinatorial approach to the synthesis of functionalized 1,3-thiazine libraries (Scheme 42) <2004AC621>. This approach – a ‘catch and release strategy’ – used a polymer-supported piperidine diacetate catalyst to carry out the initial Knoevenagel condensation. The resulting enone was then treated with selenourea at 90 °C in the presence of a polymeric-based sulfonic acid. This sulfonic acid not only promotes the cyclization to the selenazine, but also sequesters the selenazine, which is the only basic molecule in the reaction mixture. Multiple filtrations and washings remove unreacted starting materials, reagents, and by-products. The desired 2-amino-1,3-selenazine **159** can be isolated by treatment of the resin-bound compound with triethylamine which is significantly more basic than the aminoselenazine (Scheme 42).

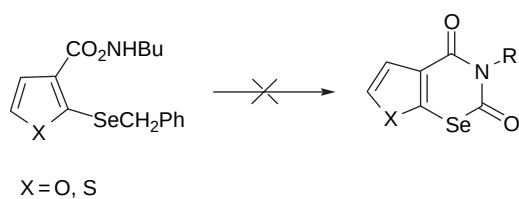
Treatment of an *N*-substituted-2-benzylseleno-*N*-trimethylsilylbenzamide **160** with phosgene in ether affords the corresponding benzoselenazine-2,4-dione **161** (Scheme 43) <1995AJC1221>. This reaction appears to proceed by nucleophilic addition of selenium to the chlorocarbamate carbonyl followed by chloride displacement of the Se-benzyl group. The reaction proceeds in yields of 60–90% based on the starting amide when the amide contains a phenyl or primary alkyl group. Only 50% yield was obtained with an *N*-isopropyl substituent, and the reaction failed completely with more sterically demanding groups such as *N*-cyclohexyl or *N*-*tert*-butyl. Attempts to extend the reaction to the furan or thiophene ring systems also failed (Scheme 44). The selenobenzyl precursors for the reaction can be prepared also by an alternative route as shown in Scheme 45.



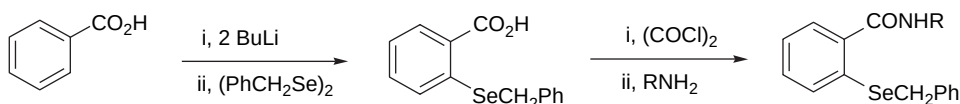
Scheme 42



Scheme 43



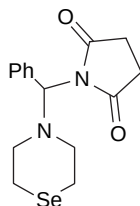
Scheme 44



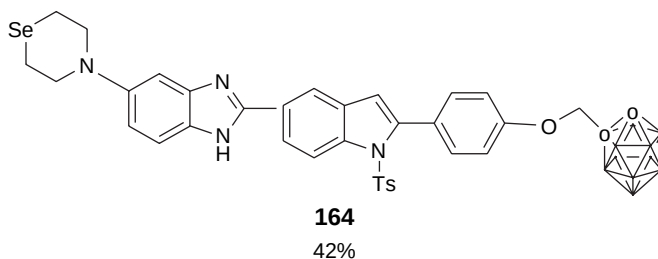
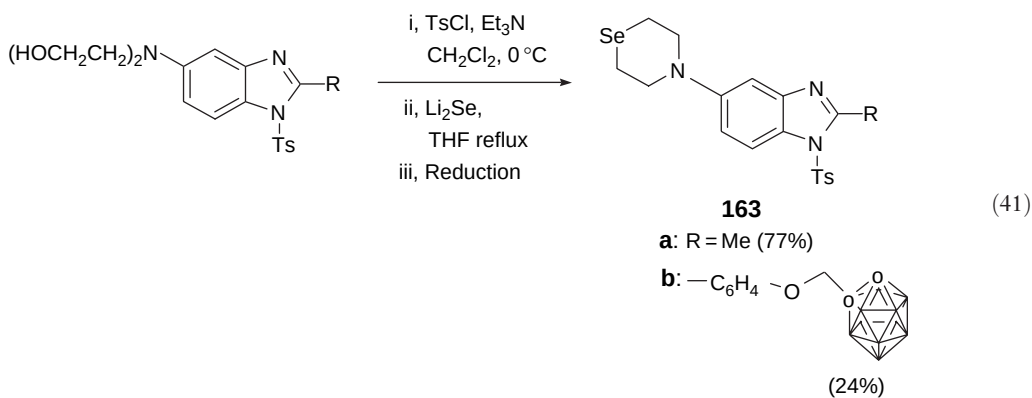
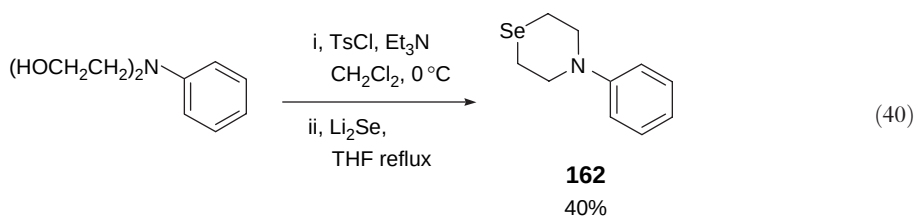
Scheme 45

9.15.9.3 1,4-Selenazines

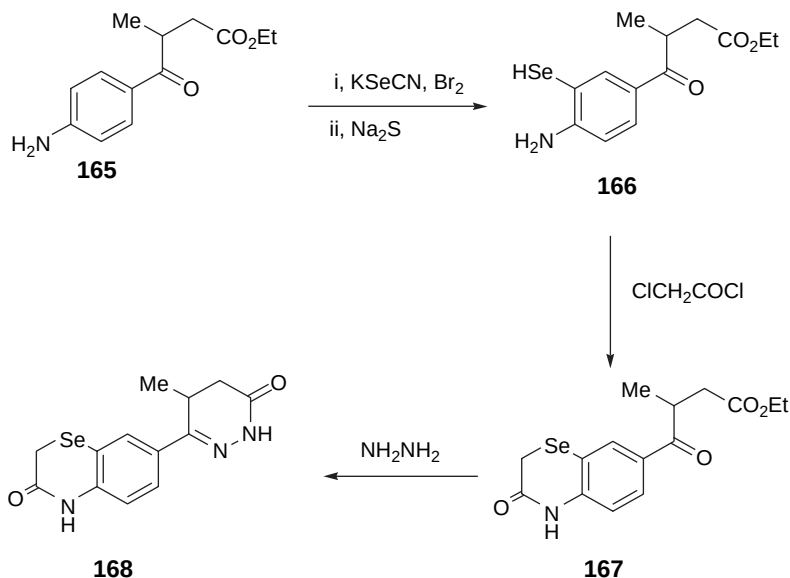
X-Ray structural data for a 1,4-selenazine, *N*-[α -(*N*-succinidyl)-benzyl]selenamorpholine **21** have been described previously (see Section 9.15.3.1).

**21**

Tetrahydro-1,4-selenazines such as **162** and **163** can be prepared by simple ring closure of bis-(2-hydroxyethyl)arylamine ditosylates with lithium selenide (Equations 40 and 41) <2000HCA2926>. The reaction works well not only in simple cases, but also in much more complicated systems, affording 1,4-selenazine molecules incorporating boron cages such as **163b** and **164** <2000HCA2926>.

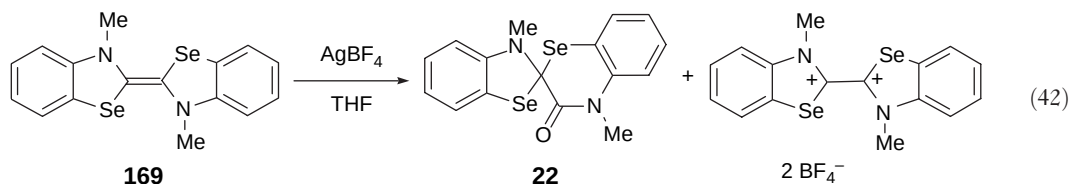


The 1,4-selenazin-3-one **168** was prepared as an analog of the cardiotoxic drug bemoradan (where Se=O) <1992JME172>. This ring system can be prepared in a series of reactions by the treatment of the amine **165** with bromine–potassium selenocyanate, followed by sodium sulfide (Scheme 46). The resulting aminoselenol **166** can be cyclized to the selenazinone **167** by treatment with chloroacetyl chloride. Treatment with hydrazine completes the synthesis of **168**.



Scheme 46

The spiro 1,4-benzoselenazin-2-one **22** was prepared as a by-product in the chemical oxidation of a diselenadiazafulvalene **169** using silver tetrafluoroborate (Equation 42) <2001CC1336>. The structure of **22** was confirmed by an X-ray crystal determination.



9.15.9.4 Oxaselenazines

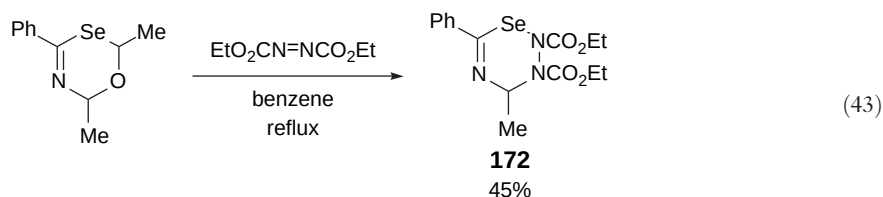
9.15.9.4.1 Reactions

Thermal reversion of 6*H*-1,3,5-oxaselenazines **170** generates 1,3-selenaza-1,3-butadienes **171** which prove to be useful reactive intermediates in synthesis <1997CL701> (cf. Section 9.15.6.2.2, Table 6, and Schemes 37–39). Thus, treatment of oxaselenazines **170** with excess alcohol or thiol at reflux affords the corresponding ring-opened products of nucleophilic addition (Table 7). No nucleophilic addition product was observed in the attempted reaction of **170** with propylamine <2001BCJ511>.

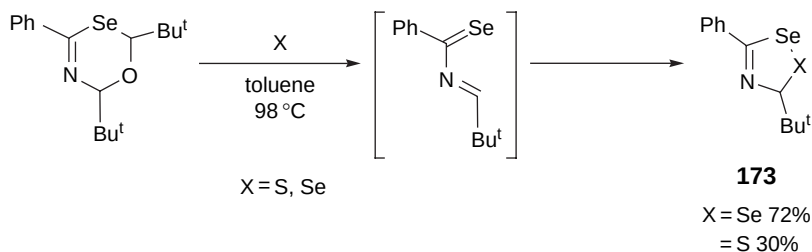
Treatment of an oxaselenazine with an excess of an acetylenic dienophile at reflux affords the 4*H*-1,3-selenazine (see Table 6). Similarly, treatment of an oxaselenazine with diethyl azodicarboxylate affords the dihydro-4*H*-selenatriazine **172** (Equation 43) <1997CL701>.

Table 7 Preparation of substituted selenoamides from 6*H*-1,3,5-oxaselenazines **170**

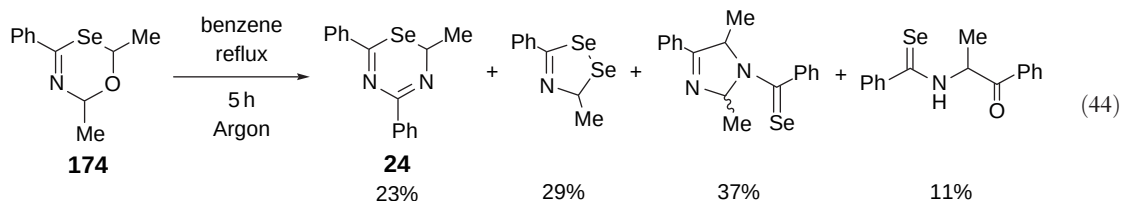
No.	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Nucleophile	Solvent	Yield (%)
i.	Ph	Me	Me	MeOH	MeOH	62
ii.	Ph	Me	Me	EtOH	EtOH	66
iii.	Ph	Bu ^t	Bu ^t	EtOH	EtOH	53
iv.	4-ClC ₆ H ₄	Me	Me	MeOH	MeOH	92
v.	4-ClC ₆ H ₄	Me	Me	EtOH	EtOH	85
vi.	Ph	Me	Me	PhSH	Benzene	85
vii.	Ph	Me	Me	PhCH ₂ SH	Benzene	82



Treatment of 6*H*-1,3,5-oxaselenazines with an excess of selenium affords 1,2,4-diselenazoles **173**, presumably through the previously mentioned intermediate 1,3-selenaza-1,3-butadienes (**Scheme 47**) <2004TL6187>. Significant scrambling of the selenium and sulfur atoms was observed in the thermal reaction with sulfur.

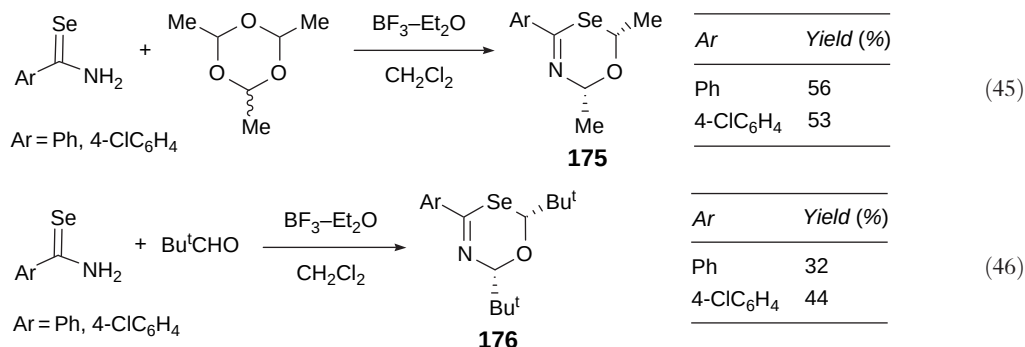
**Scheme 47**

Thermolysis of 6*H*-1,3,5-oxaselenazine **174** in the absence of a trapping agent affords a complex mixture of products including the 2*H*-1,3,5-selenadiazine **24** (**Equation 44**) <1997CL701>.



9.15.9.4.2 Synthesis

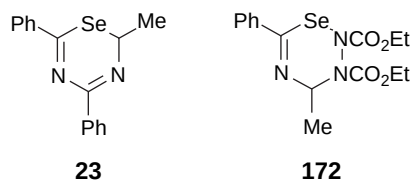
6*H*-1,3,5-Oxaselenazines **175** and **176** can be prepared readily by the reaction of aryl selenoamides with aldehydes or aldehyde equivalents in the presence of boron trifluoride etherate (Equations 45 and 46) <2001BCJ511>. The products were single isomers shown to have *cis*-stereochemistry by nuclear Overhauser effect (NOE) experiments.



9.15.10 Selenadiazines, Selenatriazines, and Diselenazines

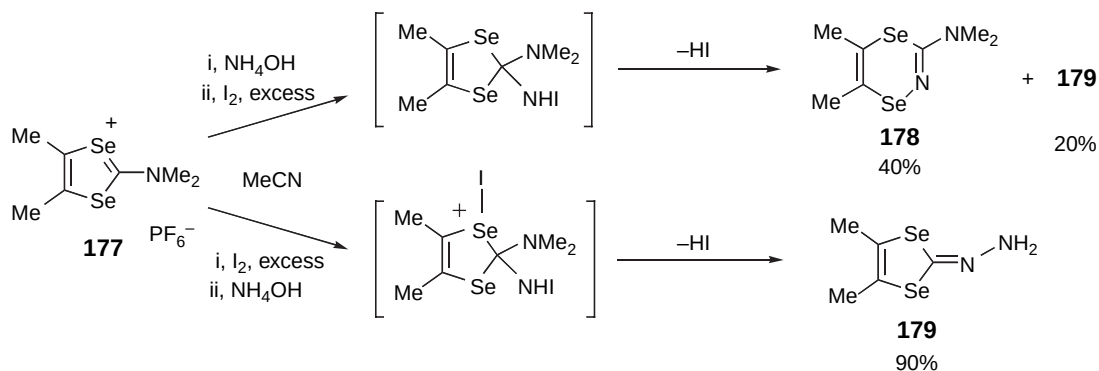
9.15.10.1 Selenadiazines and Selenatriazines

1,3,5-Selenadiazines are formed by the thermal decomposition of 6*H*-1,3,5-oxaselenazines <1997CL701, 2001BCJ511> (see Equation 44). The available spectroscopic data could not be used to distinguish between the selenadiazine structure and other isomeric possibilities. The X-ray crystal structure of 2,4-diphenyl-6-methyl-1,3,5-selenadiazine **23** confirmed this structural assignment <2001BCJ511> (see Section 9.15.3.1). The dihydro-4*H*-selenatriazine **172** could be prepared from a 1,3,5-oxaselenazine (see Equation 43).



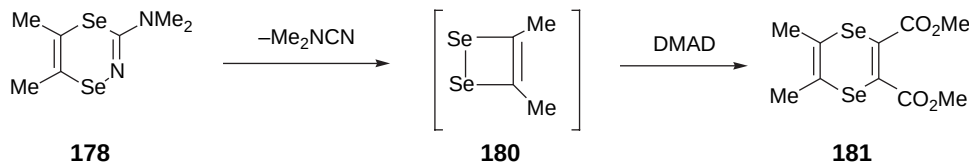
9.15.10.2 Diselenazines

The 1,4,2-diselenazine ring system **178** can be prepared starting from a 1,3-diselenolium cation salt **177** upon addition of iodine and excess ammonium hydroxide (Scheme 48) <1996CC2375>. The order of addition in this reaction is especially important. Initial treatment of the salt with ammonia followed by iodine affords the desired diselenazine. If the order of addition is reversed, the hydrazone **179** is formed in excellent yield.



Scheme 48

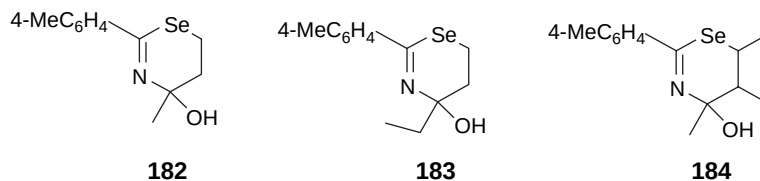
The diselenazine **178** appears to be an excellent precursor for generation of the reactive intermediate 1,2-diselenete **180**, which can be trapped, leading to 1,4-diselenin derivatives such as **181** (Scheme 49) <1996CC2375>.



Scheme 49

9.15.11 Compounds of Biological Interest

A number of 4-hydroxy-1,3-selenazines (see Table 5 and Section 9.15.9.2) exhibit antibacterial properties against both *Escherichia coli* and *Staphylococcus aureus* <1998MI179>. The corresponding thiazine compounds and 1,3-selenazole show no inhibitory activity against either of these organisms. The *p*-tolyl derivatives **182–184** proved to be especially active against both Gram-positive and Gram-negative bacteria. 4*H*-1,3-Selenazines were investigated also as specific inhibitors of protein kinases and appear to be useful compounds for studying eukaryotic elongation factor-2 kinase <2000BBA207>. Lack of regulation of these kinases is often associated with proliferative diseases, such as cancer, atherosclerosis, and psoriasis.



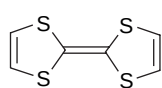
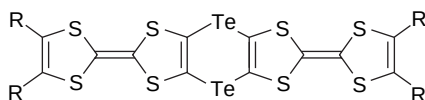
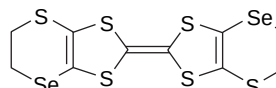
1,4-Selenazines such as **163b** and **164** have been prepared in order to evaluate their utility in boron-neutron-capture-therapy (BNCT) and positron-emission tomography (PET) <2000HCA2926>. In the BNCT area, researchers were looking for Se-containing molecules that might carry high numbers of boron atoms into a tumor cell. Upon neutron-capture by the nonradioactive ^{10}B nucleus, ionizing radiation is generated capable of damaging the DNA or other essential components of the tumor cell. Of particular interest in the PET area is the fact that ^{73}Se is a positron-emitting radionuclide with $t_{1/2} = 7.1$ h.

Selenazinone **168**, the selenium analog of the cardiotonic drug bemoradan (**168**, $\text{Se}=\text{O}$), proved to be much less potent biologically than the parent compound <1992JME172>. The benzo-1,2-selenazine **144** was prepared as a potential glutathione peroxidase (GPx) mimic <2000JOC8152>. This compound showed high GPx activity and was also a potent inhibitor of TNF- α -induced endothelial alterations. It was reported to be in clinical development as a therapy for ulcerative colitis. 1,2-Oxaselenane Se-oxide **50** proved also to be an effective glutathione peroxidase mimetic, although the five-membered ring homolog **51** was a more effective catalyst <2003JA13455>.

Combinatorial synthesis has been used widely in medicinal chemistry for the preparation of molecular libraries for biological evaluation. The preparation of the 2-amino-1,3-selenazine **119** was carried out in a 'catch and release' combinatorial approach for the synthesis of functionalized 1,3-thiazine libraries <2004AGE621> (see Scheme 42).

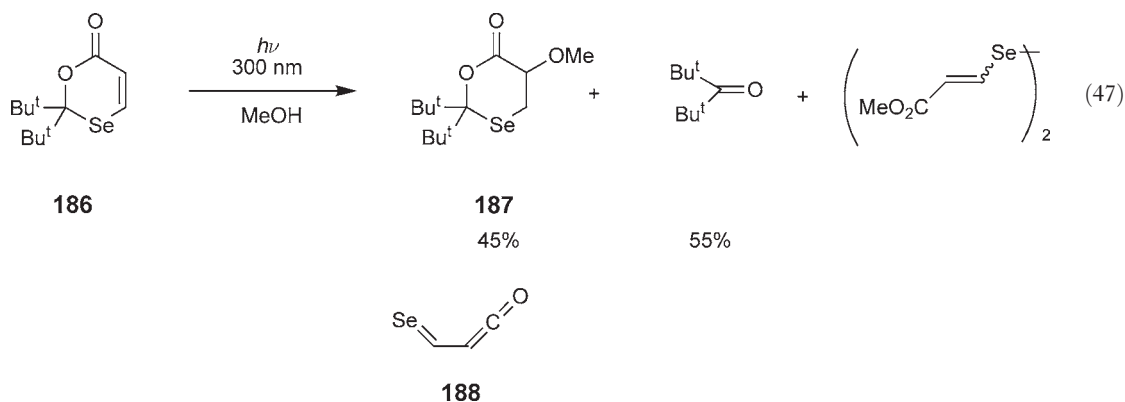
9.15.12 Compounds with Potential Technical Utility

Investigations into the electronic properties of selenium- and tellurium-substituted derivatives of the organic semiconductor tetrathiafulvalene (TTF) **185** continue to attract technical interest. A number of novel compounds of this type, **20a** and **20b** <1994TL8489, 1994CC2115> and **125** <2002JOC4218>, have been reported.

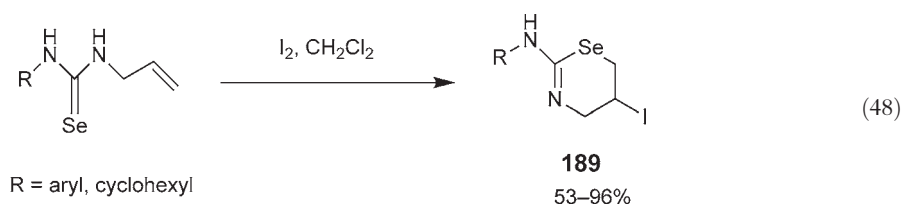
**185****20****125****a:** R = MeS**b:** R = Me

9.15.13 Further Developments

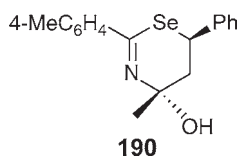
Irradiation of the sterically hindered 6*H*-1,3-oxaselenin-6-one **186** affords the 1,3-oxaselenanone solvent addition product **187** as well as the corresponding ketone and divinyldiselenide arising from cycloreversion (Equation 47) <2007ARK7>. Without solvent the ketone and polymeric materials are formed. The diselenide and polymeric products are assumed to arise from a selenoformylketene intermediate **188**.



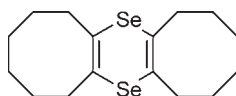
N-Allylselenoureas react with iodine to afford 5-iodo-4*H*-5,6-dihydro-1,3-selenazines **189** by iodocyclization (Equation 48) <2006CL626>.



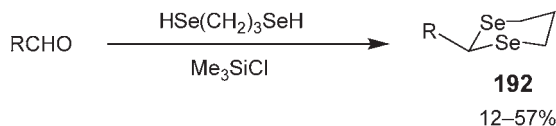
The crystal structure of a 5,6-dihydro-4*H*-1,3-selenazine **190** has been published <2006AX(E)1347>.



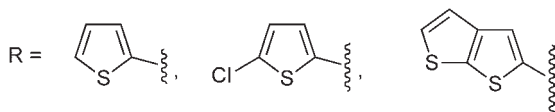
Thermal decomposition of cycloocten-1,2,3-selenadiazole in ethylene glycol affords the bis-fused 1,4-diselenin **191** in 75% yield <2006MI787> [cf. Scheme 24].

**191**

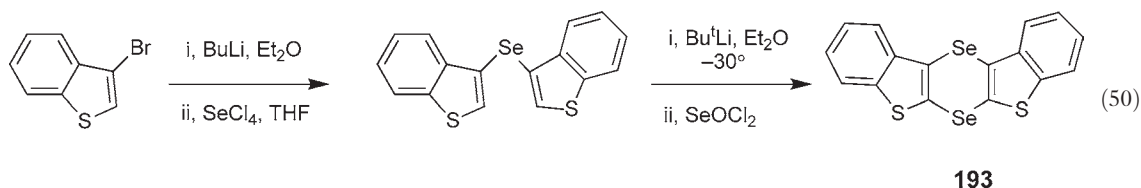
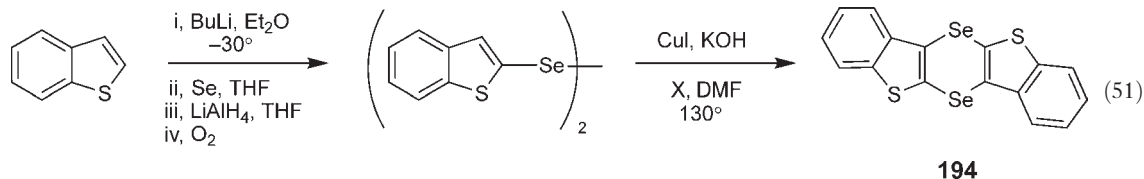
Thiophene-substituted 1,3-diselenanes **192** can be directly prepared by reaction of propane-1,3-diselenol in chlorotrimethylsilane, which appears to promote the reaction <2006RJGC1123>. The detailed mass spectra of these diselenanes are also reported.



(49)



Syn- and *anti*-bis-benzothienyl-1,4-diselenins **193** and **194** have been prepared by metallation sequences (Equations 50, 51). The crystal structures of **193** and **194** were determined and compared with the corresponding dithiins <2006CL422>. These fused diselenins exhibit unusual redox properties, being less stable in the oxidized form than the corresponding dithiins.

**193****194**

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Biographical Sketch



Frank Guziec was born in Chicago, studied at Loyola University of Chicago where he received a B.S. (honors) degree in 1968. He received his Ph.D. degree in 1972 at MIT under the direction of Prof. John C. Sheehan. He carried out postdoctoral work at Imperial College, London with Prof. D.H.R. Barton, at MIT with H. G. Khorana and at Wesleyan University with Max Tishler. He has served on the chemistry faculties of Tufts University, New Mexico State University, and is currently Dishman Professor of Science at Southwestern University. He carried out sabbatical research in the Pharmaceutical Sciences Department at DeMontfort University, Leicester, UK with Laurence Patterson under a Fulbright Fellowship and with Henk Hiemstra at the University of Amsterdam. His scientific interests include the chemistry of organoselenium compounds, extrusion reactions, functionalizing deamination reactions, and sterically hindered molecules. Collaborating with his wife Lynn Guziec he is also involved in the design and synthesis of anticancer compounds.



Lynn James Guziec was born in Long Beach, California; studied at Russell Sage College, Troy, NY, where she received her BA, special honors in Chemistry, in 1979. She received her Ph.D. in 1988 from New Mexico State University under the direction of Frank Guziec, Jr. She remained as a college professor at New Mexico State University until 1995. She has worked at her present position at Southwestern University as assistant professor since 1996. In 1998 she received an M.Sc. in biological sciences from the University of Warwick, UK. Her research interests include heterocycles, organosulfur, and organoselenium compounds as well as the synthesis of medicinal and anticancer compounds.

9.16

Six-membered Rings with Two or More Heteroatoms with at least One Phosphorus

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9.16.1 Introduction

Perhaps the most significant advance in the chemistry of this class of heterocycles since the publication of CHEC-II(1996) is the rapid increase in our knowledge of the properties and reactions of fully saturated ring systems. Saturated six-membered heterocycles of phosphorus and one or two other heteroatoms have not only become species of interest in their own right, but also as reagents for the synthesis of other organic molecules. In contrast, although our knowledge of fully or partly unsaturated systems has grown, many of the new synthetic methods and chemical properties are extensions of those covered in CHEC-II(1996). Because of this, and since the last review in CHEC-II(1996) has comprehensively reviewed the subject of aromatic ring systems in this classification, this chapter focuses mainly on saturated ring systems in this classification, along with the main advances in aromatic ring systems.

9.16.2 Nomenclature

Saturated and fully unsaturated six-membered heterocycles of phosphorus are known as phosphinanes and phosphinines, respectively (Hantzsch–Widman system <1983PAC409>). When there are other heteroatoms in the ring, a numerical locant to identify the position of the heteroatom precedes the name of the ring, which would also contain names of other heteroatoms present in the ring. These are ‘oxa’ for oxygen, ‘thia’ for sulfur, ‘aza’ for nitrogen, ‘sila’ for silicon, and ‘phospha’ for another phosphorus. As phosphorus has the lowest priority in the selection referred to here, the ‘stem’ remains as phosphinane and phosphinine (1982 revision rule RB-1.4) and the heteroatom identifier precedes the stem immediately after the numerical locant. For example, the ring system in compound **1** is referred to as 1,3,2-oxazaphosphinane (Figure 1). It should be noted that in much of the recent literature, an older version of nomenclature, referring to the saturated rings as phosphorinanes and phosphorinines, is still used widely and therefore remains acceptable. Indeed, the Chemical Abstracts Service (CAS) still uses the older nomenclature.

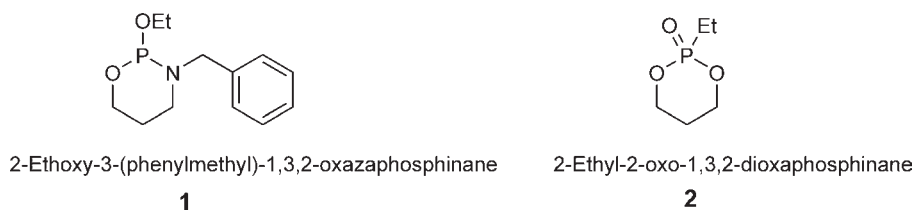


Figure 1

A suffix of ‘oxide’, with an appropriate numerical locant to identify the position, is used to denote substitution on a ring $\lambda^5\delta^4$ -phosphorus atom; so, for example, compound **2** is referred to as 1,3,2-dioxaphosphinane-2-oxide. However, again the older version of nomenclature remains widely used where a prefix of oxo- or thio-, with an appropriate numerical locant, is used (Figure 1).

9.16.3 Conformational and Structural Studies

The conformational preferences of six-membered carbocyclic rings are undoubtedly some of the best and widely understood aspects of conformational analysis. However, a number of research groups, in particular Bentrude, have explored extensively the effect of introducing one or more ring heteroatoms into the equilibrium between chair and boat conformations of a six-membered ring containing phosphorus. The conformations of these rings are influenced significantly by phosphorus <1984JA2353, 1985JA2083, 1986JA6669, 1991JOC6127> and nitrogen <2001TL743> substituents. For example, although 3-(diphenylmethyl)-2-(2-iodobenzoyl)-1,3,2-oxazaphosphinane-2-oxide **3** adopts a twisted chair conformation, 3-(triphenylmethyl)-2-(2-iodobenzoyl)-1,3,2-oxazaphosphinane-2-oxide **4** assumes a twisted boat conformation (Figure 2) <2001TL743>.

One interesting aspect of 2-oxo-substituted phosphinanes is the preference of the P=O to be in axial or equatorial positions. Unexpectedly, a number of X-ray crystallography <2001TL743> and nuclear magnetic resonance (NMR) studies (see later in this section) of phosphinanes, where the phosphorus atom is adjacent to an oxygen or nitrogen

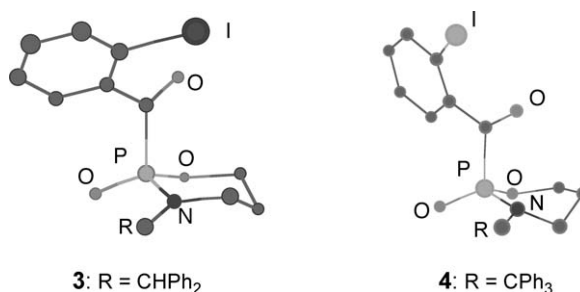


Figure 2

atom, have identified the P=O to be in an equatorial position which is in contrast to what might have been expected from an analogy to the anomeric effect. This is indeed the case in compounds **3** and **4**, even though the ring conformation in each is significantly different. The origins of this effect have not been established unambiguously but it has been shown that it is accompanied by trigonalization of the adjacent oxygen or nitrogen atom, suggesting a delocalization of the nitrogen or oxygen p orbital (lone pair) into an accessible phosphorus d orbital rather than the P=O σ^* -orbital <2001TL743>.

The observation of an equatorial preference for a P=O bond can of course be overridden by steric demands of other (i.e., not nitrogen) substituents of a phosphinane ring. An important feature observed in 2-oxophosphanes is that when the P=O does occupy an axial position, the hydrogen atoms of the ring which are in the axial position are also subject to the magnetic anisotropic effect and are shifted downfield in the ^1H NMR spectra. This observation can be used as a diagnostic tool to identify the configuration of the phosphorus atom <2002ARK205>.

Further investigations have focused on the influence of the ring heteroatoms on peripheral substituents. In particular, Denmark has investigated computationally carbanions adjacent to the phosphorus atom contained in diazaphosphinane, oxazaphosphinane, and dioxaphosphinane, for example, **5** and **6**, and has found them to be trigonal, again suggesting delocalization (Figure 3). This observation is particularly relevant in the context of the reactions of these species, which will be discussed in due course <1996AGE2515, 1998HAC209>.

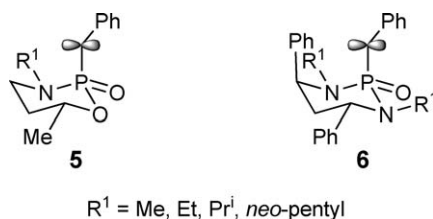
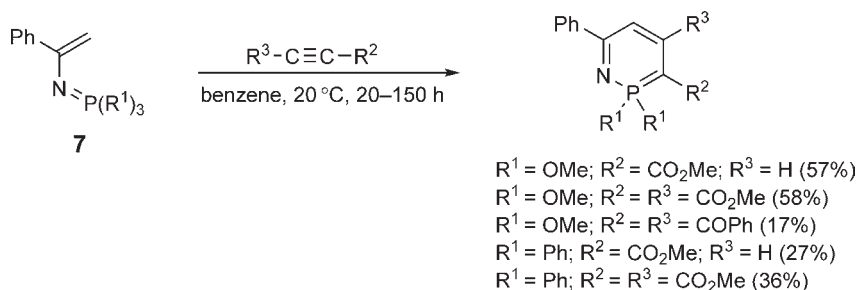


Figure 3

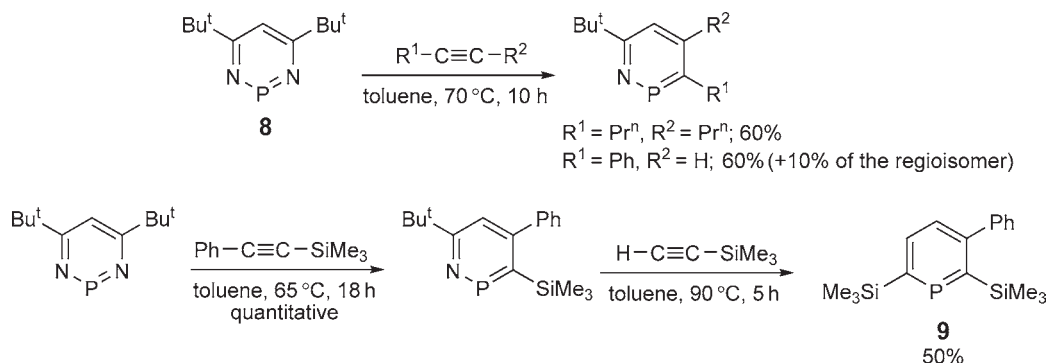
9.16.4 Ring Systems with At Least One Phosphorus and One Nitrogen or One Phosphorus Atom (But No Chalcogens)

9.16.4.1 Fully Unsaturated Rings with Two Heteroatoms: Azaphosphinines and Diphosphinines

There have been relatively few new synthetic routes to fully unsaturated phosphinines and in particular azaphosphinines. A full communication on an earlier report concerning the synthesis and reactivity of λ^5 -1,2-azaphosphinines has now appeared <1996CHEC-II1019>. A further report <1996CHEC-II1019> on the preparation of λ^3 -1,2-azaphosphinines via Diels–Alder cycloaddition of 1-iminophosphorane **7** to alkynes has also appeared (Scheme 1) <1998H(48)1903>. More significantly, a number of preparations of λ^3 -1,2-azaphosphinines via cycloaddition/cycloreversion between λ^3 -1,3,2-diazaphosphinines **8** and acetylenes have been reported <1996JA11978, 1998EJO2039, 1999PS251, 1999CEJ2109, 2000EJI2565, 2001JOC1054, 2002EJI2034, 2003EJI687, 2003HAC326, 2004CEJ4080, 2005EJI125>. The cycloadditions appear to have a narrow window, affording phosphinine **9** at higher temperatures through a further cycloaddition/cycloreversion process (Scheme 2) <2004CEJ4080>.

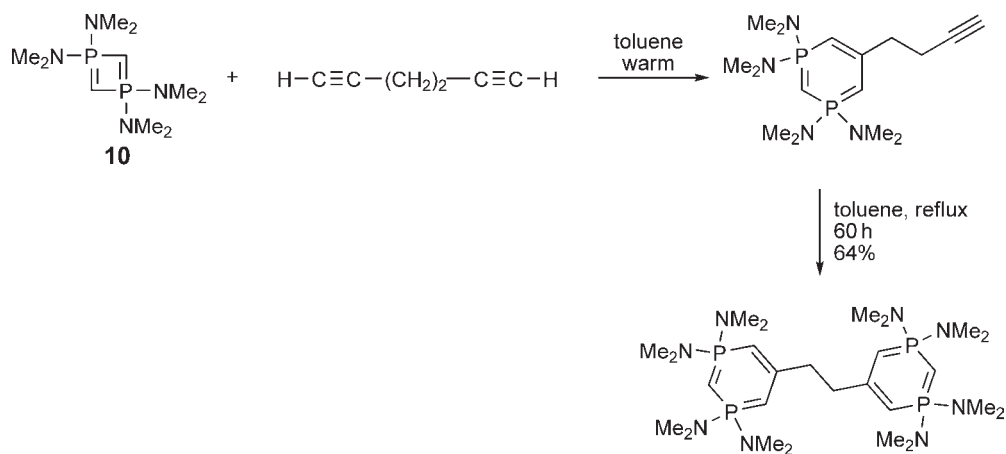


Scheme 1



Scheme 2

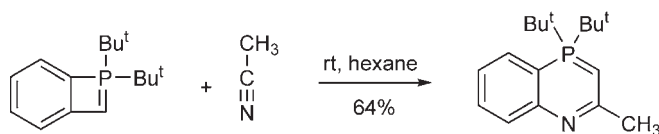
An ‘insertion’ reaction between an acetylene and a diphosphetidine **10** has been shown to afford 1,3-diphospinines (Scheme 3) <1997JOM(529)233>.



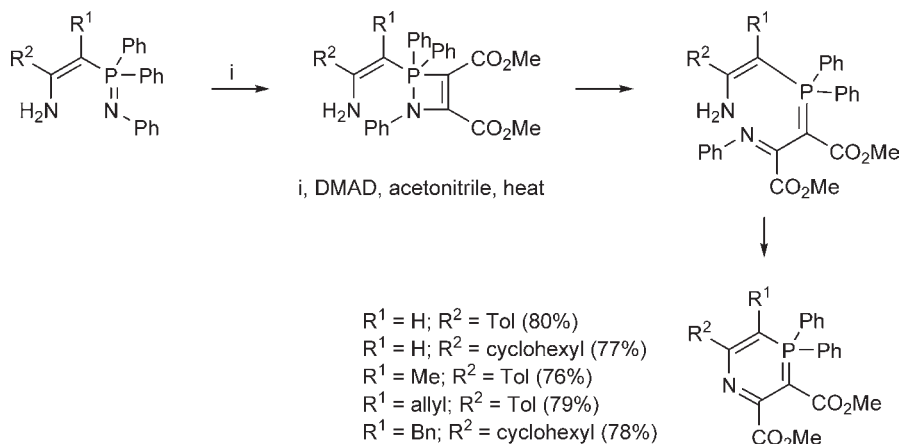
Scheme 3

A route to a 1,4-azaphosphinine is reported through a sequence involving cycloaddition and electrocyclic ring expansion (Scheme 4) <1996CEJ68>.

A series of 1,4-azaphosphinines have been prepared through a sequence involving cycloaddition and electrocyclic ring expansion followed by ring closure (Scheme 5) <1996J(P1)1481>.



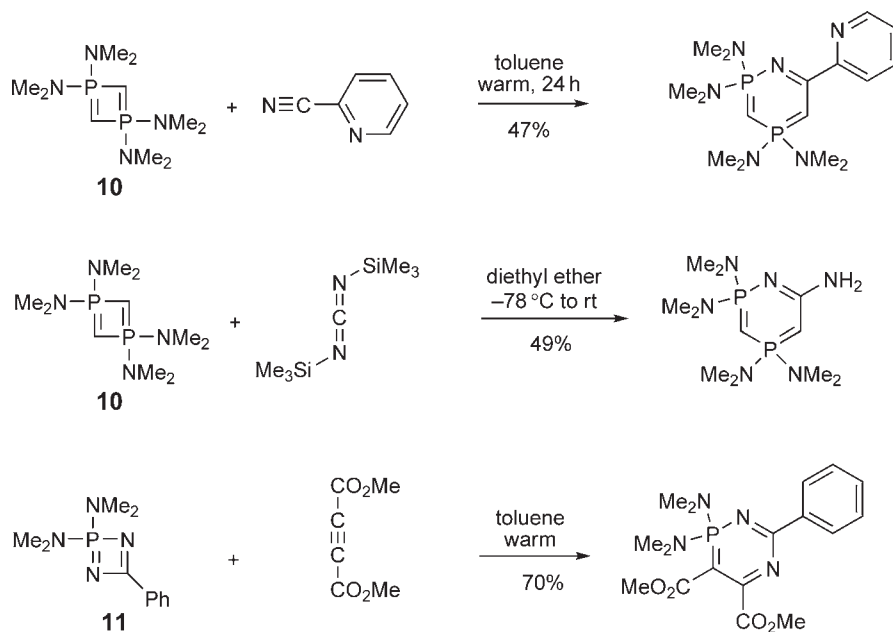
Scheme 4



Scheme 5

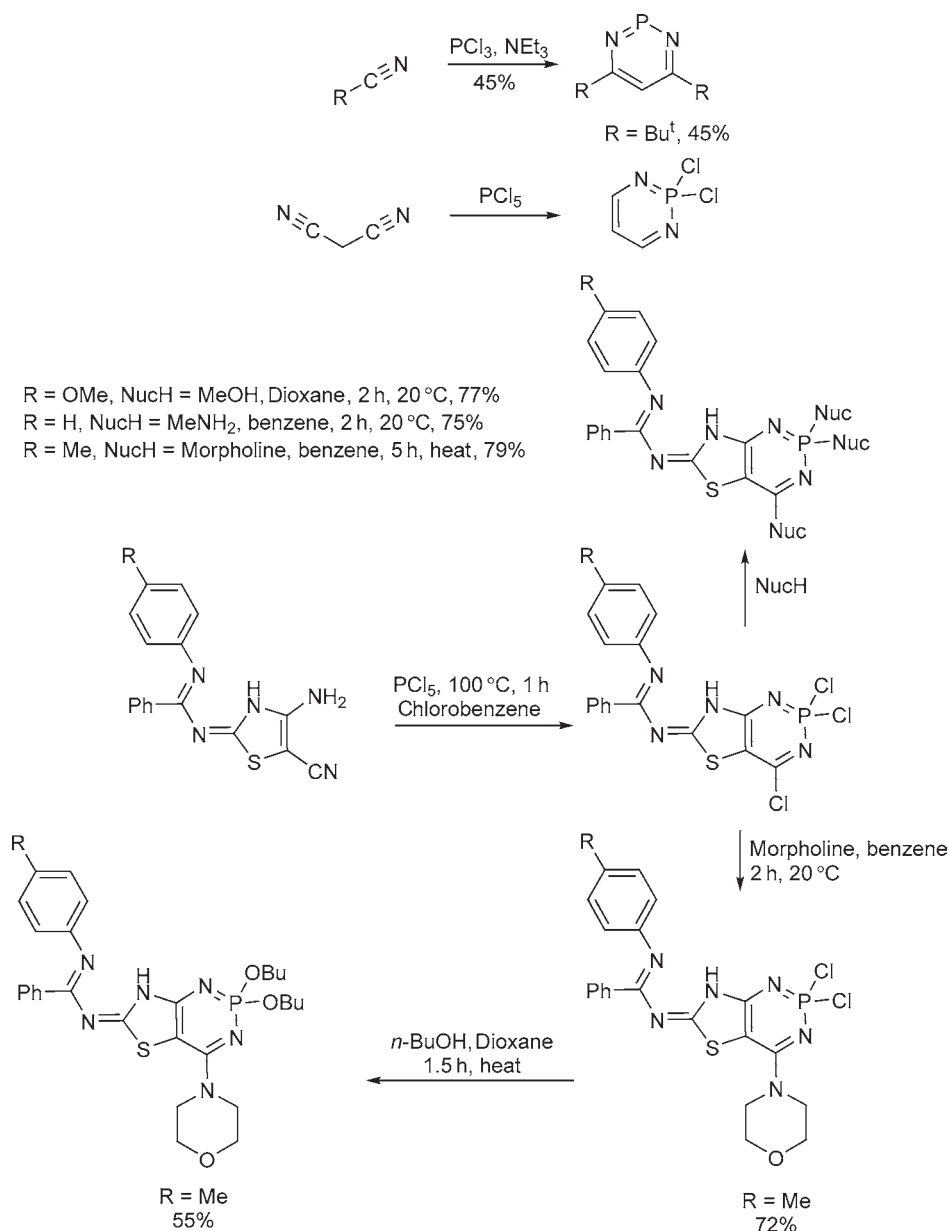
9.16.4.2 Fully Unsaturated Rings with More Than Two Heteroatoms (Excluding Phosphazenes)

Interestingly, reaction of the same diphosphetidine **10** with a carbodiimide or a nitrile affords, respectively, an example of a 1,2,4-azadiphosphinine or a 1,4,3-azadiphosphinine ring system [<1999ZNB1478, 1998ZNB443>](#). In contrast, the reaction of diazaphosphetidine **11** with an acetylene provides a 1,3,4-diazaphosphinine ([Scheme 6](#)) [<1996PS429>](#).



Scheme 6

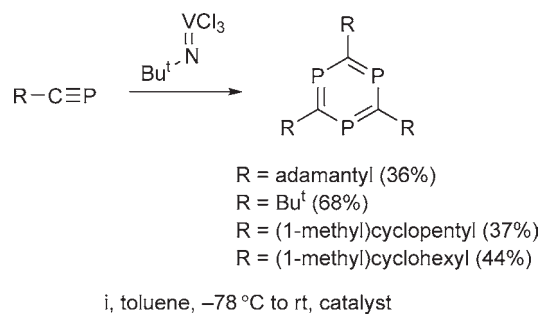
An example of a λ^3 - [<1996JA11978>](#) and two examples of λ^5 -1,3,2-diazaphosphinines [<2002PS2199, 2003PS2127>](#) have been reported. These reactions proceed through successive displacements of chlorine atoms from PCl_3 (for λ^3 -phosphorus) and PCl_5 (for λ^5 -phosphorus). Further displacement of chlorine atoms leads to diversification of structures obtained in this method ([Scheme 7](#)).



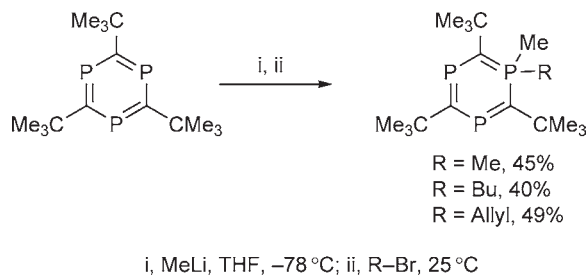
Scheme 7

1,3,5-Triphosphinines are prepared through a trimerization of phosphalkynes attached to tertiary carbons ([Scheme 8](#); see also [Scheme 48](#) for an alternative product) [<2000CEJ4558>](#).

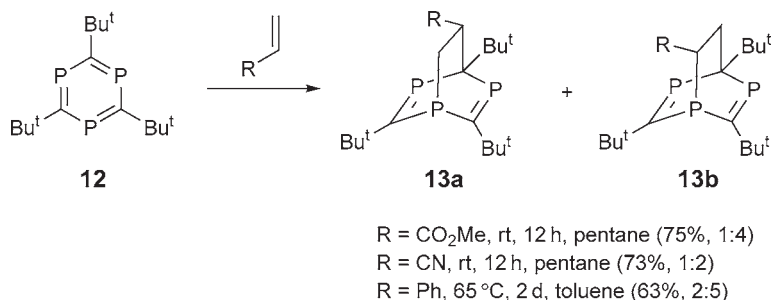
Two interesting reactions of triphosphinines are reported in the literature. Conversion of λ^3 - to λ^5 -triphosphinines through addition of an organometallic nucleophile and quenching by an electrophile has been reported ([Scheme 9](#)) [<2003S1526>](#). Cycloaddition of 1,3,5-triphosphinine **12** to alkenes is also reported and, interestingly, the resulting cycloadducts **13a** and **13b** are stable and can be isolated ([Scheme 10](#)) [<1999PS261, 2001EJO3425>](#).



Scheme 8

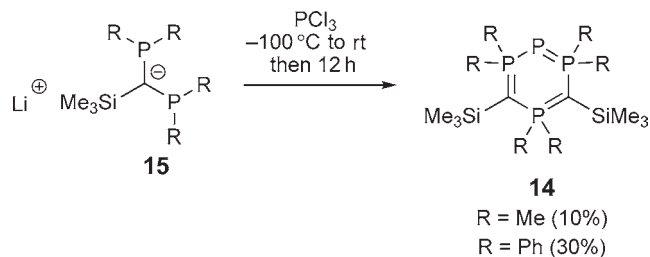


Scheme 9

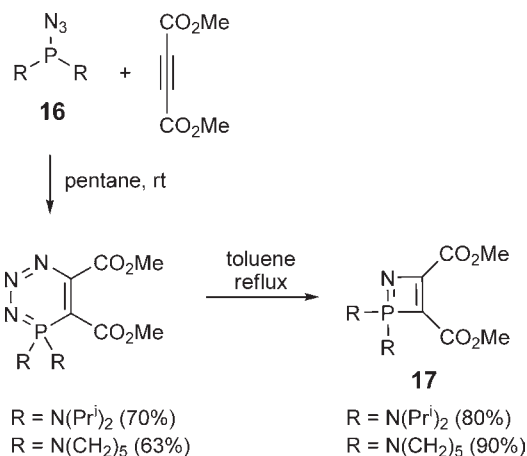


Scheme 10

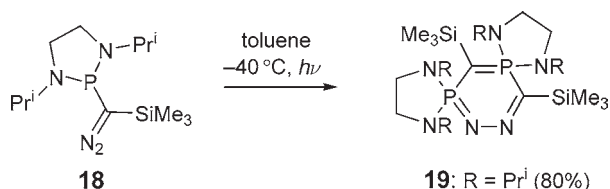
1,2,3,5-Tetraphosphinines **14** are obtained in moderate yields from the reaction between lithium salt **15** and PCl₃ followed by slow warming (Scheme 11) <1997JOM(529)151>. Cycloaddition of azidophosphine **16** to dimethyl acetylenedicarboxylate (DMAD) yields a 1,2,3,4-triazaphosphinine, which undergoes an interesting ring contraction with extrusion of nitrogen to afford azaphosphetidine **17** (Scheme 12) <1994JA8087, 1996PS429>. Finally, photo-initiated dimerization of **18** leads to the formation of 1,2,3,5-diazadiphosphetidine **19** (Scheme 13) <2004CEJ1982>.



Scheme 11



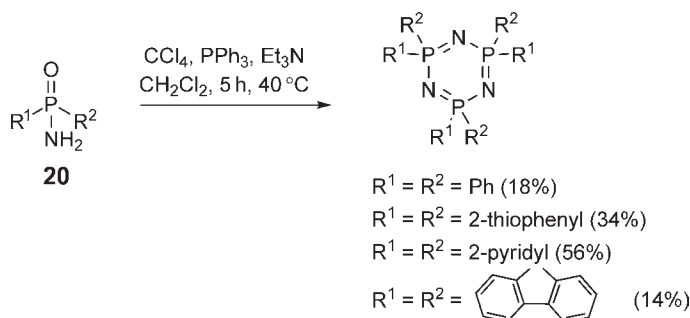
Scheme 12



Scheme 13

9.16.4.3 Phosphazenes

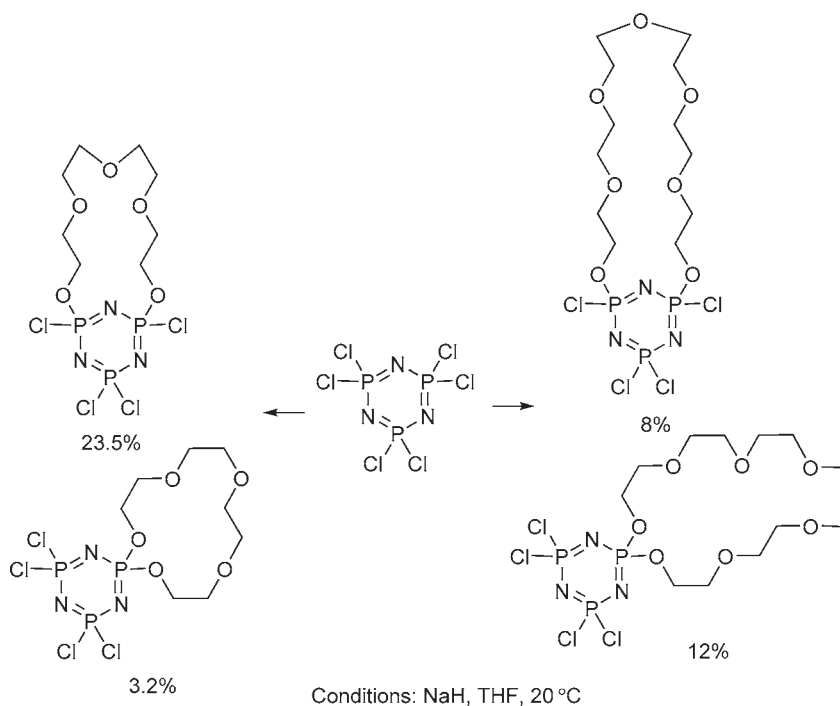
Phosphazenes are a large group of heterocyclic compounds, which have been covered previously in this series. However, two particular aspects of their chemistry are discussed here as they are relevant in the context of fully unsaturated phosphorus containing rings. The first of these is the synthesis of *P*-aryl-substituted phosphazenes through a condensation of phosphonamidates, for example, **20** (Scheme 14) <1996PS33>. The other is the role of ring size on 1,1- vs. 1,3-substitution (Scheme 15) <1995JOC7433, 2006JCD1302>.



Scheme 14

9.16.4.4 Fully or Partly Saturated Rings with Two Heteroatoms

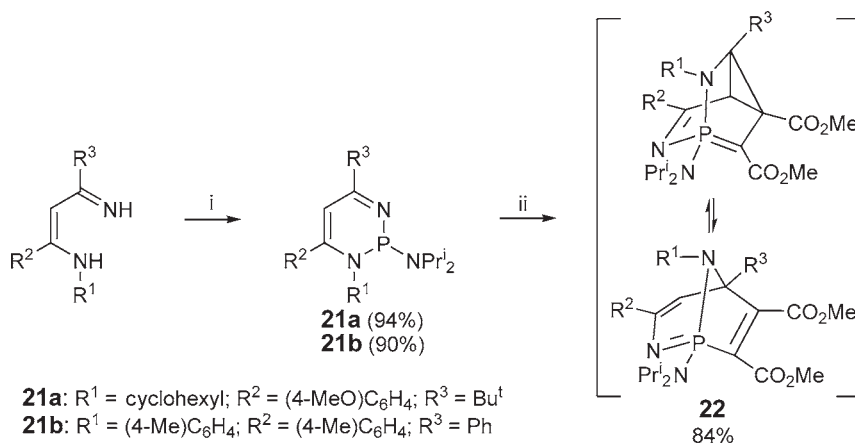
There have been numerous and varied methods presented in the literature for the preparation of saturated azaphosphinanes and diphosphinanes. These avenues include cycloaddition, nucleophilic displacement, amide formation, and Michael addition. Many of these reactions are common across the ring systems but, nevertheless, are discussed individually for ease of reference.



Scheme 15

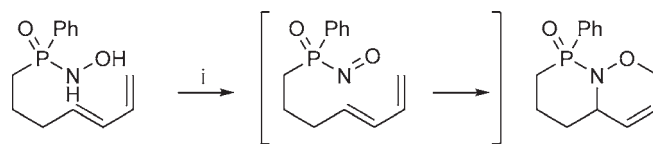
9.16.4.4.1 1,2-Azaphosphinanes

Preparation of didehydro-1,3,2-diazaphosphinanes **21a** and **21b** are reported, and cycloaddition of didehydro-1,3,2-diazaphosphinane **21a** as the diene component has been investigated as a means for the preparation of bridged 1,2-azaphosphinane **22** (Scheme 16) <1997JOM(529)233, 1998EJO1425>. However, cycloaddition reactions not involving either heteroatom in the diene component have been also employed for the synthesis of 1,2-azaphosphinanes (Scheme 17) <2002JOC5422, 2002JOC6174>.



i, Pr₂NPCl₂, Et₃N, CH₂Cl₂, 20 °C; ii, DMAD, Diethyl ether, -20 °C

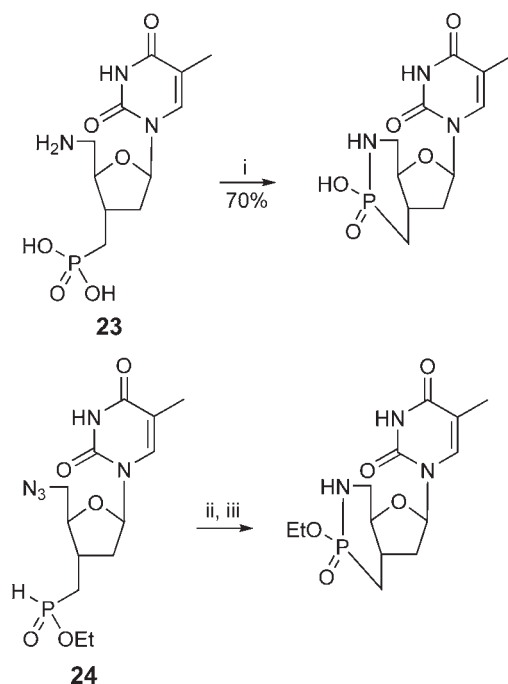
Scheme 16



i, tetrabutylammonium periodate, CH_2Cl_2 , rt

Scheme 17

While cyclizing amidation of amino $\lambda^5\delta^4$ -phosphorus acid/esters (e.g., **23**) remains a powerful method, there have been now examples of cyclizing amidation of azido $\lambda^5\delta^4$ -phosphorus esters (e.g., **24**) (Scheme 18) <2001SL473, 2004AGE3471>.

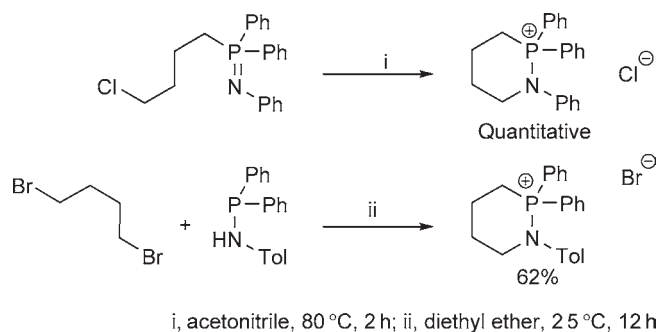


i, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide EDCI
 ii, $\text{CF}_3\text{C}(\text{OTMS})=\text{N}(\text{TMS})_2$, pyridine, 0–20 °C
 iii, TBAF, THF, 3 h, 20 °C

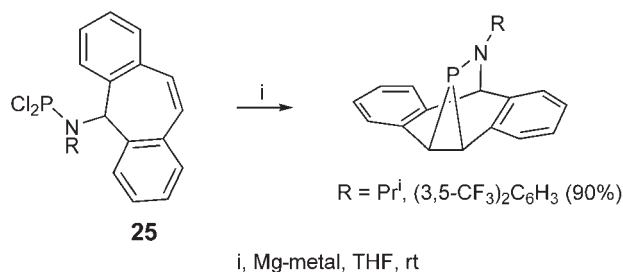
Scheme 18

Nitrogen substitution of iminophosphoranes <2002CHE95, 2002PS1701, 1999PS11> and phosphorus amides <2003SL801> has also been used for the synthesis of 1,2-azaphosphanes (Scheme 19).

The remaining methods to the title compounds involve addition of phosphorus to an alkene or aromatic ring. An interesting feature that adds to the diversity of the chemistry of organophosphorus compounds is that $\delta^3\lambda^3$ -phosphorus can exhibit both nucleophilic and electrophilic properties, depending on its substituents. For instance, dichlorophosphine **25** is sufficiently electron deficient to be attacked by an alkene (Scheme 20) <1999AGE1623, 2002PS1771, 2000T143, 2003C187>.



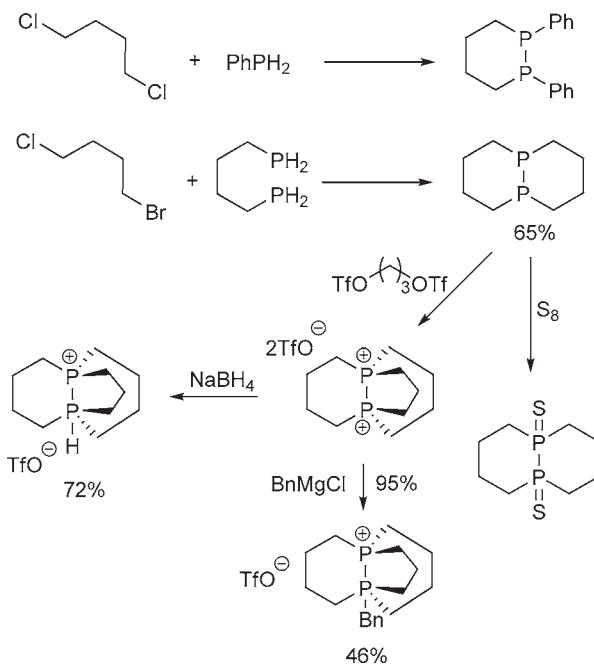
Scheme 19



Scheme 20

9.16.4.4.2 1,2-Diphosphanes

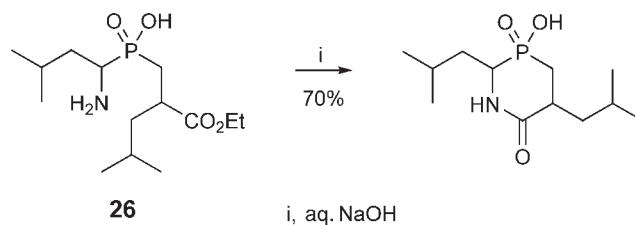
Interestingly, electrophilic substitution of phosphines leads to formation of 1,2-diphosphanes, presumably via an oxidation step ([Scheme 21](#)) <1997JPR482, 1998J(P1)1643, 1998J(P1)1657, 2001J(P2)288>. The P–P bond is surprisingly stable, surviving a number of chemical transformations ([Scheme 21](#)).



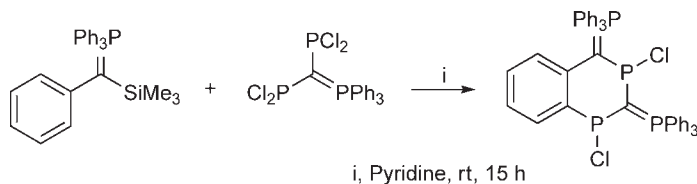
Scheme 21

9.16.4.4.3 1,3-Azaphosphanes and 1,3-diphosphanes

Kafarski has reported an unexpected cyclization leading to a 1,3-azaphosphinane during hydrolysis of **26** (Scheme 22) <2003JME2641, 1996JOC6601>. An example of a 1,3-diphosphinane has been reported by Schmidpeter (Scheme 23) <1996ZNB773>.

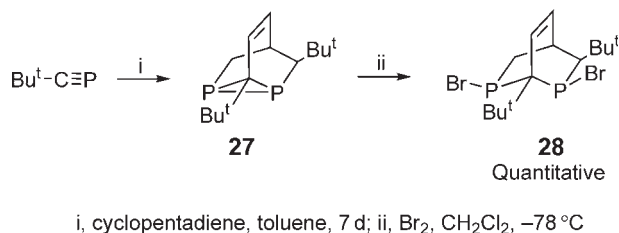


Scheme 22



Scheme 23

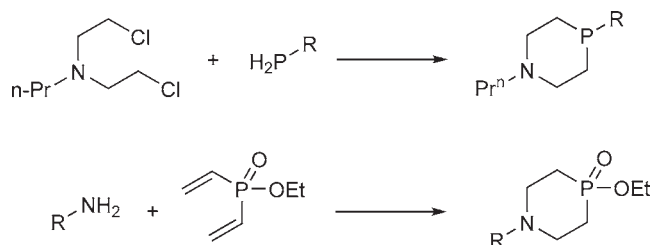
One of the fascinating structures obtained from cycloadditions of phosphalkynes is the bicyclic diphosphinane **27**, which affords bicyclic diphosphinane **28** after treatment with bromine (Scheme 24) <1995BSF652, 1998S427>.



Scheme 24

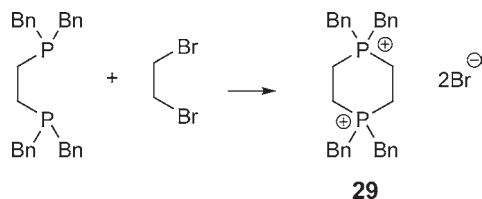
9.16.4.4.4 1,4-Azaphosphanes and 1,4-diphosphanes

Perhaps the most reliable route to these ring systems is through nucleophilic addition. Addition of phosphorus nucleophiles to nitrogen mustards <1998JOM(553)39, 2006TL1567> and addition of nitrogen and phosphorus nucleophiles to bisvinylphosphinates (Scheme 25) <1997PS141, 2000RCB495> have both been employed.



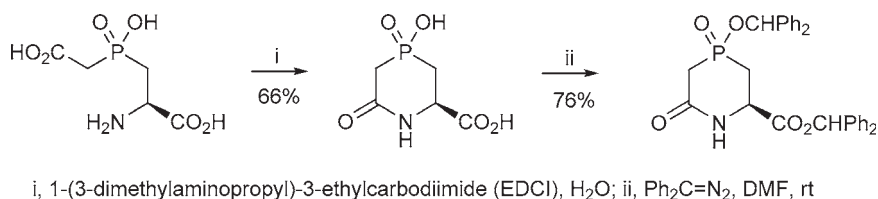
Scheme 25

Nucleophilic displacement has also been used for the synthesis of 1,4-diphosphanes, for example, **29** (Scheme 26) <1995PS55, 2001JCD1890, 2006TL1567>.



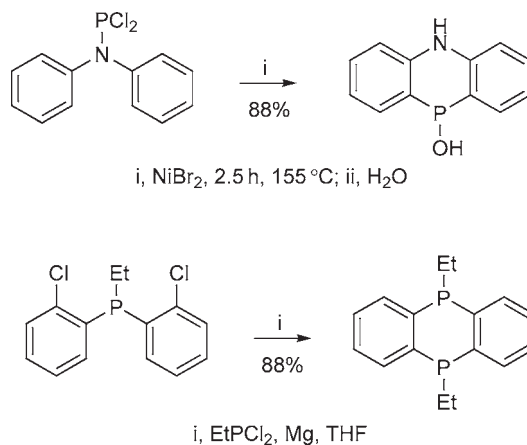
Scheme 26

Although not strictly speaking a consequence of their heterocyclic nature, amide formation has been used to construct the azaphosphinane ring system (Scheme 27) (see also Scheme 18) <1998JME4550>.



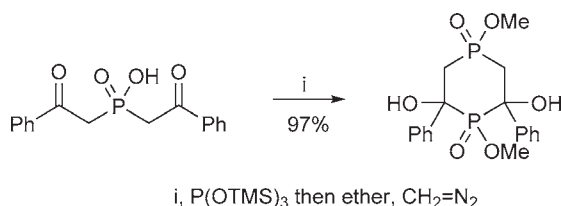
Scheme 27

However, as shown in the following examples, 1,2-azaphosphinane and 1,2-diphosphinane rings can be generated via electrophilic addition of a benzene ring to a chlorophosphine (Scheme 28) <1997PJC446, 1996BCJ1223, 2001JCD1890>.



Scheme 28

In addition to the nucleophilic displacement and conjugate addition routes outlined for the synthesis of 1,4-diphosphanes, double addition of a phosphorus nucleophile to a 1,4-diketone has also been employed for the synthesis of this ring system (Scheme 29) <1997RJC1947>.

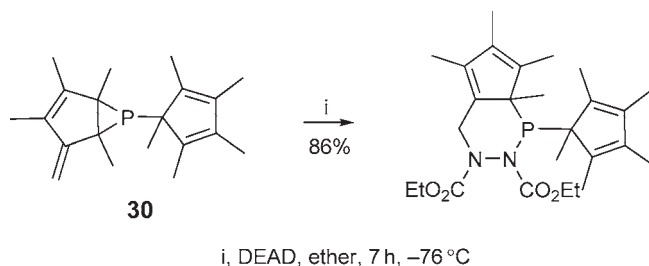


Scheme 29

9.16.4.5 Fully or Partly Saturated Rings with Three Heteroatoms

9.16.4.5.1 1,2,3-Diazaphosphanes

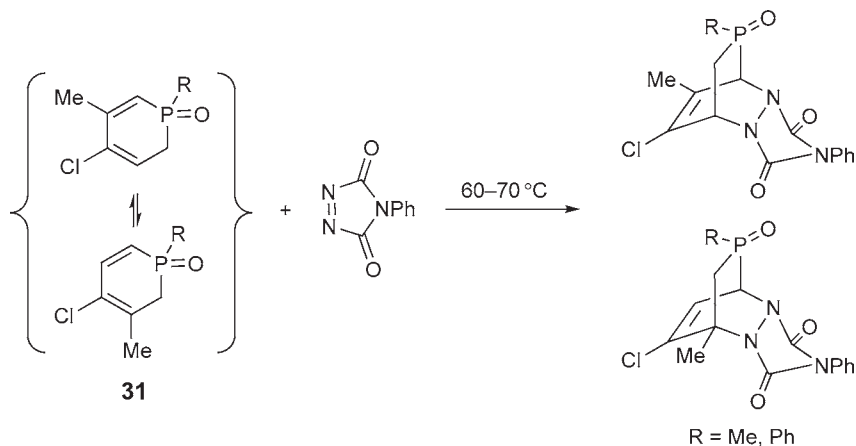
There is only a single example of this ring system in recent literature and that is one obtained from the cycloaddition of **30** with diethyl azodicarboxylate (DEAD) (**Scheme 30**) <1996CC1705>.



Scheme 30

9.16.4.5.2 1,2,4-Diazaphosphanes

Diels–Alder cycloaddition of compound **31**, which exists in equilibrium between two conjugate forms, with 4-phenyl-1,2,4-triazoline-3,5-dione affords a mixture of the two expected cycloadducts in good yields (**Scheme 31**) <2001HAC365, 2002HAC626>.

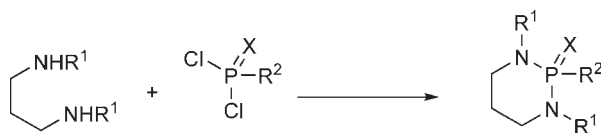


Scheme 31

9.16.4.5.3 1,3,2-Diazaphosphanes

This is by far the largest group in this category of heterocycles. However, despite the numerous examples of 1,3,2-diazaphosphanes in the literature, there are relatively few methods for their synthesis. Indeed, the vast majority of the methods are essentially a reaction between a phosphon(r)yl dichloride and a 1,3-diaminopropane. Some examples are shown in **Scheme 32** <1995PS107, 1996T12323, 1996JOC8551, 1996PS123, 1999EJO1701, 2000PS231,

1998BMC73, 2003OBC2283, 1998J(P1)1027, 1999JOC1958, 2004T10505>. There are, however, variations on this general theme. For example, one or both nitrogens may be secondary amines, one or both nitrogens may be aromatic, one can be an amide nitrogen, and one or both nitrogens can be part of an aromatic heterocyclic ring (**Scheme 33**) <2001IJB822, 2002PS399>. Reactions can be performed with a variety of phosphorylating agents, including phosphorus pentasulfide (**Scheme 34**) <1995PS65, 1995PS69, 1997PS1, 1997PS11, 2002HAC63, 2003PS211, 1995CB627, 1996ZNB1627, 1995CB695, 1995ZNB1818>.



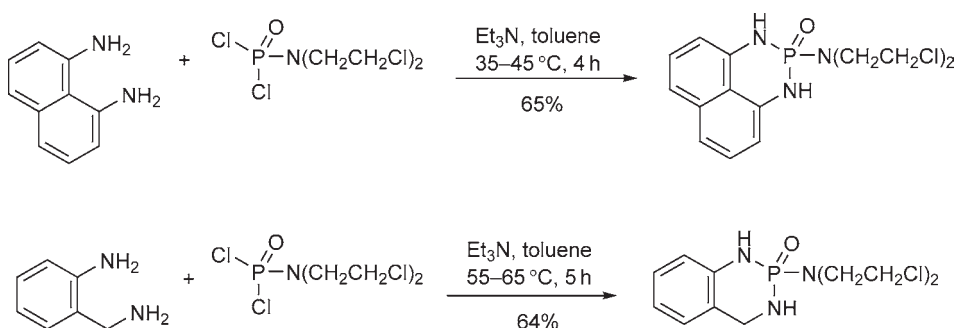
X = O, R¹ = Me, R² = Ph, Et₃N, benzene, 20 °C, 45 min (90%)

X = O, R¹ = Me, R² = Me, Et₃N, benzene, 20 °C, 2 h (83%)

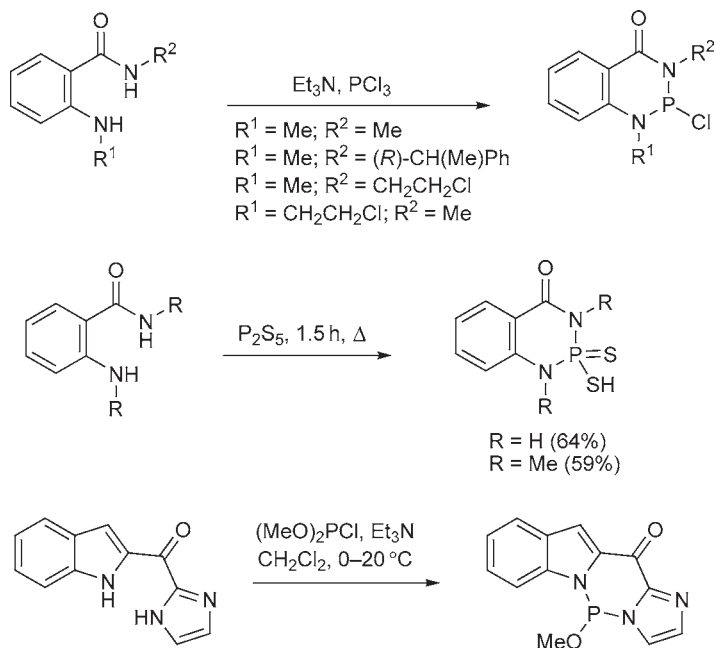
X = O, R¹ = CH₂Ph, R² = Et, Et₃N, CH₂Cl₂, rt, 18 h (68%)

X = S, R¹ = Me, R² = Prⁱ, Et₃N, CH₂Cl₂, rt, 16 h (82%)

Scheme 32

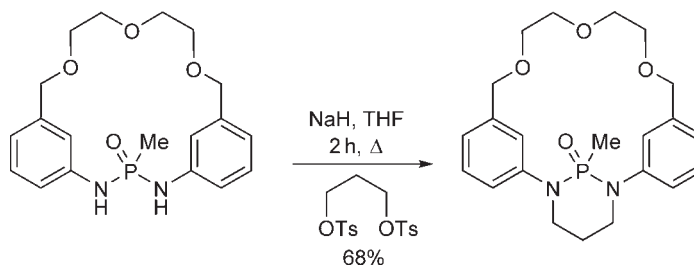


Scheme 33



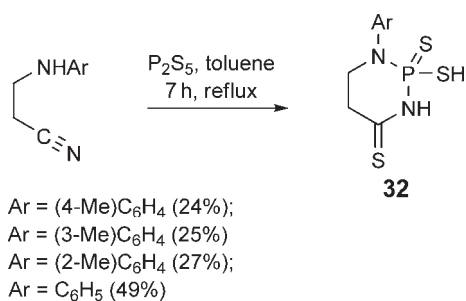
Scheme 34

The only other significant method for the synthesis of 1,3,2-diazaphosphinanes is alkylation of the nitrogen of a bis-phosphonamide (**Scheme 35**). Due to reduced delocalization, the nitrogen of a phosphonamide is more reactive than that of a carboxamide. Nevertheless, the reaction requires a relatively strong base, which can limit its application.



Scheme 35

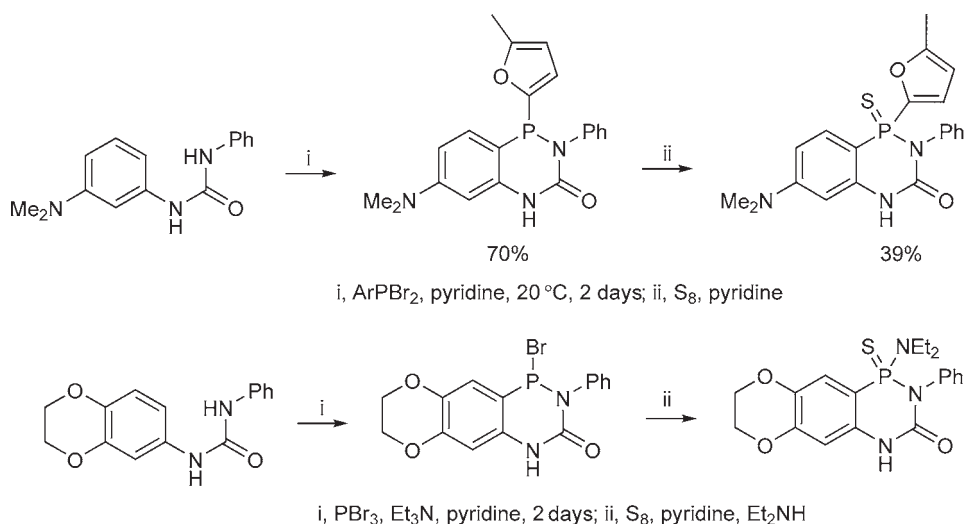
Finally, an unexpected reaction leading to a 1,3,2-diazaphosphinane **32** has been reported (**Scheme 36**) <2004M1113>.



Scheme 36

9.16.4.5.4 1,3,4-Diazaphosphinanes

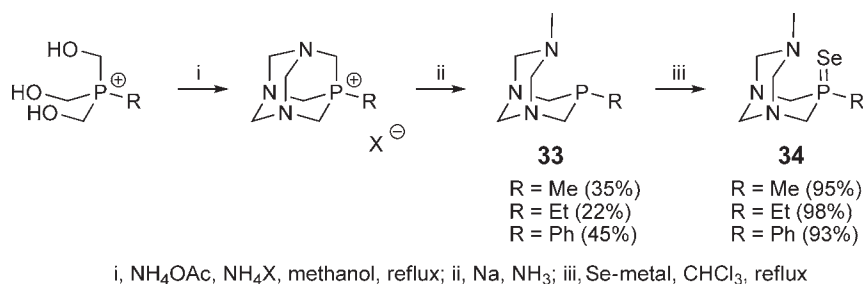
Examples of this ring system have been synthesized by 'insertion' of an electrophilic phosphorus species between a nitrogen and an electron-rich aromatic ring (**Scheme 37**; see also **Scheme 41** and related citations for a similar method applied to a different ring system) <2002CHE659>.



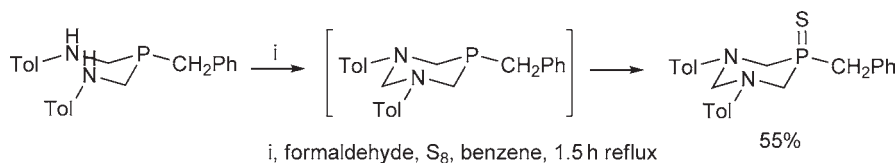
Scheme 37

9.16.4.5.5 1,3,5-Diazaphosphinanes

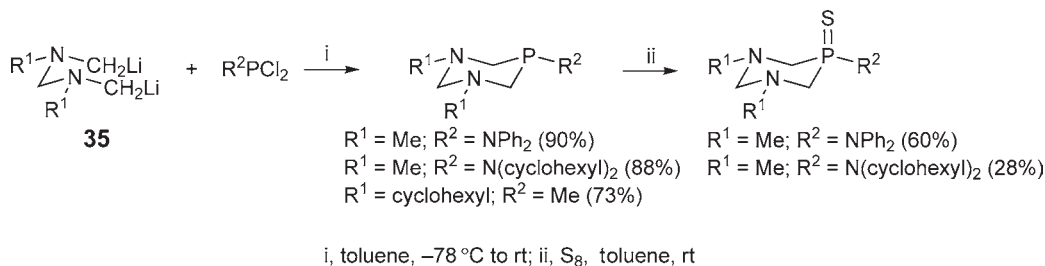
Fused analogs of this ring system, such as compounds **33** and **34**, are obtained as outlined in [Scheme 38](#) <1995CB891, 1990PS37, 1997AXC195>. As is the case with the corresponding 1,3,5-dioxaphosphinane ring (see [Scheme 76](#) and related text), the diazaphosphinane ring system can be prepared through an amination formation ([Scheme 39](#)) <1999RJC891, 2002RJC1754>. Finally, an unprecedented reaction involving ‘insertion’ of electrophilic phosphorus into lithiated **35** is reported ([Scheme 40](#)) <1997CB1777>.



Scheme 38



Scheme 39



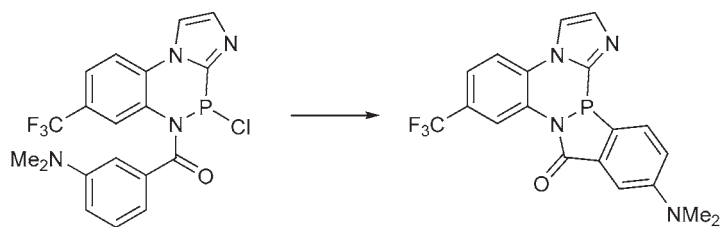
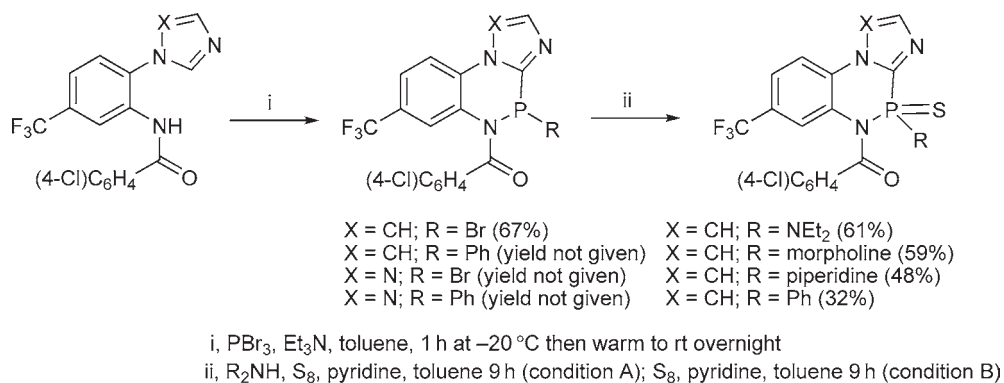
Scheme 40

9.16.4.5.6 1,4,2-Diazaphosphinanes

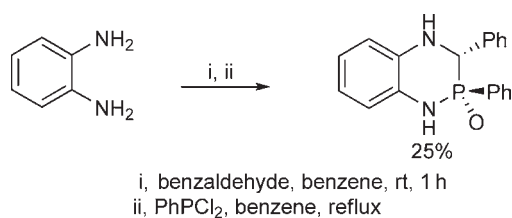
An example of this ring system has been synthesized by ‘insertion’ of an electrophilic phosphorus species between a nitrogen and an electron-rich aromatic ring ([Scheme 41](#); see also [Scheme 37](#) for a similar method applied to a different ring system) <2002HAC84, 2002HAC146, 2002CHE349>.

As is the case with the corresponding 1,4,3-oxazaphosphinane ring (see [Scheme 66](#) and related text), the 1,4,2-diazaphosphinane ring system can be prepared through reaction of a diamine, an aldehyde, and dichlorophenylphosphine ([Scheme 42](#)) <1999S40>.

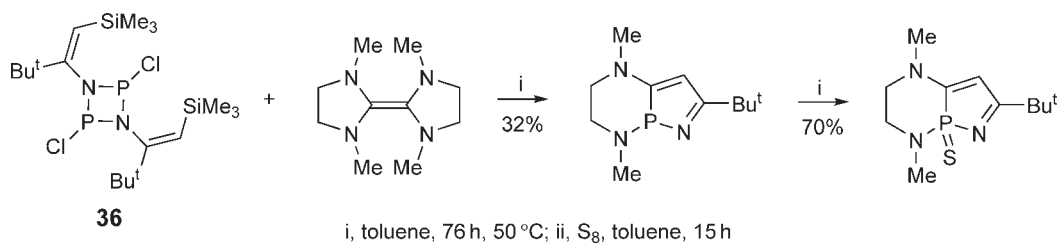
The remaining two methods reported for the synthesis of this ring system are an unusual rearrangement of **36** ([Scheme 43](#)) <1998EJI751>, and a ring closure through nucleophilic displacement ([Scheme 44](#)) <2002HAC63, 2001JCX445>.



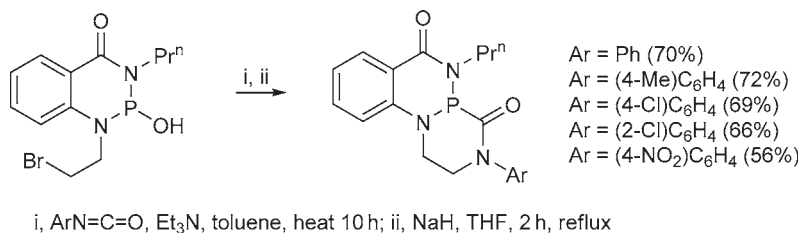
Scheme 41



Scheme 42



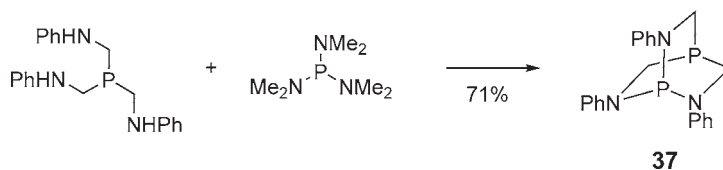
Scheme 43



Scheme 44

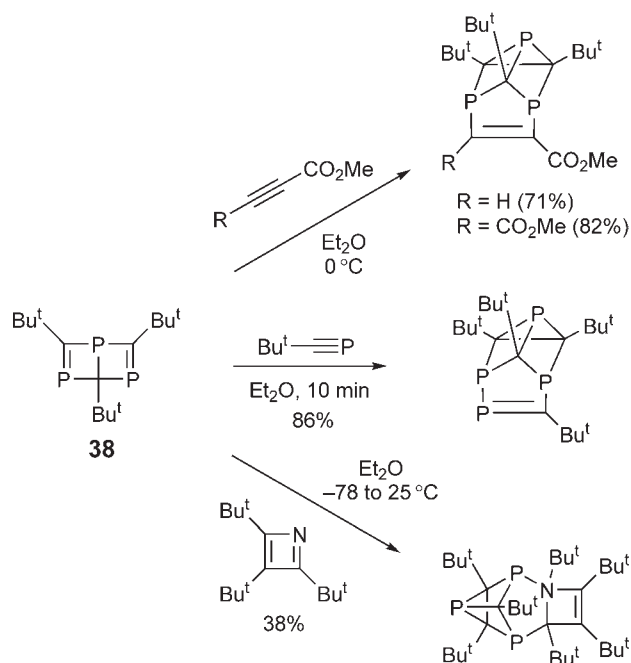
9.16.4.6 Fully or Partly Saturated Rings with More Than Three Heteroatoms

In general, saturated ring systems with four or more phosphorus or nitrogen heteroatoms are rare. Verkade has reported on the synthesis of the bicyclic ring system **37** using transamidation of a phosphorus acid amide (**Scheme 45**) <2001HAC114>. This methodology has been also applied successfully to the synthesis of oxygen-containing analogs (see **Scheme 84** and related text) <2001HAC114, 2003JOM(669)32>.



Scheme 45

Regitz and co-workers have obtained a plethora of rings containing a large number of heteroatoms. Thus, cycloadditions of **38** afford a series of complex heterocycles (**Scheme 46**) <1997JOM(529)215>, whereas the reactions of **39–41** afford a range of other exotic rings (**Scheme 47**) <1997AGE1337, 1999EJO587, 1998S1305>.



Scheme 46

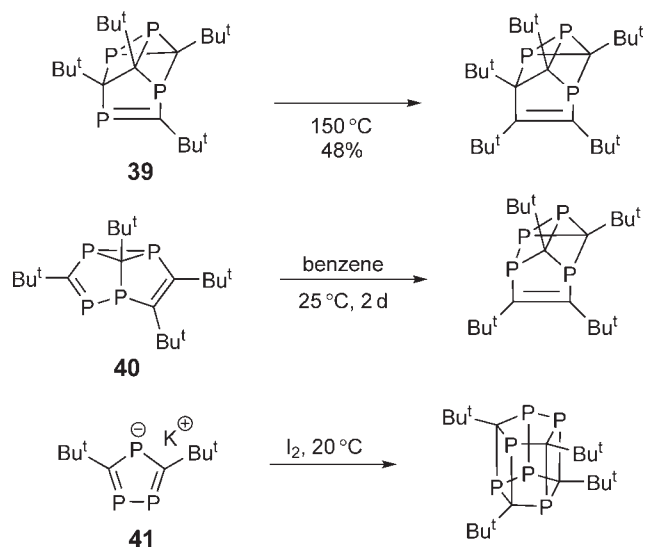
Finally, a series of reactions between a phosphalkyne and iminevanadyl species afford complex heterocyclic rings with high nitrogen and phosphorus atom contents (**Scheme 48**; see also **Scheme 8** for a related reaction and product) <2001ZNB951, 1998AGE1233>.

9.16.5 Ring Systems with At Least One Phosphorus and At Least One Chalcogen Atom

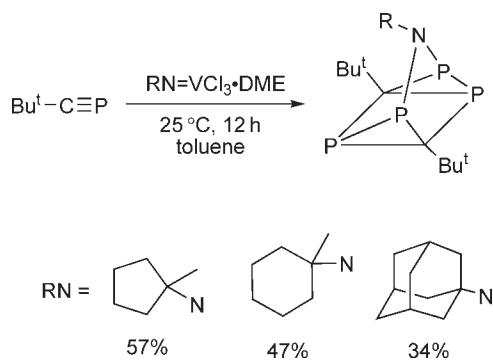
9.16.5.1 Ring Systems with One Phosphorus and One Oxygen or One Sulfur Atom

9.16.5.1.1 1,2-Oxaphosphanes and 1,2-thiaphosphanes

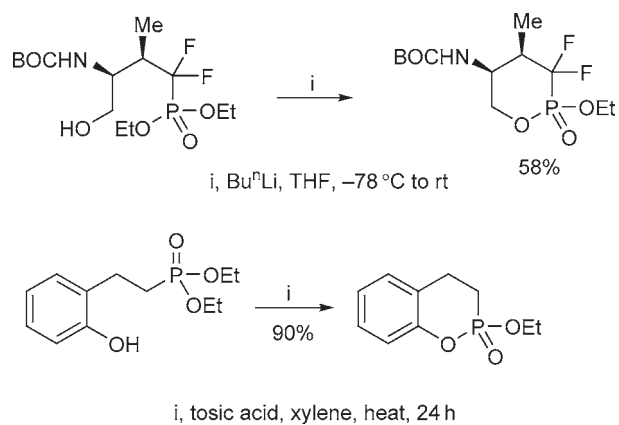
As was the case with amidation and 1,2-azaphosphanes, intramolecular esterification is the most common route to the 1,2-oxaphosphinane ring system (**Scheme 49**) <1995JOC2563, 1995J(P1)785, 1996JOC4666, 1996JA10168,



Scheme 47

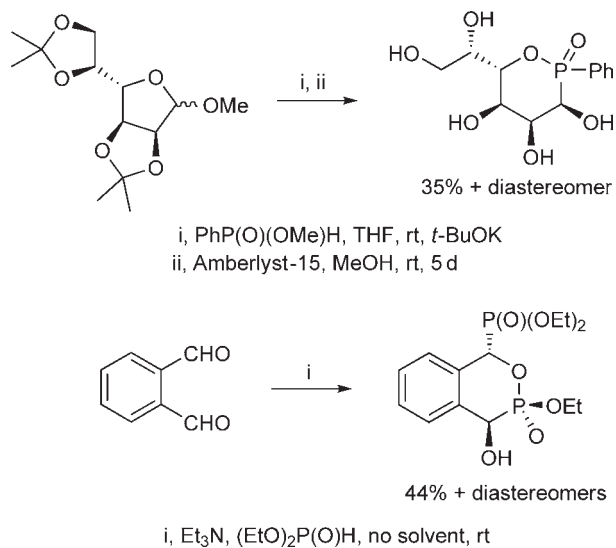


Scheme 48



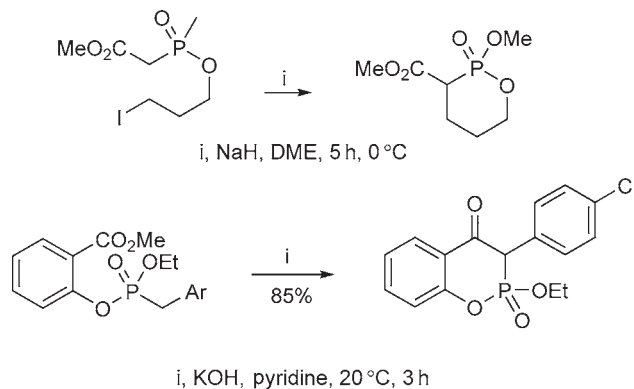
Scheme 49

1996TL5801, 1998PS45, 1999BMC279, 1999SL1903, 2000JOC1984, 2000CC1691, 2001JA10436, 2001TL8841, 2002TA233, 2002CC1600, 2003JOC7634>. The esterification step can sometimes be latent, occurring subsequent to a P–C bond formation (**Scheme 50**) <2000JOC2667, 2002HAC157, 2005TL3741>.

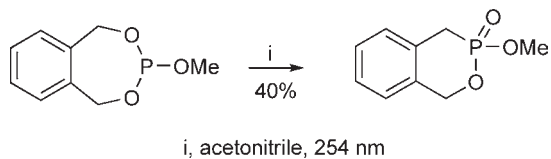


Scheme 50

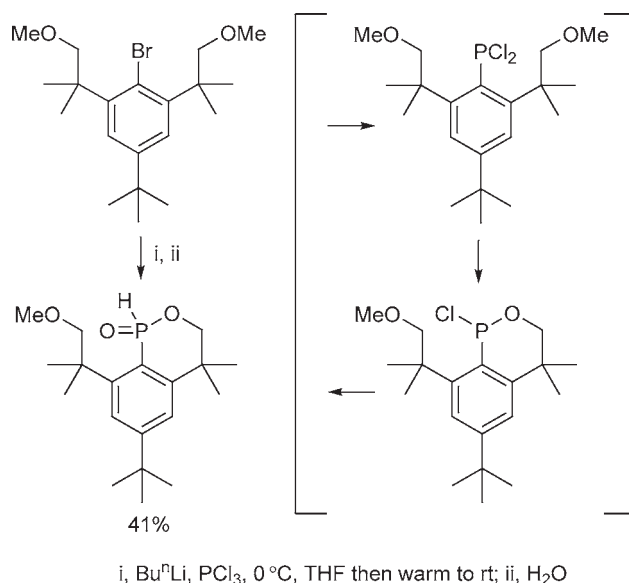
Among other routes to the 1,2-oxaphosphinane ring system are: anionic ring closures (**Scheme 51**) <2005OL4919, 1996J(P2)2221>, photolytic Arbuzov reaction (the mechanism of which was investigated) (**Scheme 52**) <2002JOM(646)239>, and an unusual reaction of a highly congested aryl phosphinedichloride (**Scheme 53**) <2000T43, 1999PS557>.



Scheme 51

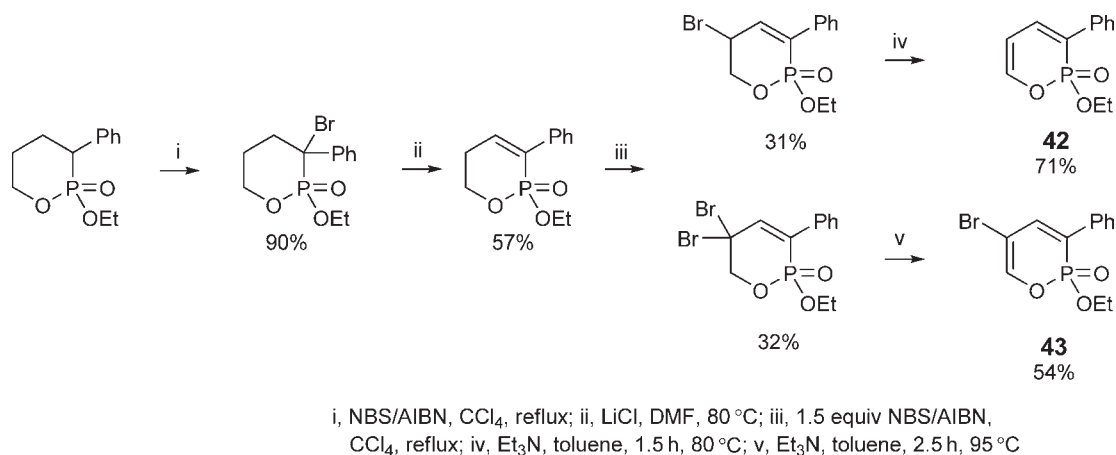


Scheme 52



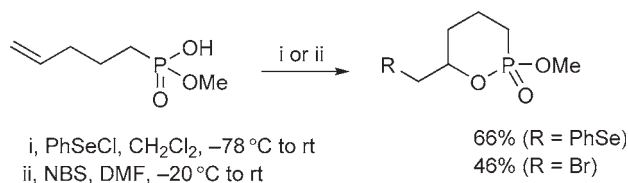
Scheme 53

Compounds **42** and **43**, phosphinane analogs of the well-investigated (2*H*)pyran-2-ones and their 5-bromo derivatives <1992TL7839>, have been synthesized but were found to be much poorer dienes than their carbon analogs (Scheme 54; also see Scheme 31 for a similar reaction) <2002JOM(646)153>.

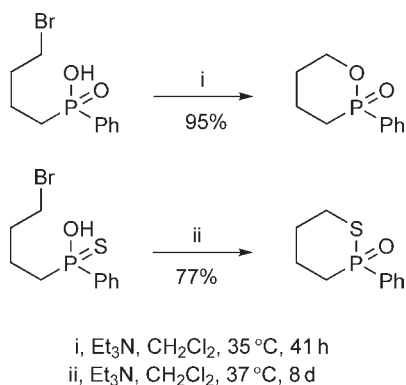


Scheme 54

The final route for the synthesis of 1,2-oxaphosphinanes is through an intramolecular cyclization (Schemes 55 and 56). The mechanism of this reaction has been investigated <1997H(46)463, 1999J(P1)1347, 1995CC83, 1998PS265>. Formation of a six-membered ring is favored over a five-membered ring (unlike the all-carbon analog) and, as will be shown shortly, the analogous reaction is particularly useful for the formation of 1,2-thiaphosphinanes.

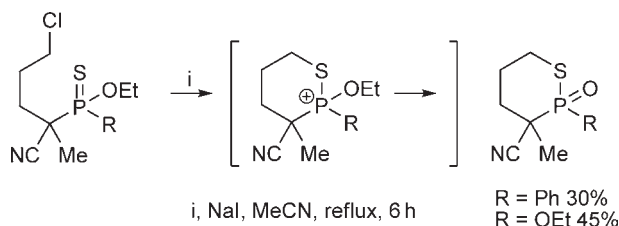


Scheme 55



Scheme 56

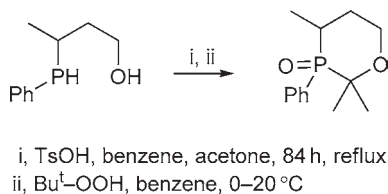
1,2-Thiaphosphinanes are synthesized via an intramolecular cyclization analogous to that seen for the synthesis of 1,2-oxaphosphinane (Scheme 57) <1999PS569, 1999PS589, 1998PS209, 2002PS1787, 2002HAC1, 2001RJC359>.



Scheme 57

9.16.5.1.2 1,3-Oxaphosphinanes

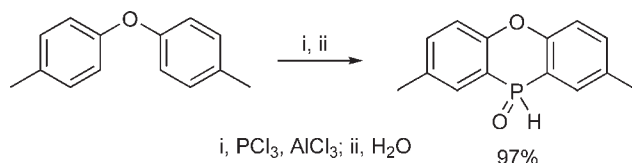
Only a single route to this ring system is reported in the period covered by this chapter (Scheme 58) <2005JOC7473>. There are no reports of the 1,3-thiaphosphinane ring in the period covered by this chapter.



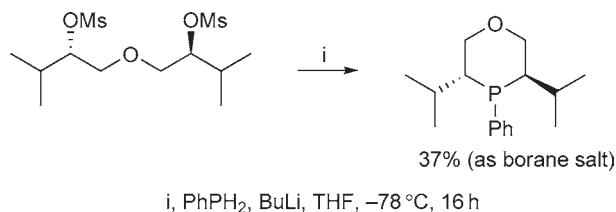
Scheme 58

9.16.5.1.3 1,4-Oxaphosphinanes and 1,4-thiaphosphinanes

A double Friedel-Crafts phosphination or equivalent (Scheme 59) <1999AGE336, 2004ASC789, 1996BCJ1223, 1996PS545, 1997JA1208, 2004HAC437, 1999PS601>, as well as a double nucleophilic substitution (Scheme 60), have been used for the synthesis of the 1,4-oxaphosphinane ring system. A reaction, analogous to the one used for the preparation of 1,4-diphosphinane (see Scheme 29), is used for the synthesis of 1,4-thiaphosphinane <1997RJC1947>.



Scheme 59



Scheme 60

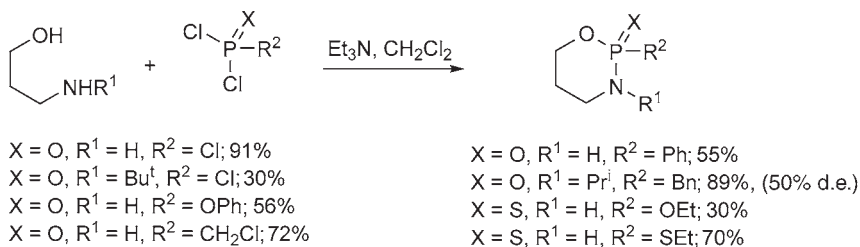
9.16.5.2 Ring Systems with One Phosphorus, One Oxygen, and One Other Heteroatom

9.16.5.2.1 1,3,2-Oxazaphosphinanes

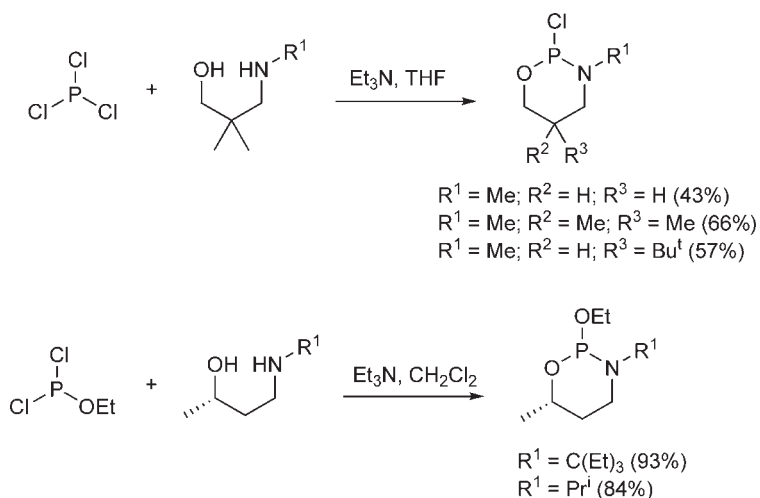
This ring system has been studied extensively in the literature mainly because it is a constituent of phosphamide antitumor compounds and also due to its application in asymmetric synthesis [<1995JA11879, 1995TL6631, 2000SL1769, 2003SL513>](#).

The synthesis of this ring system is not particularly different from those used for the analogous 1,3,2-diazaphosphinane ([Schemes 32–34](#)) and 1,3,2-dioxaphosphinane ([Schemes 75 and 76](#)) rings. The main method is basically a reaction between a phosphon(ryl) dichloride and a 1,3-aminopropanol ([Schemes 61 <1995RCB2147, 1995JA11879, 1994JOC2922, 1998JOC618, 2003CPB113, 2005EJO1189, 1995TA1813, 1996PS473> and 62 <1994JOC2922, 1995JOC4767, 1995JOC7535, 1995PS69>](#)). There are, as before, variations on this general theme. For example, the nitrogen may be substituted by alkyl or aryl groups [<1995RCB2147>](#), or even be part of an aromatic heterocycle [<1995PS69, 1996TL977, 1997TL3797>](#). A range of synthetically accessible and commercially available phosphon(ryl) dichlorides can be used. A method which is particularly advantageous is the formation of 1,3,2-oxazaphosphinane-2-oxides through Arbuzov reaction of 1,3-oxazaphosphinanes [<2000SL1769, 2000SL1771, 2003SL513>](#), although this may lead to unwanted side products ([Scheme 63](#)) [<2001TL743>](#).

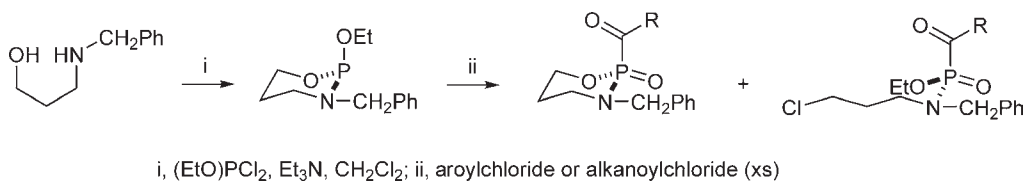
While cyclizing amidation of $\lambda^5\delta^4$ -phosphorus acid/esters remains a powerful method ([Scheme 64](#)) [<1994AJC903, 1996JOC6601, 1997T12961, 1998JME4550, 2001TL8841, 2003JME2641>](#), there have now been examples of cyclizing amidation of $\lambda^5\delta^4$ -phosphorus into an azide ([Scheme 65](#); see also [Scheme 18](#)) [<1998NN1231>](#).



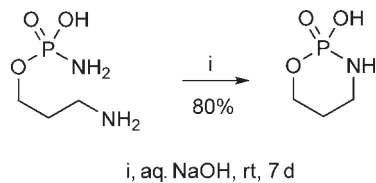
Scheme 61



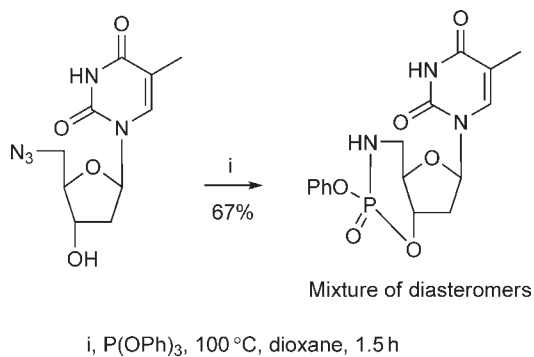
Scheme 62



Scheme 63



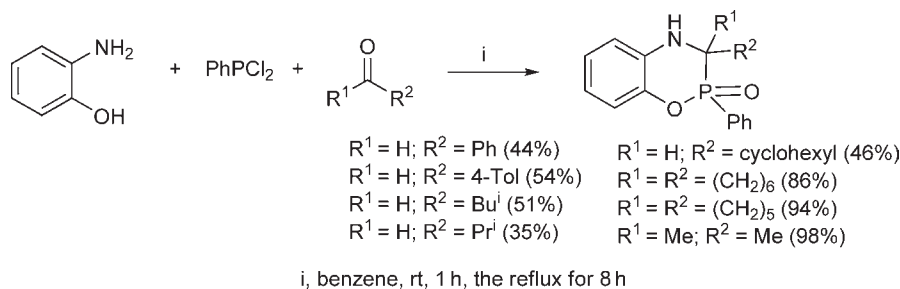
Scheme 64



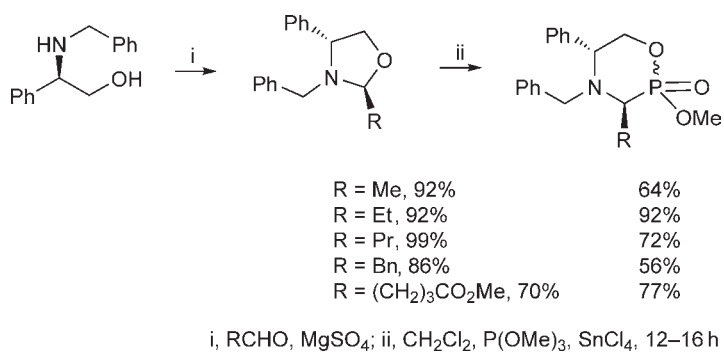
Scheme 65

9.16.5.2.2 1,4,3-Oxazaphosphinanes

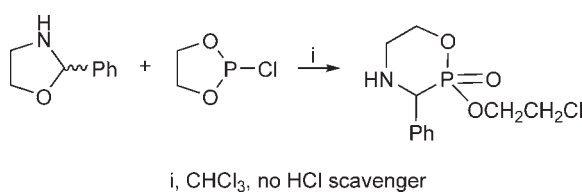
The main route to this ring system is through intramolecular addition of a phosphorus ester to an imine which may be generated *in situ* (Scheme 66; see also Scheme 42 and related text) <1999S40>, or masked as an aminoral (Schemes 67 <1996JOC3687> and 68 <2003HAC56, 2001MC222, 2001MC222, 2001RJC1319, see also 1997T3627, 1997BML2477>).



Scheme 66

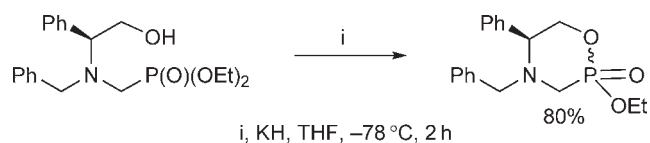


Scheme 67

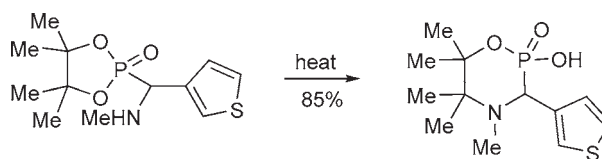


Scheme 68

Of course, transesterification remains a feasible route, as discussed before (Scheme 69) <2002T8973>. The only nonclassical route reported for this ring system is a thermal rearrangement (Scheme 70) <1999PS229>.

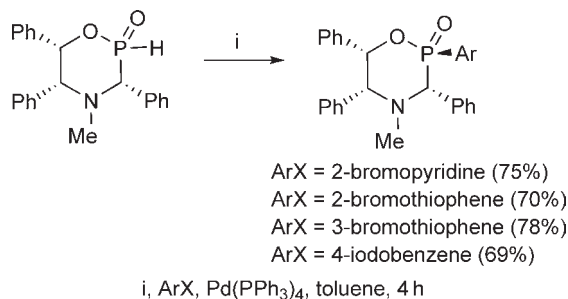


Scheme 69



Scheme 70

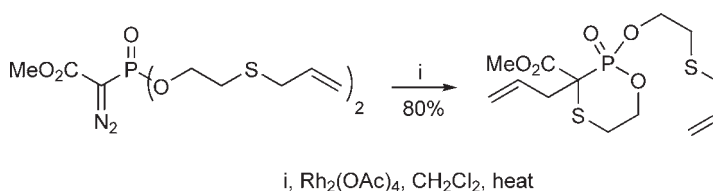
As mentioned before, ring systems containing phosphorus, oxygen, and nitrogen have many applications in synthetic chemistry. Cristau *et al.* have made extensive use of 1,4,3-oxazaphosphinanes as chiral reagents (Scheme 71) <2003TL3183, 2005T7029, 2005JOC7035, 2005JOM(690)2472>.



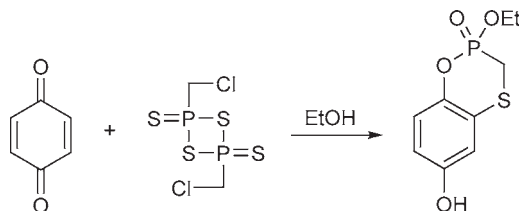
Scheme 71

9.16.5.2.3 1,4,2-Thioxaphosphinanes

Insertion of sulfur into a carbene followed by [2,3]-sigmatropic rearrangement of the attached allyl group has led to the formation of an example of the 1,4,2-thioxaphosphinane ring system (Scheme 72) <2001SL605>. This ring system is also reported through an unusual reaction of quinones (Scheme 73) <1996PS199>.



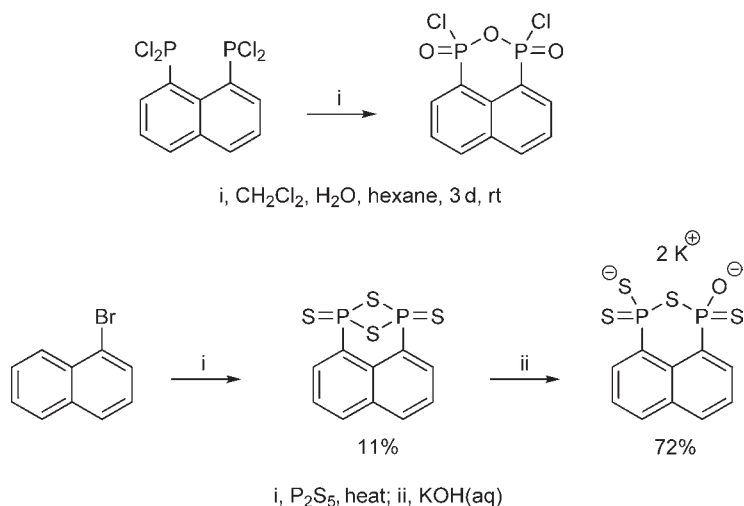
Scheme 72



Scheme 73

9.16.5.2.4 1,2,6-Oxadiphosphanes and 1,2,6-thiadiphosphanes

Woollins and co-workers have reported the synthesis of a naphthalene analog of Lawesson's reagent and its subsequent reactions leading to novel phosphorus-containing heterocycles (Scheme 74) <1997CB1485, 1999EJI2327, 1997JCD1347>.

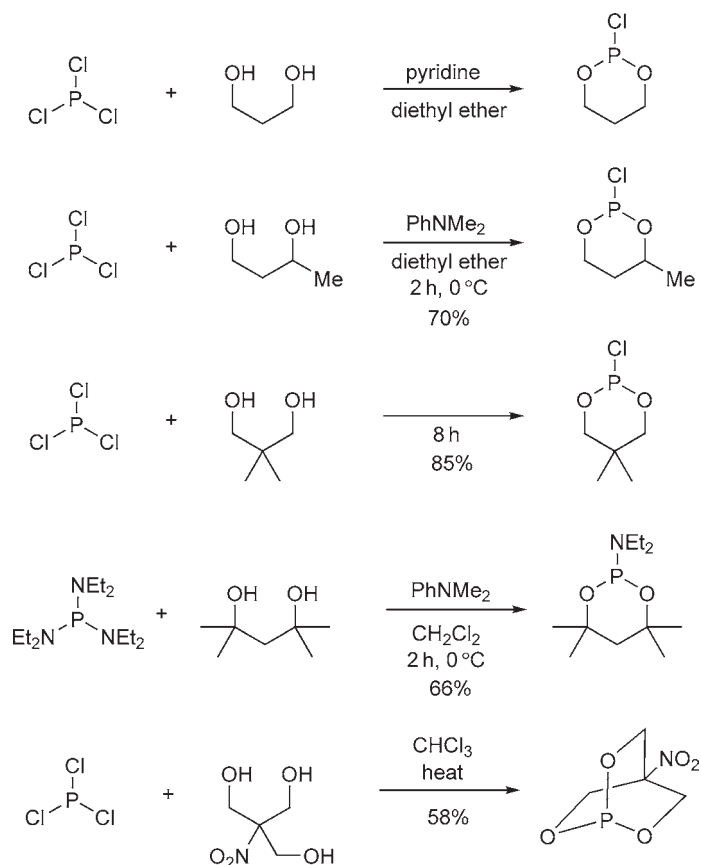


Scheme 74

9.16.5.3 Ring Systems with One Phosphorus and Two Oxygen Atoms

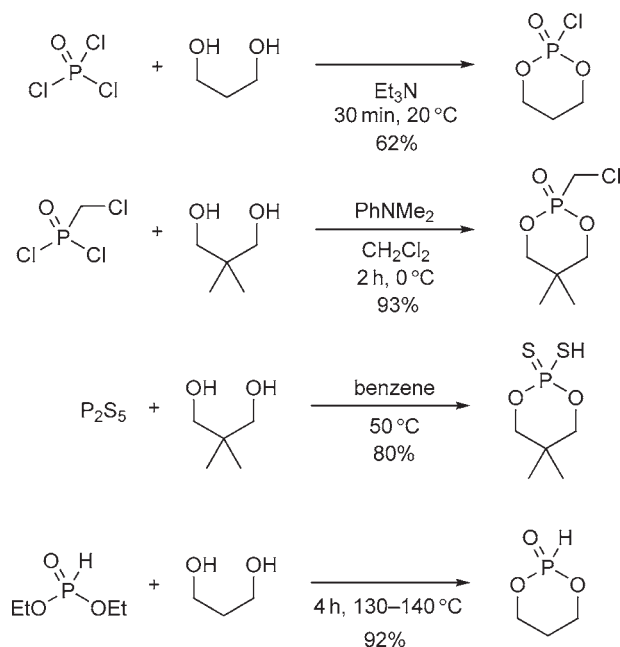
9.16.5.3.1 1,3,2-Dioxaphosphinanes

Synthetic routes to this particular ring system have continued to grow in the last decade, although they all essentially involve reactions of a 1,3-propanediol and an electrophilic $\delta^3\lambda^3$ -phosphorus reagent ([Scheme 75](#)) <2002JOM(642)191,



Scheme 75

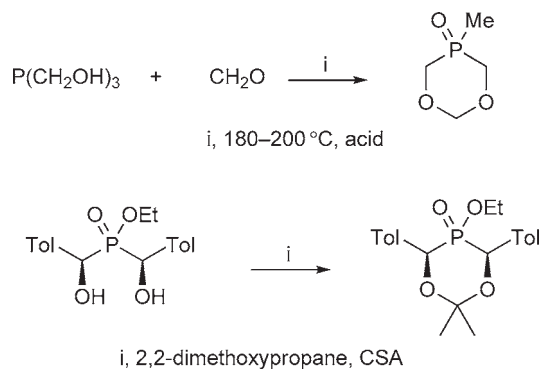
2000JOC3733, 2005TL3347, 2000H(52)799, 2003JCX341>, or $\delta^5\lambda^4$ -phosphorus reagent (**Scheme 76**) <1995PS91, 2002J(P1)1271, 2003T8821, 2000TA125, 1998JOC618>, typically one with a P–Cl bond. However, there are many variations on the general theme as can be seen in the schemes.



Scheme 76

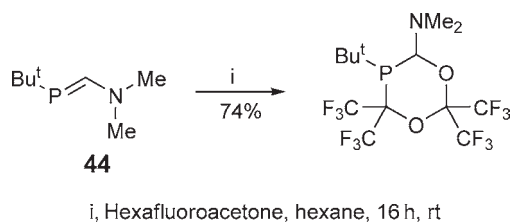
9.16.5.3.2 1,3,5-Dioxaphosphinanes

Kisanga and Verkade have reported on the formation of an acetal in the reaction of tri(hydroxymethyl)phosphite and formaldehyde (**Scheme 77**) <2001HAC114> and, similarly, a ketal formation is reported for the synthesis of another example of this ring system (**Scheme 77**) <2004TL6713>.



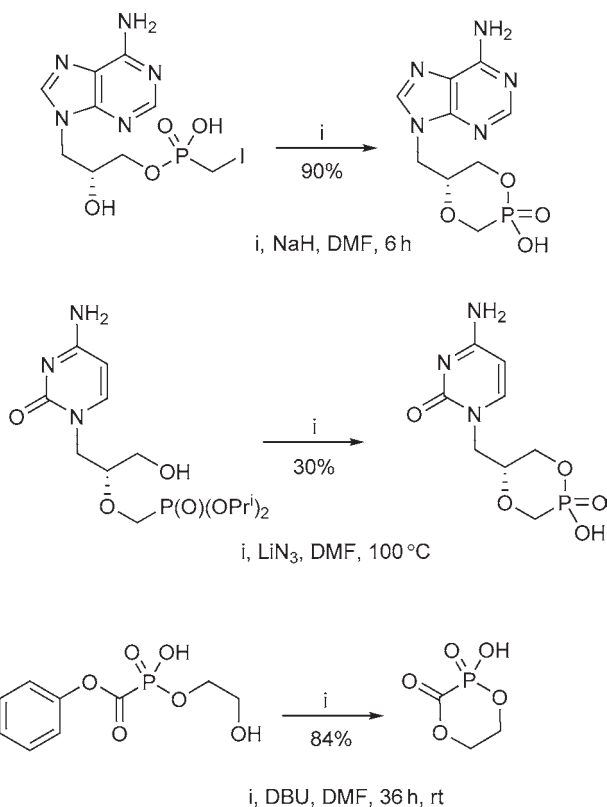
Scheme 77

Reaction of hexafluoroacetone with phosphorane **44** leads to the formation of an adduct, the structure of which is suggested as a 1,3,5-dioxaphosphinane (**Scheme 78**) <1995CB499>.

**Scheme 78**

9.16.5.3.3 1,4,2-Dioxaphosphinanes

Transesterification using a variety of bases as well as intramolecular nucleophilic displacement have been employed to synthesize members of the 1,4,2-dioxaphosphinane ring system (**Scheme 79**) <1997J(P1)3601, 1998S381, 2004BML3357, 2005JOM(690)2673, 2005AAC656>.

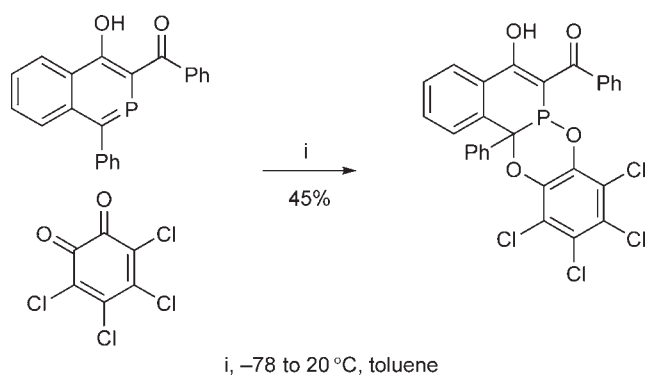
**Scheme 79**

There is also a report of this ring system being formed through a formal cycloaddition (**Scheme 80**) <2000T6259>.

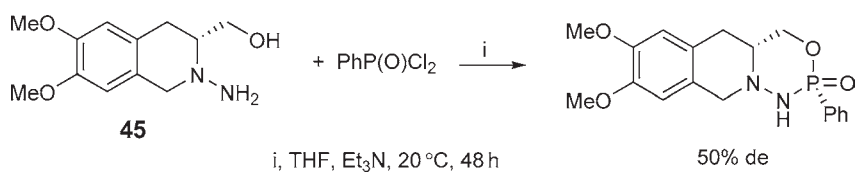
9.16.5.4 Other Ring Systems

Treatment of hydrazine **45** with phenylphosphonyl dichloride affords an example of a 1,3,4,2-oxadiazaphosphinane (**Scheme 81**) <2006T2883>.

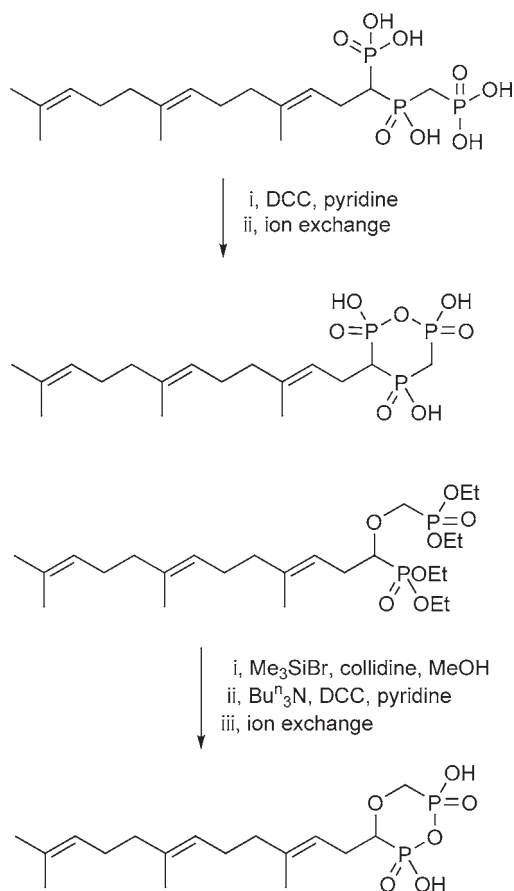
Both a 1,2,4,6-oxatriphosphinane and a 1,4,2,6-dioxadiphosphinane are reported via the dehydration of the corresponding bisphosphonic acid (**Scheme 82**) <1997BML2435, 1998BOC269>.



Scheme 80

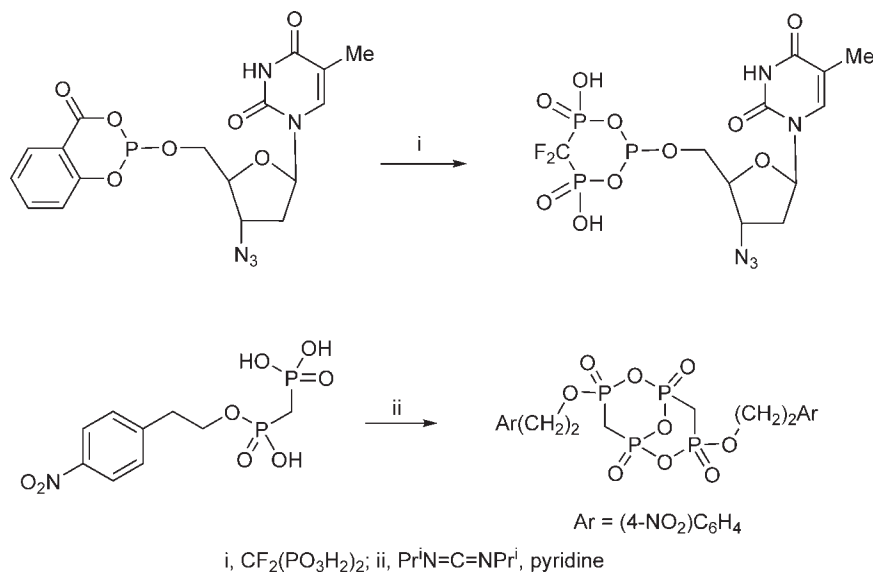


Scheme 81



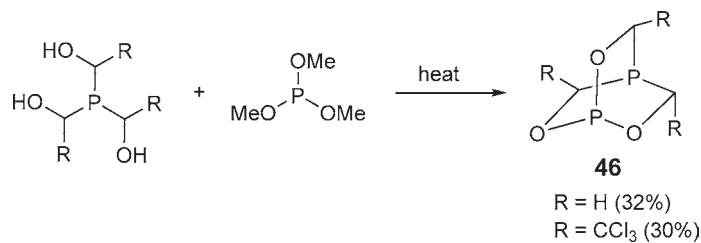
Scheme 82

Two further examples of heteroatom-rich heterocycles of phosphorus and oxygen have been reported (Scheme 83) <1998JOC1906, 1997JME2533, 2002JME703>.



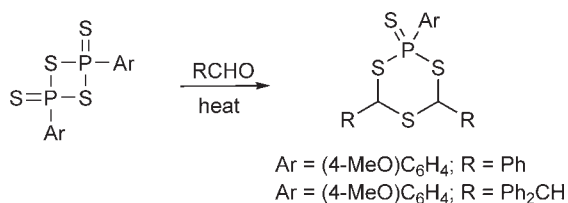
Scheme 83

Verkade and co-workers have reported on the synthesis of the bicyclic ring system **46** using transesterification of a phosphorus acid ester (Scheme 84) <2001HAC114, 2003JOM(669)32>. This methodology has also been applied successfully to the synthesis of nitrogen-containing analogs (see Scheme 45) <2001HAC114>.



Scheme 84

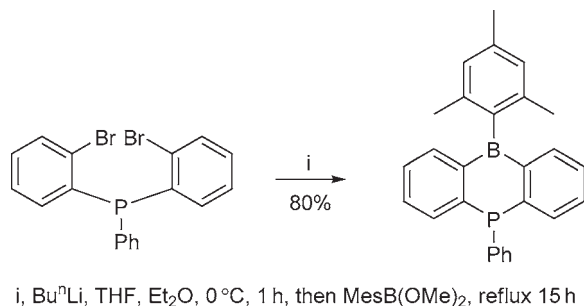
Treatment of benzaldehyde and diphenylacetaldehyde with Lawesson's reagent is reported originally to afford a cyclic 1,2,4,6-trithiaphosphorane (Scheme 85) <1996JOC5462, 2006PS249>.



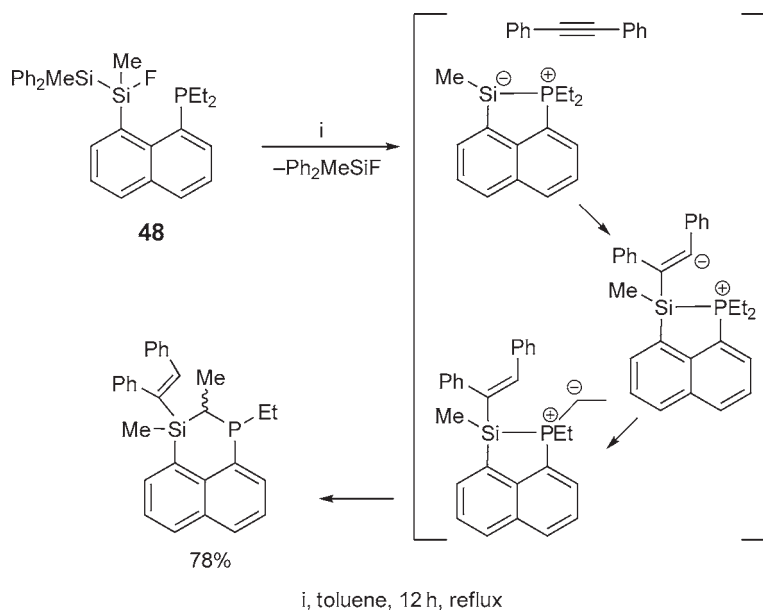
Scheme 85

9.16.6 Ring Systems with At Least One Phosphorus and At Least One Heteroatom Which Is Not Nitrogen or Chalcogen

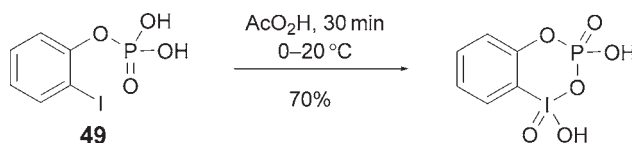
A synthesis of 1,4-boraphosphorane via halogen metal exchange between **47** and dimethyl mesitylborate has been reported (**Scheme 86**) <2005OL4373>. A phosphasilinane is reported from the thermal reaction of **48** with diphenylacetylene, which affords a sila-ylid as an intermediate (**Scheme 87**) <2001JA9210, 2002PS1409>. Oxidation of iodine in (2-iodophenol)phosphoric acid **49** leads to the formation of a cyclic 1,2,4,3-iododioxaphosphinane (**Scheme 88**) <1999BML353>.



Scheme 86

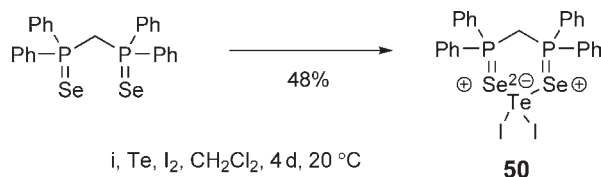


Scheme 87



Scheme 88

Finally, in this section, compound **50** represents the heterocycle with the most varied range of heteroatoms (Scheme 89) <2006EJI1294>.



Scheme 89

Relevant Website

<http://www.iupac.org> – IUPAC (International Union of Pure and Applied Chemistry).

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1996PS545
1996PS3
1996PS199
1996PS123
1996T12323
1996TL977
1996TL5801
1996ZNB773
1996ZNB1627
1997AGE1337
1997AXC195
1997BML2435

1997BML2477
1997CB1485
1997CB1777
1997H(46)463
1997JA1208
1997JCD1347
1997JME2533

1997JOM(529)151
1997JOM(529)215
1997JOM(529)233
1997J(P1)3601
1997JPR482
1997JJC446
1997PS141
1997PS11

1997PS1
1997RJC1947
1997T3627
1997T12961
1997TL3797
1998AGE1233
1998BMC73

1998BOC269
1998EJ1751
1998EJO1425
1998EJO2039
1998H(48)1903
1998HAC209
1998JME4550
1998JOC618
1998JOC1906
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9.17

Six-membered Rings with Two or More Heteroatoms with at least One Arsenic to Bismuth

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References		909

9.17.1 Introduction and Nomenclature of Six-Membered Heterocycles Containing Arsenic

This chapter outlines the synthesis and reactions of six-membered arsenic heterocycles with heteroatoms published mostly in the period 1995–2006. The importance and nomenclature of six-membered heterocycles containing arsenic atoms have been given in detail in CHEC-II(1996) <1996CHEC-II1073>. A literature survey for this chapter showed that little work had been done in this area in comparison with studies on nitrogen analogs. Although the chemistry of six-membered arsenic heterocycles with heteroatoms is restricted mainly to oxa-, thia-, aza-, phospho-, and diarsinines, during the last decade, six-membered arsenic heterocycles with boron, aluminium, gallium, indium, silicon, tin, lead, and selenium atoms have appeared in the literature. Accordingly, these heterocyclic ring systems

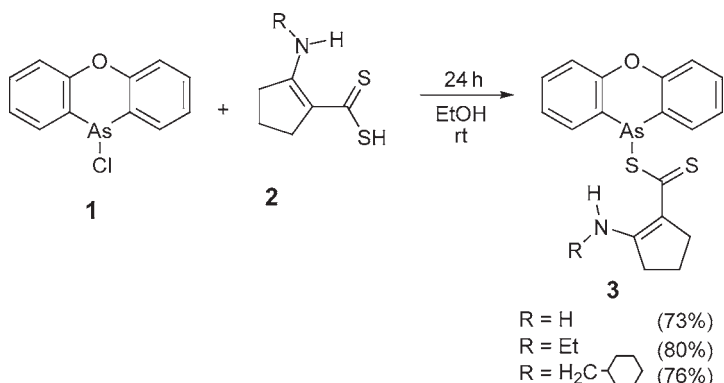
have been included in this chapter. Further, new developments in the chemistry of more common six-membered arsenic heterocycles containing oxygen, sulfur, nitrogen, and phosphorus atoms have been dealt with in detail.

9.17.2 Six-Membered Rings with Two Heteroatoms

9.17.2.1 Rings with One Arsenic and One Oxygen or Sulfur Atom

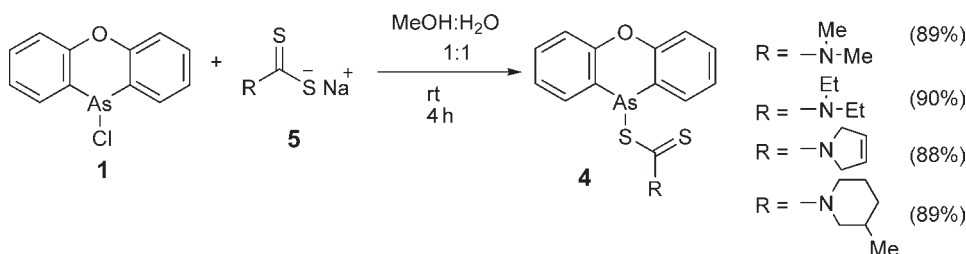
9.17.2.1.1 1,4-Oxarsinines

Phenoxarsin-10-yl derivatives of 2-aminocyclopent-1-ene-1-carbodithioic acid (ACDA), **2**, and its *N*-alkyl derivatives, viz. **3**, have been prepared by reacting 10-chloro-10*H*-phenoxarsinine **1** with the corresponding ACDA 1,1-dithioic acid **2** (Scheme 1) <1995AOM133>.



Scheme 1

Similarly, phenoxarsin-10-yl derivatives of dithiocarbamates, viz. **4**, have been obtained by the reaction of 10-chloro-10*H*-phenoxarsinine **1** with sodium dithiocarbamates **5** in good yields (88–90%) (Scheme 2) <1995JOM(493)61>.



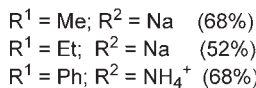
Scheme 2

Further, treatment of **1** with sodium or ammonium diorganodithiophosphinates **7** in CH₂Cl₂ yields the corresponding phenoxarsin-10-yl compounds **6** (Scheme 3) <1994JCD2191>.

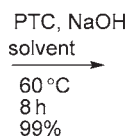
The crystal and molecular structures of the phenoxarsin-10-yl diorganodithiophosphinates **6** (R¹ = Me, Et) have been determined by Olivares *et al.* (Scheme 3) <1997ICA(255)319>.

10,10'-Oxybisphenoxarsinine (OBPA) **8** has been prepared by treatment of **1** with an 8–15% NaOH solution at the molar ratio 1:1.2–1.8 in the presence or absence of a phase-transfer catalyst (Scheme 4) <2003MIP1415620>.

The fungicide OBPA **8** is used widely in consumer products, such as shower curtains, wall coverings, and carpets. A possibility exists that microorganisms might be able to degrade OBPA to produce volatile trimethylarsine **9**. Andrewes *et al.* cultured microorganisms in a medium containing OBPA and examined the medium for possible degradation products. In the first experiment, the microorganism used was *Scapulariopsis brevicaulis*, whereas, in the second example, OBPA-tolerant microorganisms isolated from soil contaminated with arylarsenic compounds were used (Scheme 5) <2000AOM364>. However, they did not find any evidence of complete microbiological cleavage of aryl–arsenic bonds in any of the cultures, and no significant amount of trimethylarsine was detected in the headspace of *S. brevicaulis* cultures.



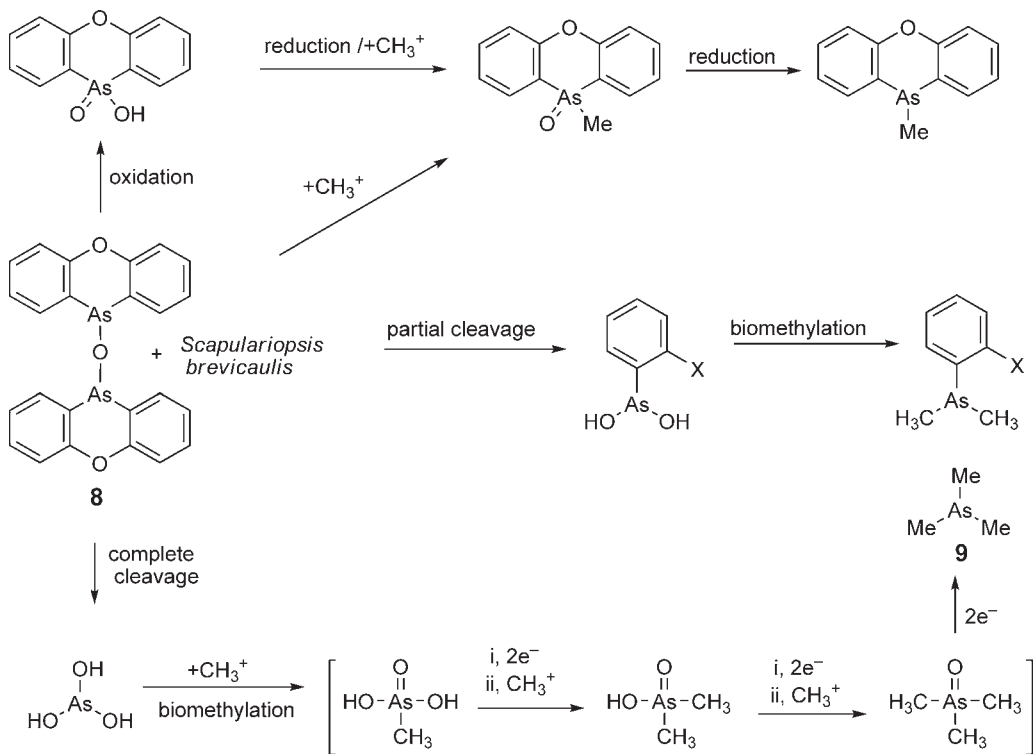
Scheme 3



PTC (phase-transfer catalyst) benzyltrimethylammonium chloride, benzyltriethyl chloride, or tetrabutylammonium chloride

Solvent = $\text{ClCH}_2\text{CH}_2\text{Cl}$, CH_2Cl_2 , or benzene

Scheme 4

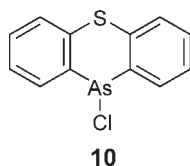


Scheme 5

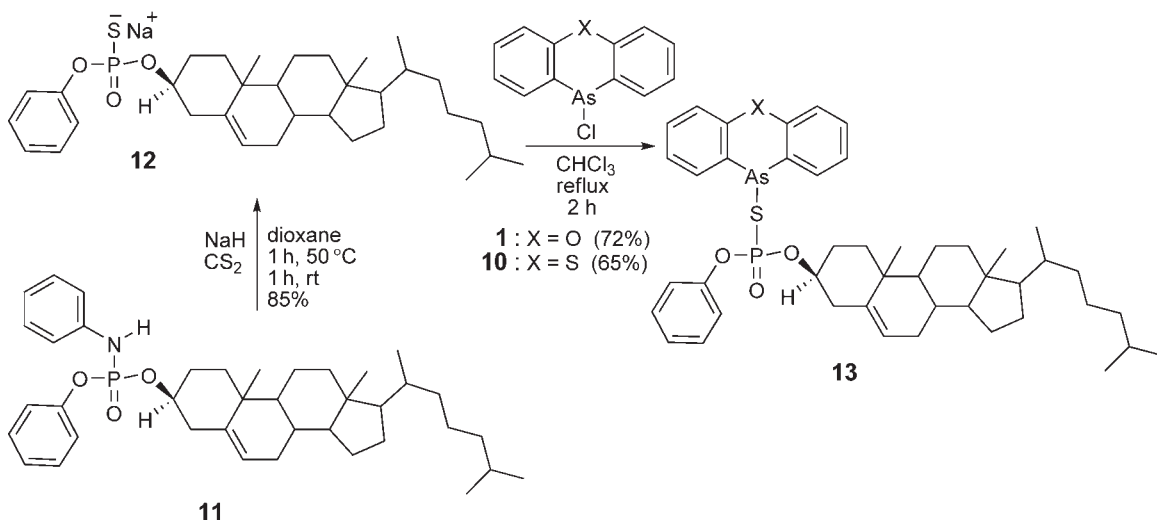
Studies on the use of OBPA **8** as an antimicrobial and fungicide in artificial leather <2000YZ795> and plastics <1999MI629> have also been performed.

9.17.2.1.2 1,4-Thiarsinines

The relationship between bond lengths and vibrational data has been investigated for 10-chloro-10*H*-phenothiarsinine **10** by means of the Varshni method. Varshni constants, which were used to estimate the halide distance in 10-chloro-10*H*-phenothiarsinine **10**, have been determined <1998SAA85>.



In order to test the coordination ability of compound **12**, the phenoxarsinine and phenothiarsinines with a bioactive cholesteryl group, viz. **13**, were prepared by reacting 10-chloro-10*H*-phenothiarsinine **10** and 10-chloro-10*H*-phenoxarsinine **1** with compound **12**. The latter is an anionic phosphorothioate ligand that incorporates a bioactive cholesteryl group, and was obtained from the phenyl phosphoramidate **11** (Scheme 6) <2000HAC6>.

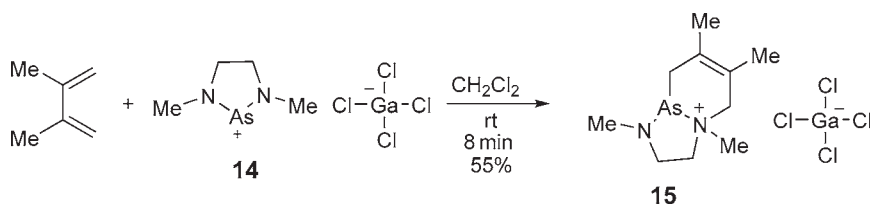


Scheme 6

9.17.2.2 Rings with One Arsenic and One Nitrogen Atom

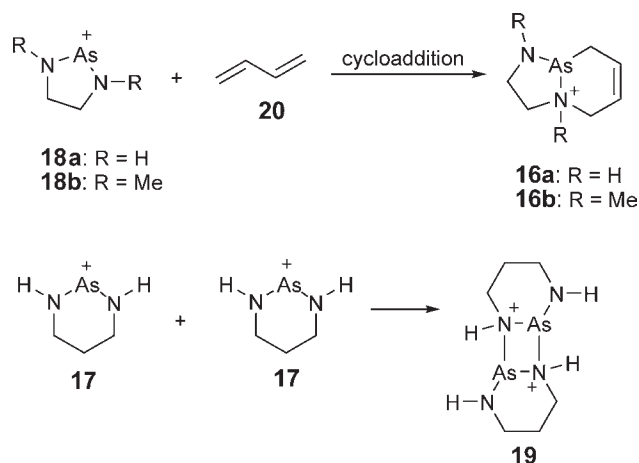
9.17.2.2.1 1,2-Azarsinines and 1,2-azarsinanes

A Diels–Alder-like cycloaddition reaction, involving one As–N bond as the olefin, of 1,3-dimethyl-1,3,2-diazarsolidinium tetrachlorogallate **14** with 2,3-dimethylbutadiene gave 1,4,6,7-tetramethyl-1,2,3,4,5,8-hexahydro-[1,3,2]diazarsolo[1,2-*a*]-[1,2]azarsinin-4-ium tetrachlorogallate **15** (Scheme 7) <1996CJC2209, 1994AGE1267>.



Scheme 7

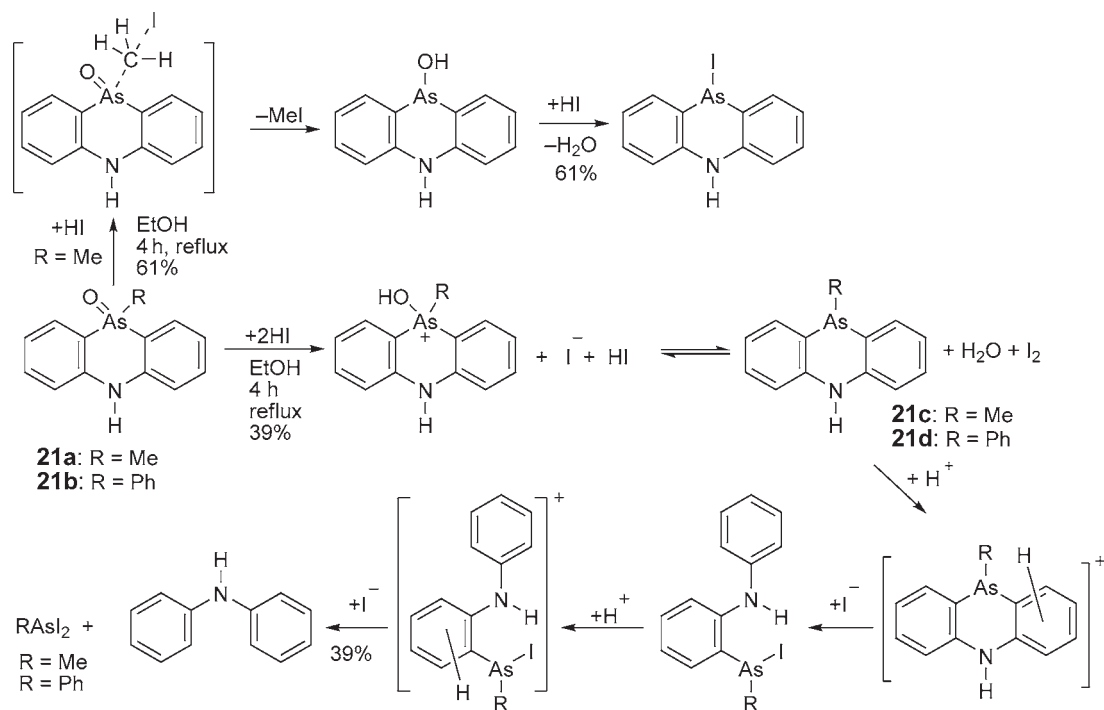
Quantum-chemical studies on 1,2-diazarsenium cations **16** and **19** have been performed by Boyd *et al.* (Scheme 8) <1998OM4014>. All interactions such as those with anions or solvent were ignored. Dimerization energies for **17** and the cycloaddition reaction of **18** with 1,3-butadiene **20** have been also investigated at Hartree–Fock (HF) and MP2 6-311G* levels of theory.



Scheme 8

9.17.2.2.2 1,4-Azarsinines

The mechanisms for the reactions of 10-methyl-10-oxide-5,10-dihydrophenarsinine **21a** and 10-phenyl-10-oxide-5,10-dihydrophenarsinine **21b** with HI were investigated by Gavrilov *et al.* by means of high-resolution mass spectrometry (Scheme 9) <2004CHE1212>. When 10-alkyl-5,10-dihydrophenarsazine 10-oxide **21a** or

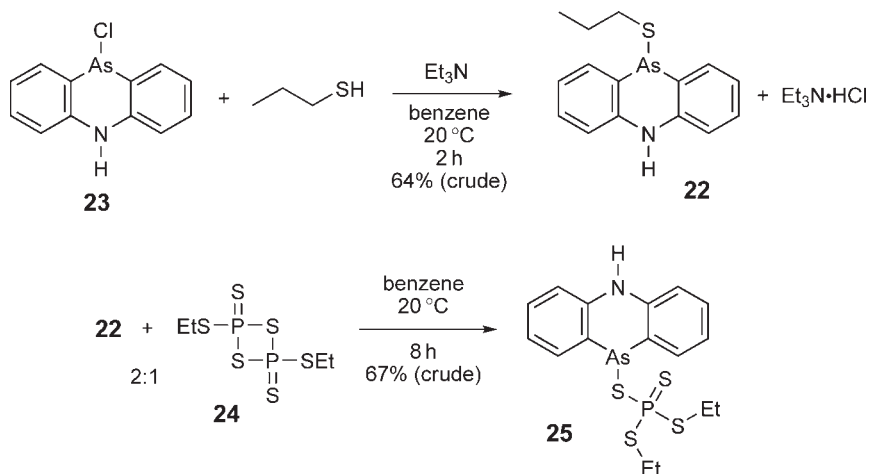


Scheme 9

10-aryl-5,10-dihydrophenarsazine 10-oxide **21b** react with hydrochloric, hydrobromic, or trichloroacetic acids, only protonation at the oxygen atom occurs. In the case of hydriodic acid, cleavage of the arsenic–carbon bond was observed. 10-Iodo-5,10-dihydrophenarsazine was obtained from the reaction of HI only with **21a** not **21b**.

Dihydrophenarsazines **21c** and **21d** formed in the first step were protonated at the benzene ring of the 5,10-dihydrophenarsazine system, where the endocyclic arsenic–carbon bonds are broken to form diphenylamine and arsines.

10-(Propylthio)-5,10-dihydrophenarsazine **22** was obtained by the reaction of 10-chloro-5,10-dihydrophenarsazine **23** with propanethiol in the presence of Et₃N under mild conditions. The reaction of **22** with 2,4-bis(ethylthio)1,3,2,4-dithiaphosphetene-2,4-disulfide **24** at room temperature afforded *S*-10-(5,10-dihydrophenarsazine)-*S'*-ethyl-*S''*-propyl-tetrathiophosphate **25** in 67% yield (Scheme 10) <2000HAC287>.



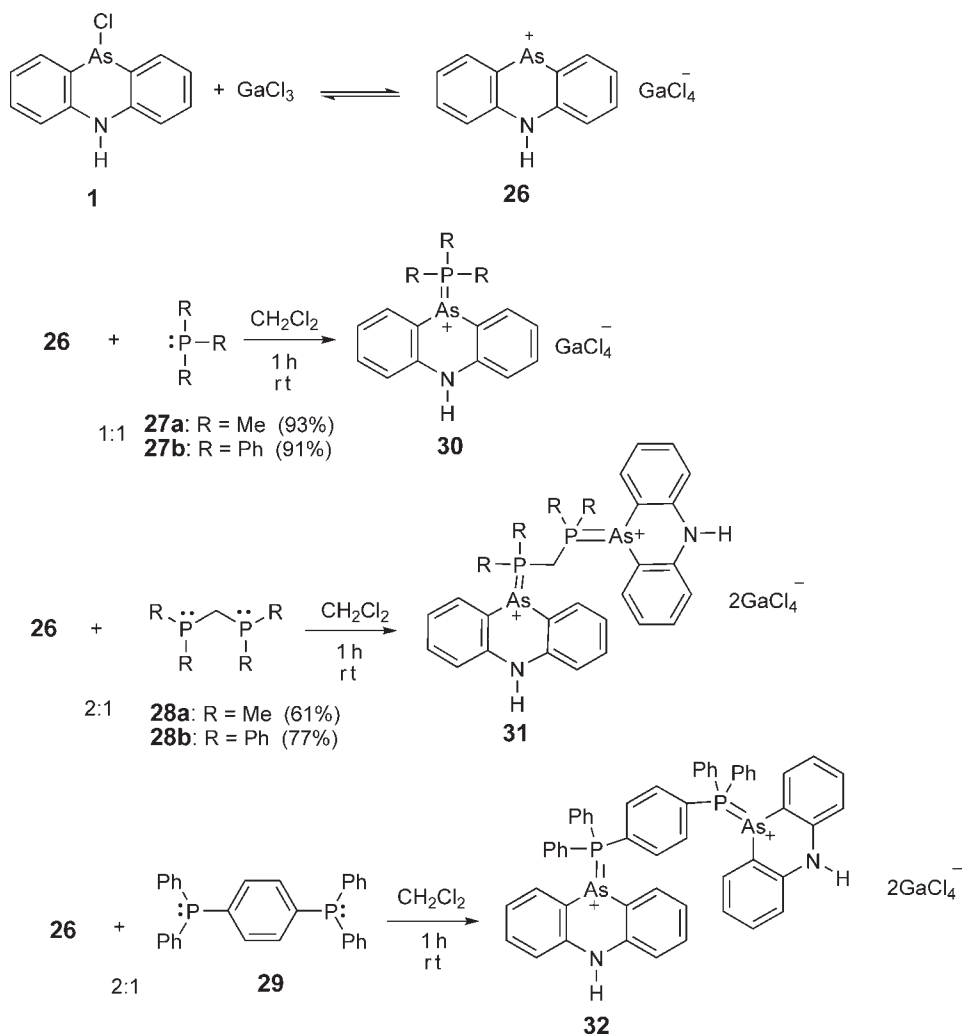
Scheme 10

The tricyclic 5-hydrophenarsazinium cation **26** has been prepared *in situ* from **1** and used as a Lewis acceptor with trimethylphosphine **27a**, triphenylphosphine **27b**, bis(dimethylphosphino)methane **28a**, bis(diphenylphosphino)methane **28b**, and 1,4-bis(diphenylphosphino)benzene **29** to give compounds **30–32** (Scheme 11) <2005IC9453>.

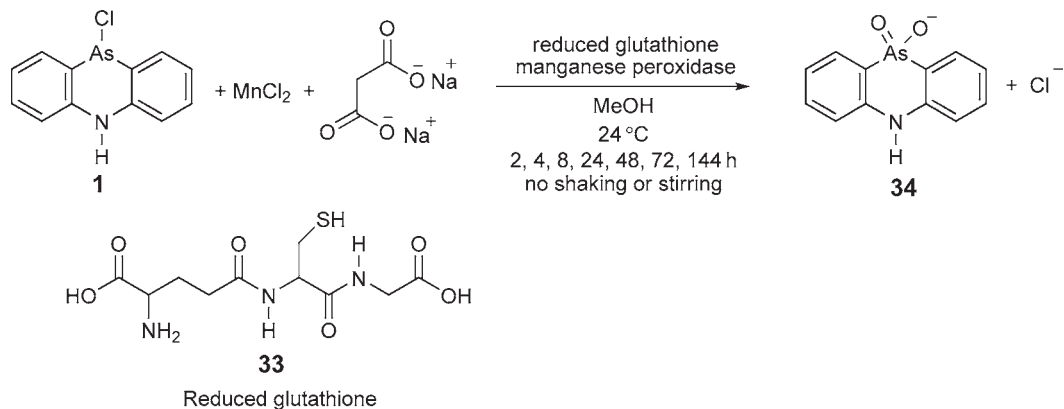
Fungal manganese peroxidase was found to convert the persistent chemical warfare agent 10-chloro-5,10-dihydrophenarsazine (Adamsite) **1** in a cell-free reaction mixture containing sodium malonate, Mn²⁺-ions, and reduced glutathione **33**, which is monomeric glutathione. The organoarsenical compound disappeared completely within 48 h, accompanied by the formation of a polar metabolite with a clearly modified ultraviolet (UV) spectrum. Thus, As(III) in the Adamsite molecule was oxidized by manganese peroxidase to the As(V)-containing **34** by the addition of dioxygen and release of chloride (Scheme 12) <2004AMB564>.

Adamsite, **1**, is a highly toxic compound and, accordingly, simple, rapid, and sensitive analytical procedures have been developed for the field determination of this chemical. One of the most effective methods for the determination of this substance in air is the use of indicator tubes with corresponding fillers. Adamsite **1** was determined by Evgen'ev *et al.* with the use of indicator tubes containing 4-chloro-5,7-dinitrobenzofurazan **35** as filler and its *N*-oxide derivative immobilized on silica gel. Adamsite **1** interacts with 4-chloro-5,7-dinitrobenzofurazan **35** to give a blue product identified as **36**, with λ_{max} = 590 nm (Scheme 13) <2003MI485>.

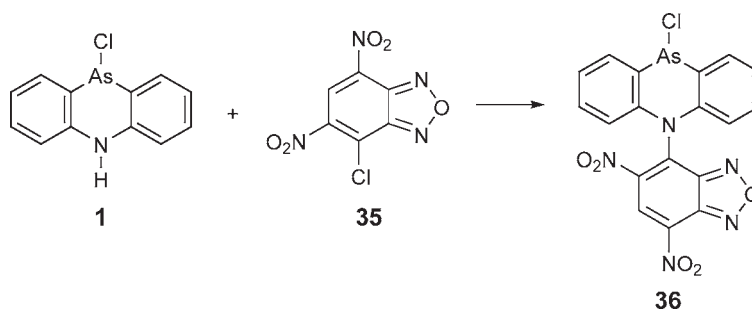
Adamsite **1** is the most difficult of the organoarsenicals to analyze. It has very high thermal stability and does not hydrolyze readily in the environment. Like most arsenicals, attempts to assess Adamsite by gas chromatography (GC) lead to rapid column deterioration and Adamsite cannot be derivatized with thiol derivatives <2003JCH(1000)253>. Schoene *et al.* developed two derivatization reactions for Adamsite. In the first, it was reacted with bromine in AcOH to give 2,2',4,4',6,6'-hexabromodiphenylamine **37**. The alternative derivatization involved pyrolytic ethylation with dimethylformamide diethyl acetal (DMFDEA) and pyridine to yield 10-ethyl-5,10-dihydrophenarsazine **38**. The reaction mixture, which is Adamsite, EtOH, pyridine, and DMFDEA **39**, was stored for 3 days in a closed vial at 90 °C. On column injection of 1 μl from this solution, no ethyl derivative could be detected, whereas splitless injection at 290 °C injector temperature afforded EtPA **38** in the expected amount (Scheme 14) <1996JCH(719)401>.



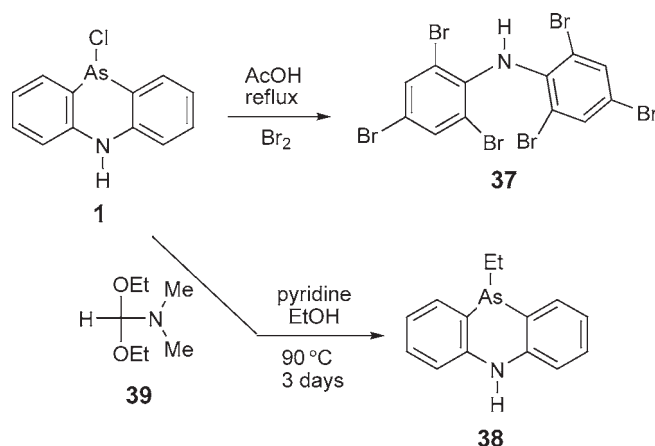
Scheme 11



Scheme 12

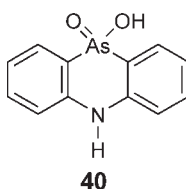


Scheme 13



Scheme 14

Greschonig *et al.* used capillary zone electrophoresis to separate phenarsazinic acid **40** and other inorganic and organic compounds in urine <1998FJA218>.

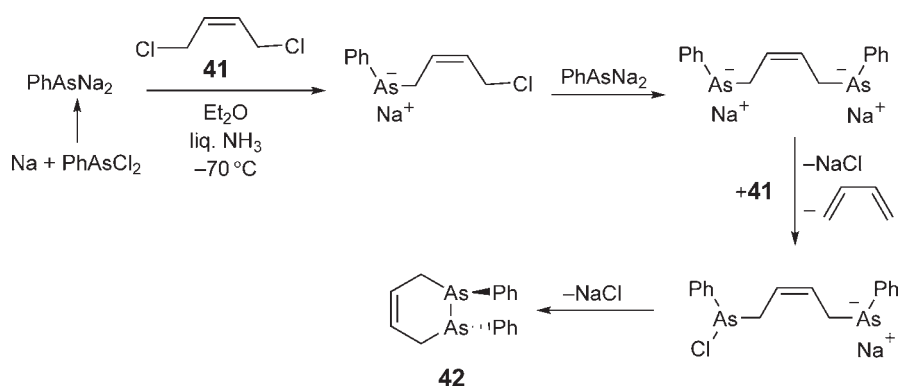


9.17.2.3 Rings with Two Arsenic Atoms

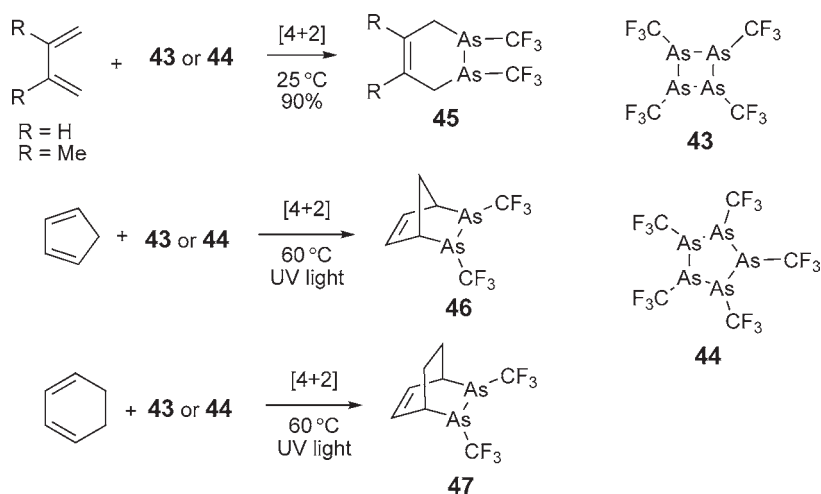
9.17.2.3.1 1,2-Diarsinines, 1,3-diarsinines, and 1,4-diarsinines

The reaction of *cis*-1,4-dichloro-2-butene **41** and Na_2AsPh gave 1,2-diphenyl-1,2,3,6-tetrahydro-1,2-diarsinine **42** in 44% yield (Scheme 15) <1994JOM(467)57>.

The reaction of dienes, 2,3-dimethyl-1,3-butadiene, isoprene, cyclopentadiene, and 1,3-cyclohexadiene, with cycloarsenic compounds, $(\text{AsCF}_3)_4$ **43** or $(\text{AsCF}_3)_5$ **44**, led to the [4+2] cycloaddition products 1,2-bis(trifluoromethyl)-1,2,3,6-tetrahydro-1,2-diarsinine **45**, 2,3-bis(trifluoromethyl)-2,3-diarsa-bicyclo[2.2.1]hept-5-ene **46**, and 2,3-bis(trifluoromethyl)-2,3-diarsa-bicyclo[2.2.2]oct-5-ene **47** (Scheme 16) <1995ZNB189>.

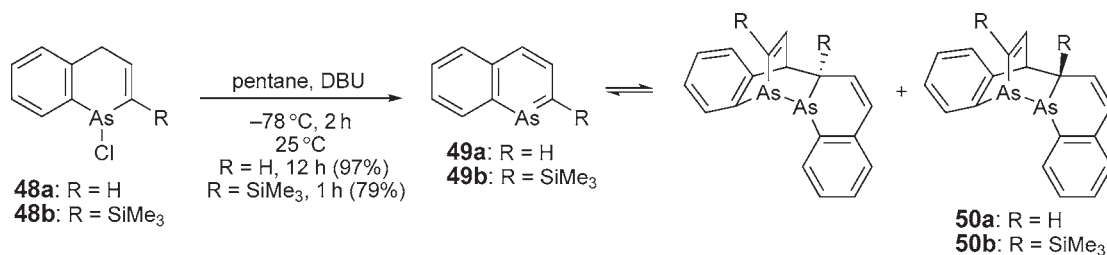


Scheme 15



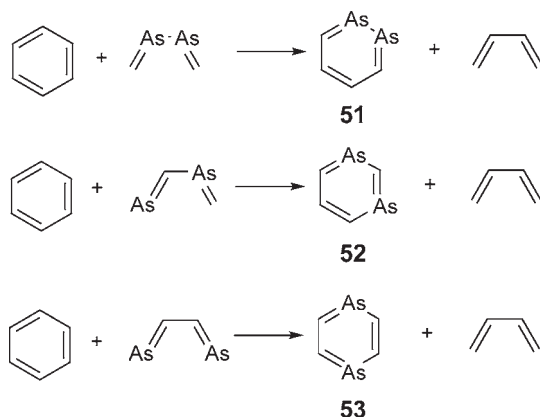
Scheme 16

The reaction of 1-chloro-1,4-dihydro-1-arsanaphthalene derivatives **48** with a suspension of DBU in pentane afforded a mixture of 1-arsanaphthalenes **49** and their Diels–Alder dimers **50**. Both **49a** and **49b** are in mobile equilibrium with their head-to-head Diels–Alder dimers **50a** and **50b** (Scheme 17) <2001OM2109>.



Scheme 17

HF, MP2, and CCSD(T) *ab initio* molecular orbital (MO) theory and hybrid density functional theory (DFT) B3LYP calculations were applied to diarsinines **51–53** to determine the reaction energies of the homodesmotic equations, structure properties, stabilities, reactivities, and heteroaromaticity (Scheme 18) <2002JOC271, 2003IAS49, 2003JMT(663)145, 2005JOM(690)4761>.



Scheme 18 Homodesmotic reactions.

9.17.3 Six-Membered Rings with Three Heteroatoms

9.17.3.1 Rings with One Arsenic and Two Oxygen Atoms

9.17.3.1.1 1,3,2-Dioxarsinanes

2-Chloro-5,5-dimethyl-1,3,2-dioxarsinane **54** was obtained in high yield from the reaction of AsCl_3 with 2,2-dimethylpropane-1,3-diol **55**. 2-(5,5-Dimethyl-1,3,2-dioxarsinan-2-yloxy)-5,5-dimethyl-1,3,2-dioxarsinane **56** could be obtained either from the reaction of As_2O_3 with 2 equiv of **55**, or by treating **54** with 0.5 equiv water and 1–2 equiv cyclohexylamine. Compound **57** could be prepared in a low yield (40%) by treatment of **54** with sodium. The same compound **57** was isolated, along with several impurities, from the reaction of **54** with 2 equiv of cyclohexylamine. 5,5-Dimethyl-2-alkoxy-1,3,2-dioxarsinanes **59** have been prepared from the treatment of compound **54** with the appropriate alcohols in the presence of Et_3N (Scheme 19) <1995J(P1)2945>.

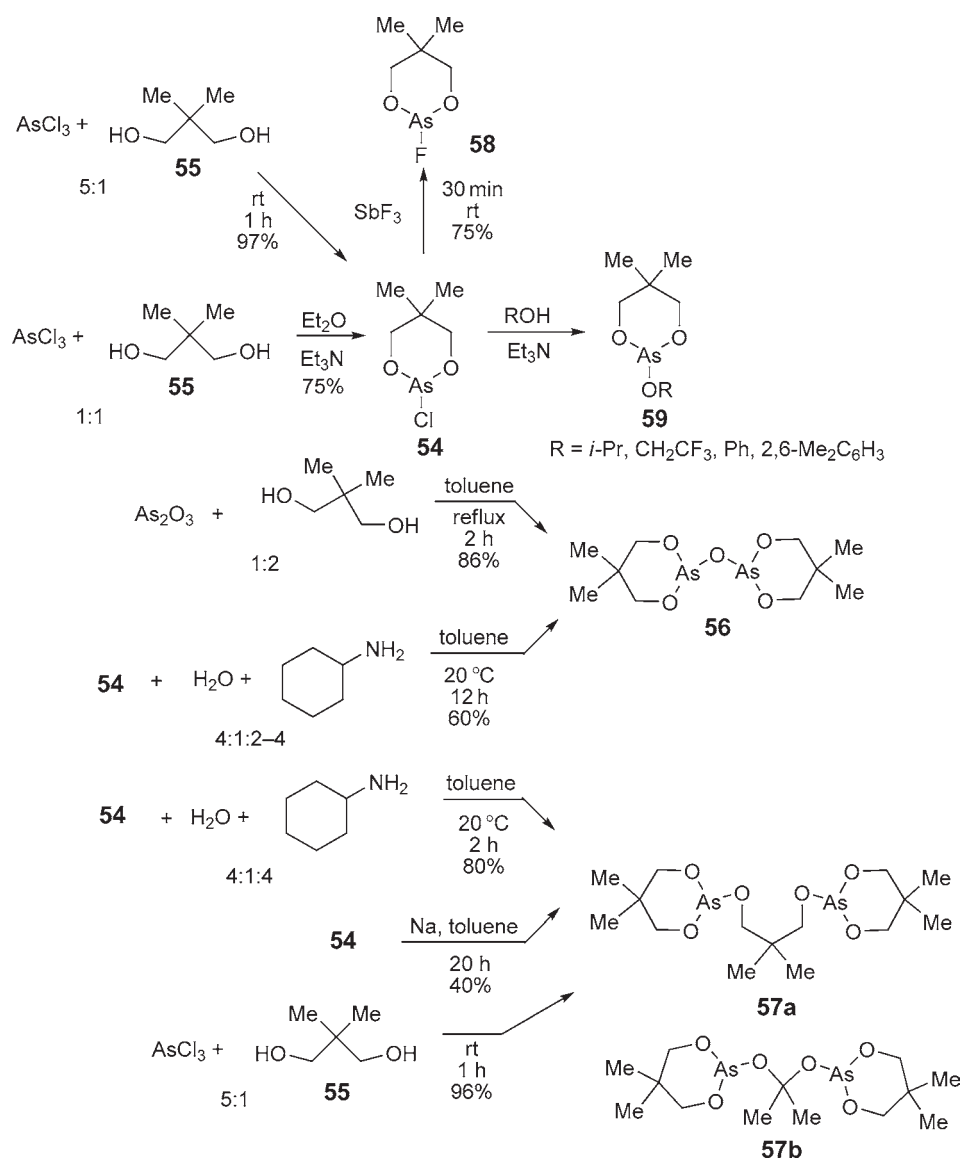
Compound **54** has also been prepared by Matos *et al.* <2002PS2859> by treatment of 5 equiv of AsCl_3 with 1 equiv of diol **55** in the presence of triethylamine using ether as a solvent (75%) or, in 97% yield, by adding 2,2-dimethylpropane-1,3-diol **55** to neat AsCl_3 . However, the addition of 5 equiv of neat AsCl_3 to 1 equiv of solid diol **55** at room temperature afforded **57a** in high yield (96%). The formula for structure **57a** is incorrectly given as **57b** in the original paper <1995J(P1)2945>. Halide exchange in **54** was accomplished by treatment with SbF_3 , resulting in the fluoro species **58** (Scheme 19).

The cyclic arsenosilicate compound, 4,4,6-trimethyl-2-(triphenylsilyloxy)-1,3,2-dioxarsinane **60**, has been synthesized using a one-pot reaction between triphenylsilanol **61**, As_2O_3 , and 2-methylpentane-2,4-diol **62** in a 2:1:2 molar ratio (Scheme 20) <2003ARK255>.

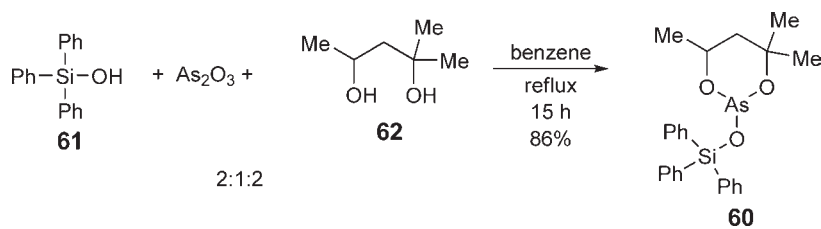
Equimolar reactions of 2-chloro-1,3,2-dioxarsinane **63** with substituted phenols in the presence of Et_3N gave aryl-1,3,2-dioxarsinanes **64** (Scheme 21) <2003PS1653>.

The treatment of diol **55** with 5,8-(5,5-dimethyl-1,3,2-dioxarsinan-2-yloxy)quinoline **65**, which was obtained from 8-hydroxyquinoline **66** and 2-chloro-5,5-dimethyl-1,3,2-dioxarsinane **54** in the presence of Et_3N , did not produce the expected compound **67**. Instead, compound **67** was obtained by reacting 8-hydroxyquinoline **66** in the presence of Et_3N and *N*-chlorodiisopropylamine **69** with **68**, which was used for the next step without isolation. The isolation of **68** lowers the total yield (Scheme 22) <1996IC6627>.

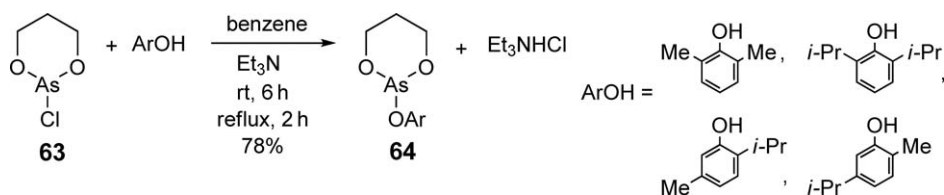
The glycolatoarsenic(III) salicylaldimine derivatives **70** have been prepared in high yields by the interaction of 2-chloro-1,3,2-dioxarsinanes **71**, prepared from the reaction of AsCl_3 with the appropriate 1,3-diols **72**, with *N*-arylsalicylaldimines **73** (Scheme 23) <2002SRI1319>.



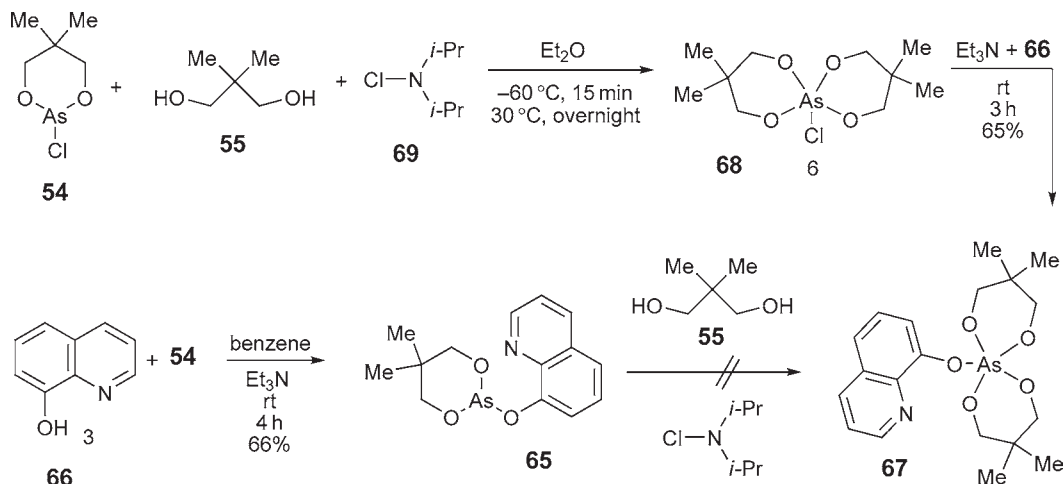
Scheme 19



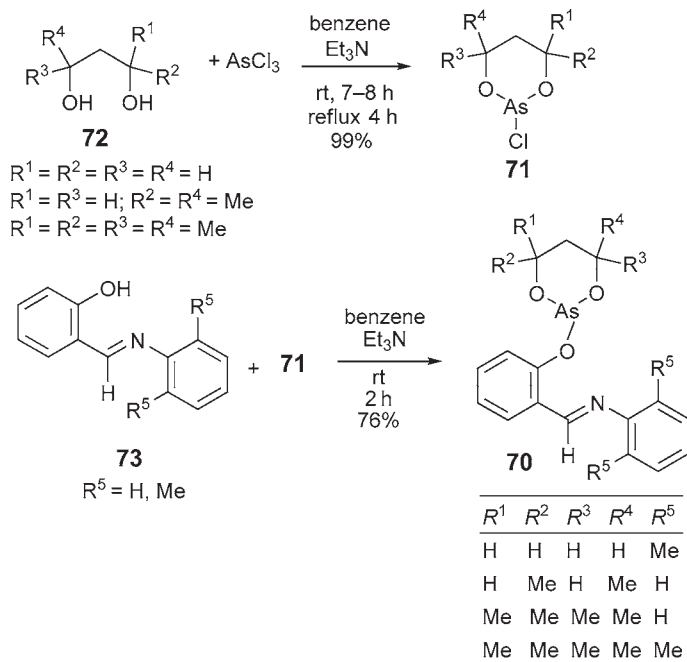
Scheme 20



Scheme 21

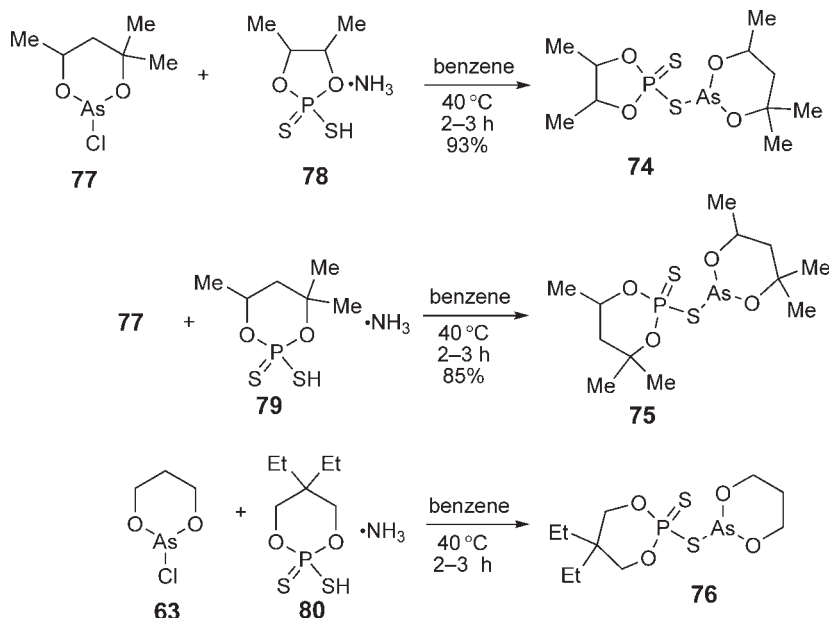


Scheme 22



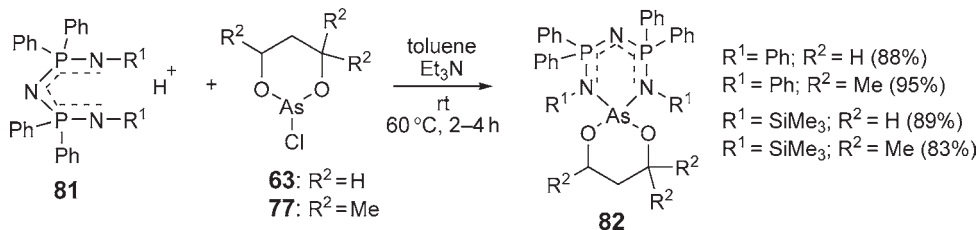
Scheme 23

O,O'-Alkylene diphosphato derivatives of arsenic(III) **74–76** were synthesized in quantitative yield by the reaction of 2-chloro-1,3,2-dioxarsinanes **63** and **77** with ammonium salts of *O,O'*-alkylene dithiophosphoric acids **78–80** under anhydrous conditions (Scheme 24) <2004IJA1134>.



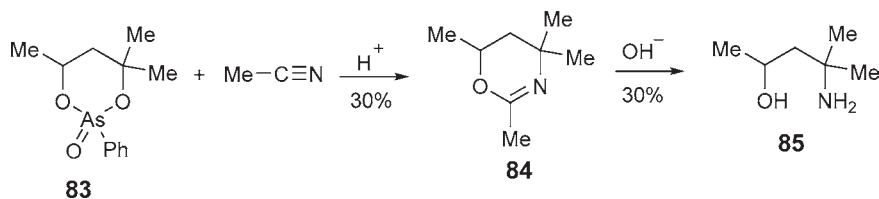
Scheme 24

The 2-chloro-1,3,2-dioxarsinanes **63** and **77** have been treated with ligands **81** in toluene in an equimolar ratio to yield spirocyclic phosphazene-arsinane compounds **82** (Scheme 25) <2003PS159>.



Scheme 25

The reaction of 1,3,2-dioxarsinane **83** with acetonitrile under acidic conditions produced 2,4,4-tetramethyl-5,6-dihydro-4*H*-1,3-oxazine **84** in low yield (30%). The latter then was converted to the amino alcohol **85** by basic hydrolysis (Scheme 26) <2005RCB1543>.



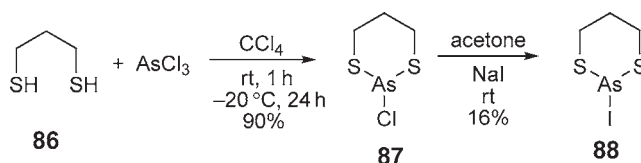
Scheme 26

The enthalpies of vaporization and formation of halogenide for 2-chloro-1,3,2-dioxarsinane **63** have been determined. The formation enthalpy of the compound in the condensed and gaseous phases has also been calculated <1996PS97>.

9.17.3.2 Rings with One Arsenic and Two Sulfur Atoms

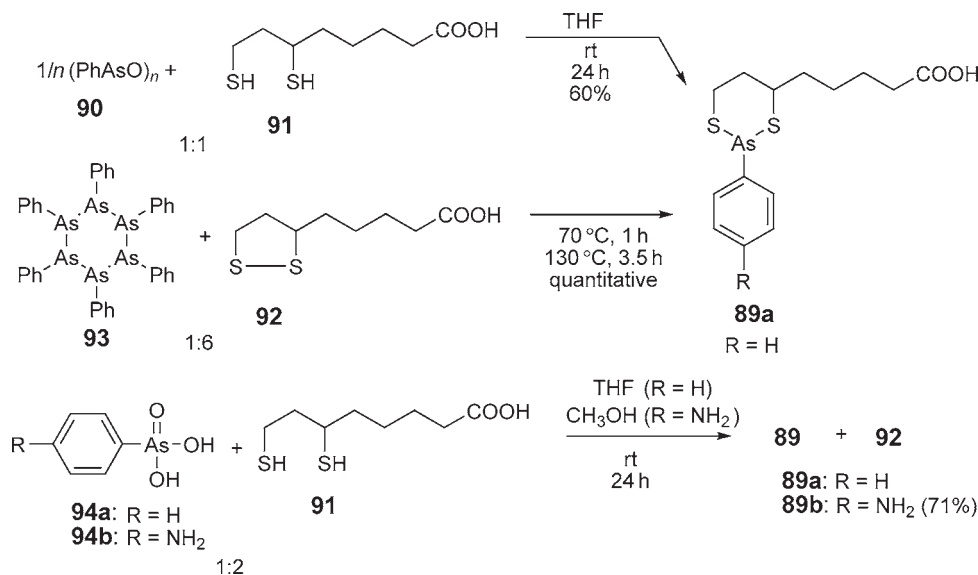
9.17.3.2.1 1,3,2-Dithiarsinanes

The cyclization of propane-1,3-dithiol (PDT) **86** with AsCl_3 afforded 2-chloro-1,3,2-dithiarsinane **87** in high yield (90%), which was then treated with NaI to give 2-iodo-1,3,2-dithiarsinane **88** in low yield (16%, Scheme 27) <2006JOM(691)1825>.



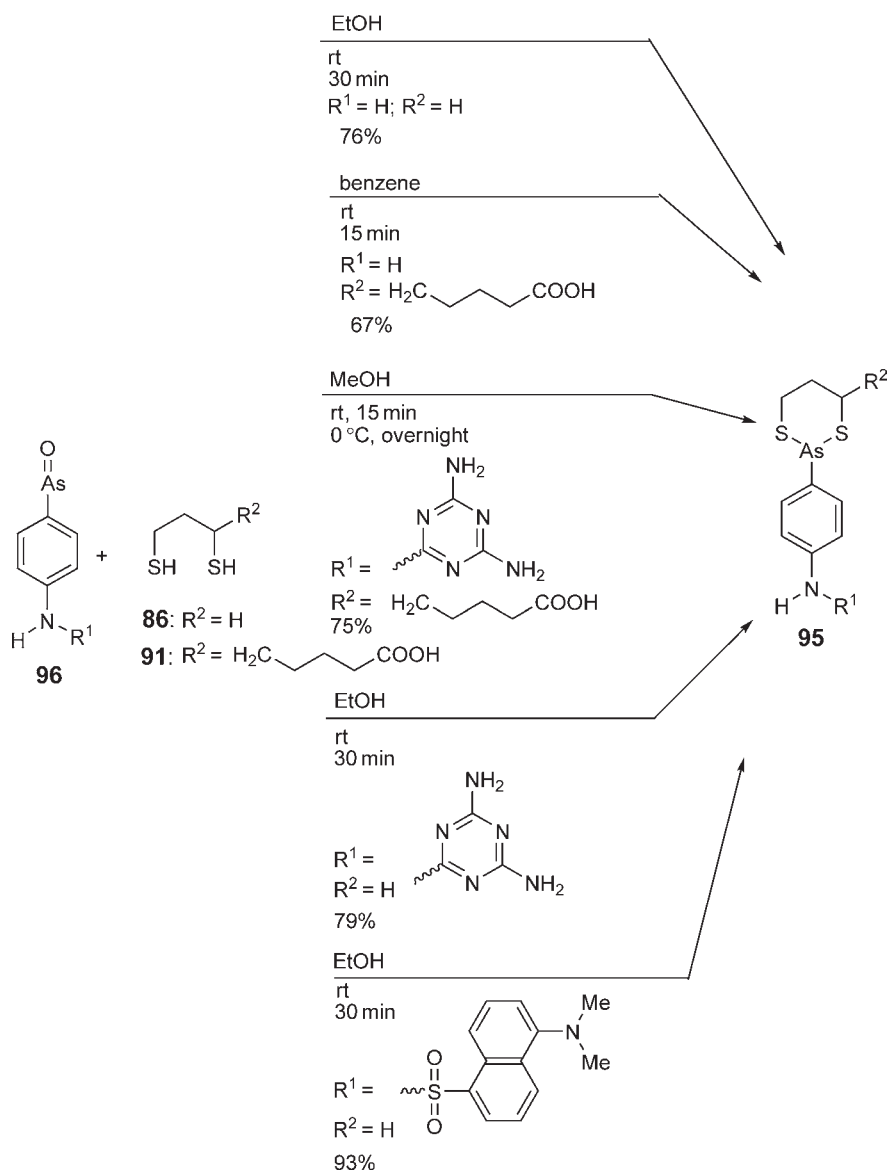
Scheme 27

The arsenic(III) dithiolates **89**, which are models for the inhibition of dithiol-containing enzymes by organoarsenic compounds, have been synthesized via three different routes. In the first method, **89** was obtained from the reaction of phenylarsoxane **90** with *rac*-dihydrolipoic acid **91**. The second method involves the heating of *rac*-lipoic acid **92** and hexaphenylcyclohexarsinane **93** to 130°C for 3.5 h in a 6:1 molar ratio to give **89a** in quantitative yield. In the last method, treatment of phenylarsonic acid **94a** and 4-aminophenylarsonic acid **94b** with *rac*-dihydrolipoic acid **91** led to **89** (71%) and **92**. X-Ray structure analysis shows that the phenyl at the 2-position adopts an axial orientation (Scheme 28) <1998EJI61>.



Scheme 28

4-Aminophenyl-1,3,2-dithiarsinane derivatives **95** have been synthesized by Loiseau *et al.* from the reactions of 4-aminophenylarsenoxides **96** with PDT **86** and dihydrolipoic acid **91**. Compound **95a** was also evaluated for anthelmintic properties on three models, infective larvae of filarial *Molinema dessetae*, infective larvae of an intestinal nematode, *Nippostrongylus brasiliensis*, and adults and larvae of *Rhabditis pseudoelongata*, a free-living nematode. The use of dithiol ligands for trivalent arsenicals gave compounds with anthelmintic activity (Scheme 29) <1999AF944>.

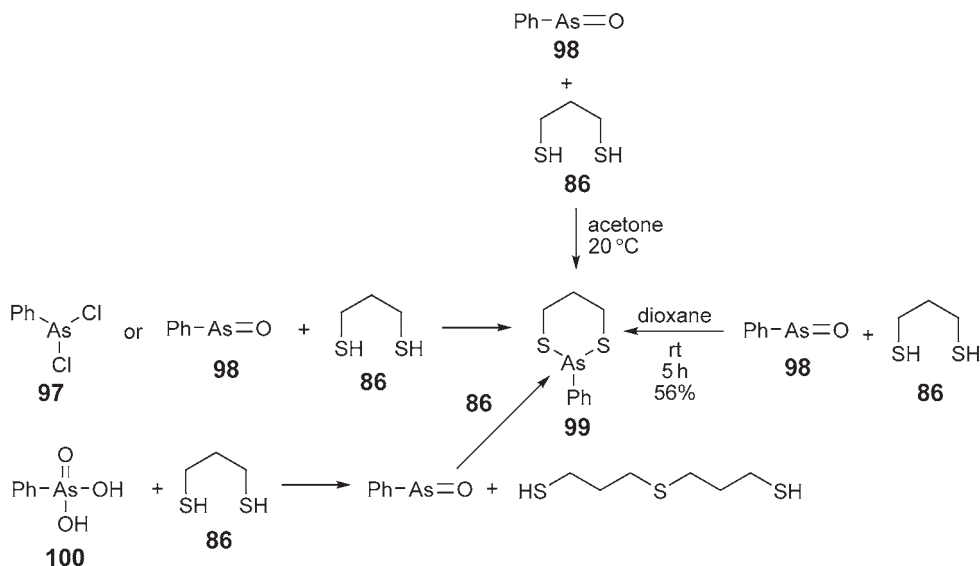


Scheme 29

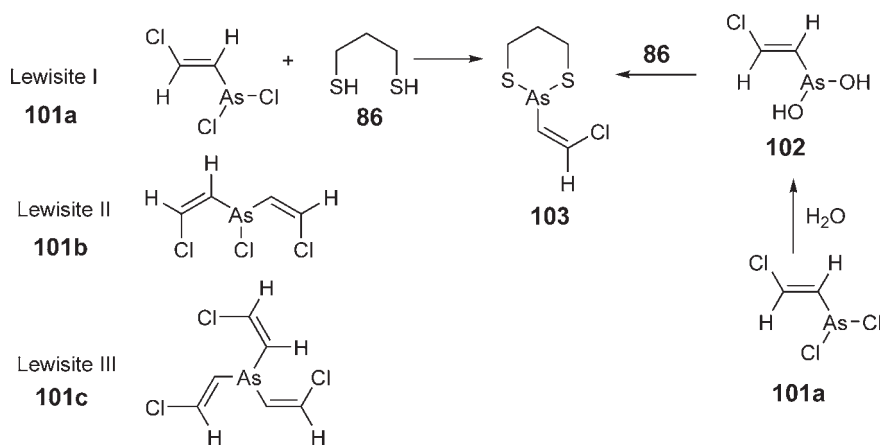
Phenylarsenic dichloride **97** and phenylarsenic oxide **98** react rapidly with PDT **86** at ambient temperature to yield stable cyclic arsenic compound **99**. When phenylarsenic acid **100** was treated with PDT **86**, it was reduced to phenylarsenic oxide **98**, which was then interacted with the second dithiol **86** to produce 2-phenyl-1,3,2-dithiarsinane **99** <2003JCH(1000)253>. Compound **99** was also prepared by Chowdhury *et al.* from the reaction of 1,3-dithiol **86** with phenylarsenic oxide **98** in dry dioxane (Scheme 30) <2002PS497>.

The analysis of chemical warfare agents, toxic arsenic compounds, and their degradation products is an important component of verification of compliance with the Chemical Weapons Convention. GC and high-performance liquid chromatography (HPLC), particularly combined with mass spectrometry, are the major techniques used to detect and identify chemicals of concern to the convention. These compounds are usually derivatized to facilitate chromatography. Trivalent arsenic forms stronger bonds with sulfur than it does with oxygen. Therefore, thiols are used for the derivatization of arsenic compounds <2003JCH(1000)253>. Phenylarsenic oxide **98**, which was first derivatized in acetone with PDT **86** to form 2-phenyl-1,3,2-dithiarsinane **99**, has been determined by means of GC and HPLC <1998FJA313>. Lewisite, dichloro(2-chlorovinyl) arsine **101**, is a highly toxic chemical warfare agent with potent vesicant properties. Weapon-grade Lewisite is composed of 90% **101a**, up to ~10% **101b**, and <1% of **101c**. Lewisite

is first derivatized with the dithiol to permit analysis by GC or HPLC. Accidental exposure to Lewisite, or its intentional use as a chemical terrorism weapon, is a public health threat, and warrants investigation for the development of analytical methods to detect biomarkers of exposure to Lewisite. Under aqueous conditions, Lewisite hydrolyzes rapidly to the nonvolatile 2-chlorovinylarsonous acid (CVAA) **102**. Wooten and co-workers developed a sensitive, simple, and automated method for measuring CVAA in human urine. The method is based on the use of solid-phase micro-extraction (SPME) and GC-MS after derivatization of the CVAA with PDT **86** to give 2-(2-chlorovinyl)-1,3,2-dithiarsinane (CVAA-PDT) **103** (Scheme 31). 2-Phenyl-1,3,2-dithiarsinane **99** is used as an internal reference for quantitation and confirmation <2003JCH(1000)253, 2002JCH(772)147>.



Scheme 30



Scheme 31

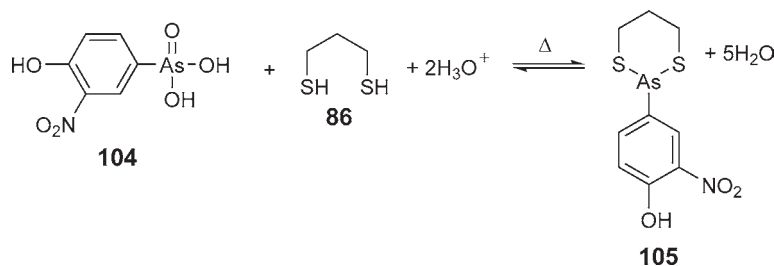
The conversion of nonvolatile 4-hydroxy-3-nitrophenylarsonic acid **104** to the volatile 4-(1,3,2-dithiarsinan-2-yl)-2-nitrophenol **105** is another example of suitable derivatization (Scheme 32) <2002JCH(772)147>.

9.17.3.3 Rings with One Arsenic and Two Nitrogen Atoms

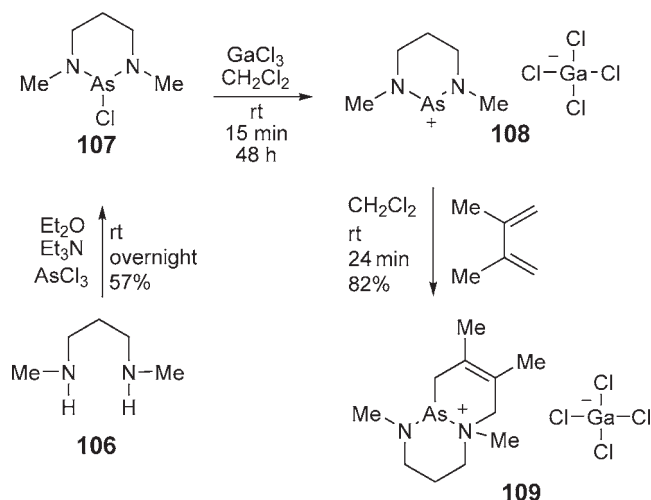
9.17.3.3.1 1,3,2-Diazarsinanes and 1,3,2-diazarsinines

The reaction of *N*¹,*N*³-dimethylpropane-1,3-diamine **106** with AsCl₃ produced 2-chloro-1,3-dimethyl-1,3,2-diazarsinane **107**, which was then treated with GaCl₃ to yield 3,4,5,6-tetrahydro-1,3-dimethyl-1,3,2-diazarsinium-(T-4)-

tetrachlorogallate **108**. The latter underwent a quantitative Diels–Alder-like cycloaddition reaction with 2,3-dimethylbutadiene, involving one As–N bond as the olefin, to give 1,5,7,8-tetramethyl-2,3,4,5,6,9-hexahydro-1*H*-[1,2]azarsinino[1,2-*a*][1,3,2]diazarsinin-5-ium tetrachlorogallate **109** (Scheme 33) <1996CJC2209, 1994AGE1267>.

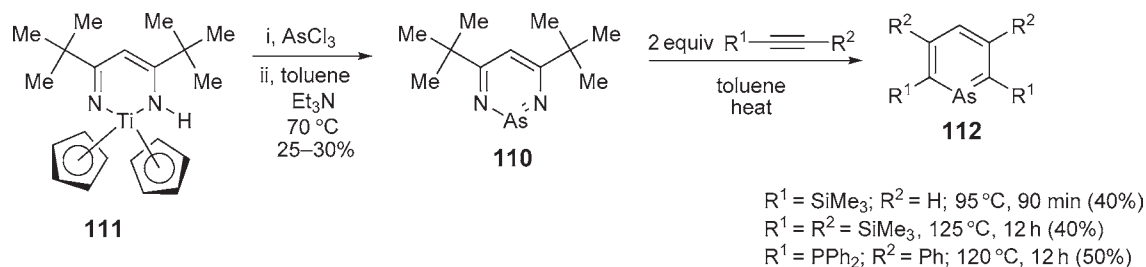


Scheme 32



Scheme 33

A di-*tert*-butyl derivative of 1,3,2-diazarsinine **110** has been prepared in 20–25% yield from the reaction of the corresponding diazatitanacycle **111** with AsCl_3 in the presence of triethylamine. The formation of the 1,3,2-diazarsinine is critically dependent on the experimental conditions, and prolonged heating of **111** and AsCl_3 with Et_3N led only to decomposition. Treatment of 4,6-di-*tert*-butyl-1,3,2-diazarsinine **110** with a variety of alkynes produced arsinines **112** in 40–50% yields (Scheme 34) <1997OM4089>.

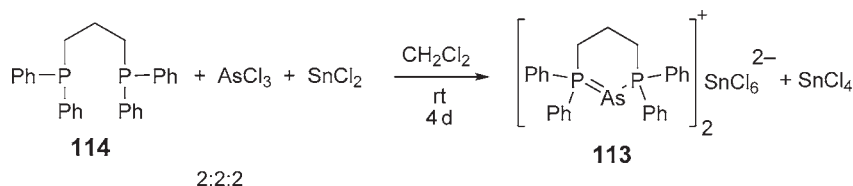


Scheme 34

9.17.3.4 Rings with One Arsenic and Two Phosphorus Atoms

9.17.3.4.1 1,3,2-Diphospharsinines

Structural and ^{31}P nuclear magnetic resonance (NMR) solution studies on 1,4,5,6-tetrahydro-1,1,3,3-tetraphenyl-1,3,2-diphospharsinium cation **113** have been performed by Barnham *et al.* Thus, **113** was obtained from the reaction of 1,2-bisdiphenylphosphinopropane **114** with AsCl_3 in the absence or presence of SnCl_2 (Scheme 35) <2001HAC501>.

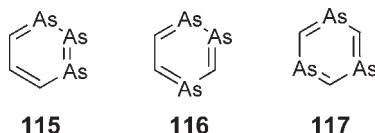


Scheme 35

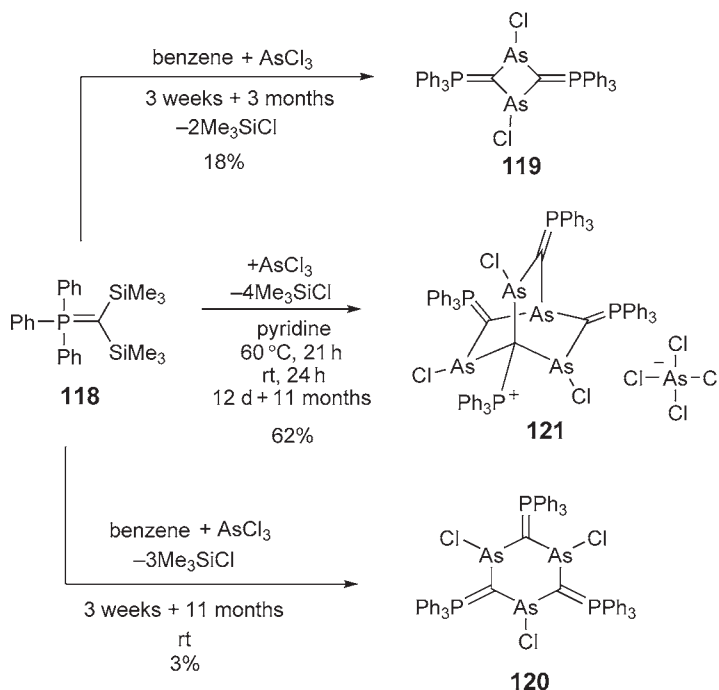
9.17.3.5 Rings with Three Arsenic Atoms

9.17.3.5.1 Triarsinines

The electronic structure and properties of triarsinines **115–117** have been investigated using hybrid DFT B3LYP <2005JOM(690)4761>. In addition, the electronic structure and properties of 1,3,5-triarsinine **117** were studied by Mracec *et al.* by means of Hückel molecular orbital (HMO) calculations <1996MI89>.



Treatment of **118** with AsCl_3 in benzene in a 1:1 molar ratio at room temperature gave **119** in 18% yield after nearly 4 months. After nearly 1 year, compound **120** was isolated from the mother liquor in only 3% yield. When **118** was reacted with AsCl_3 in pyridine, compound **121** could be obtained in 62% yield, also after a considerable time period (Scheme 36) <2000CEJ3531>.



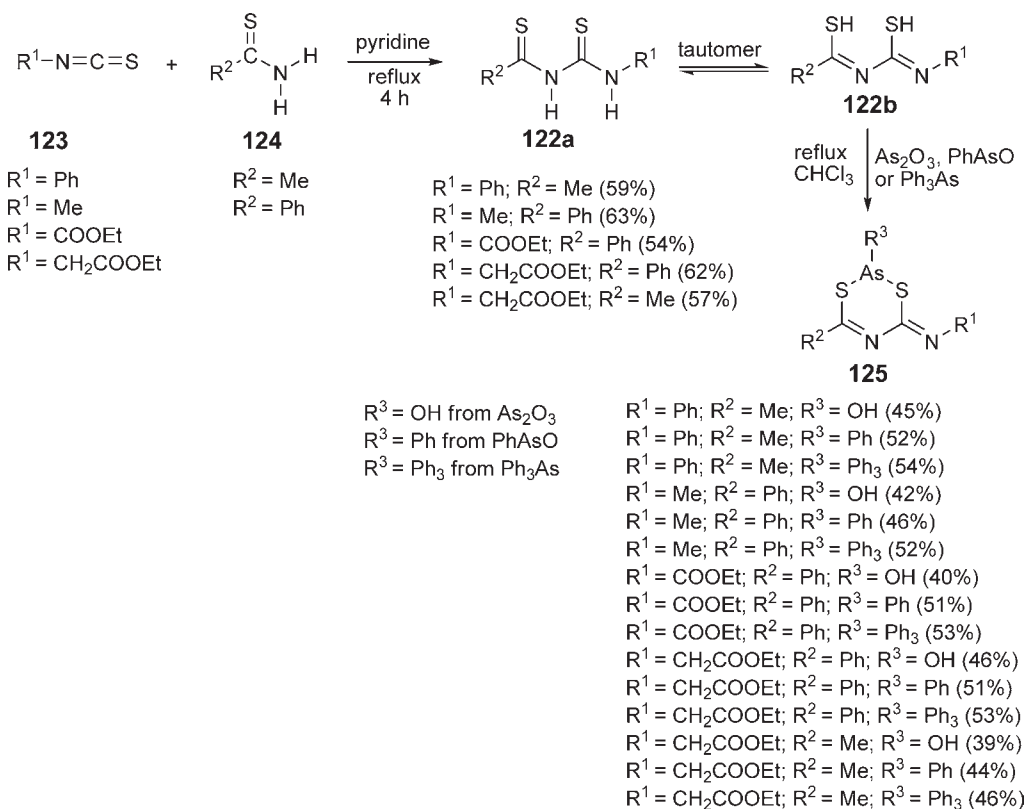
Scheme 36

9.17.4 Six-Membered Rings with Four Heteroatoms

9.17.4.1 Rings with One Arsenic, One Nitrogen, and Two Sulfur Atoms

9.17.4.1.1 1,3,5,2-Dithiazarsinines

The cyclization of several thiourea derivatives **122**, which were obtained from the reactions of a number of isothiocyanates **123** and thioamides **124**, with As_2O_3 , phenylarsine oxide, and triphenylarsine, afforded the corresponding 1,3,5,2-dithiazarsinine compounds **125** (Scheme 37) <2002PS497>. Tautomerism between the thiourea **122a** and imine-thiol **122b** forms has been observed by ^1H and ^{13}C NMR.

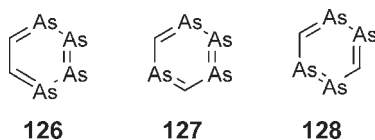


Scheme 37

9.17.4.2 Rings with Four Arsenic Atoms

9.17.4.2.1 Tetrarsinines

The electronic structure and properties of tetrarsinines **126–128** have been investigated using hybrid DFT B3LYP <2005JOM(690)4761>.

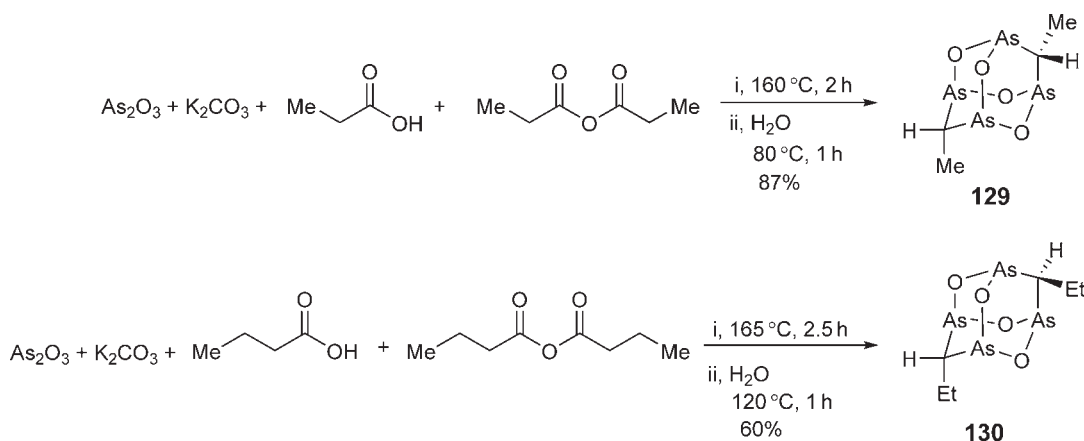


9.17.5 Six-Membered Rings with Five Heteroatoms

9.17.5.1 Rings with Three Arsenic and Two Oxygen Atoms

9.17.5.1.1 1,3,5,7-Tetraarsa-2,4,6,8-tetraoxadamantenes

9,10-Dimethyl-1,3,5,7-tetraarsa-2,4,6,8-tetraoxadamantene **129** and 9,10-ethyl-1,3,5,7-tetraarsa-2,4,6,8-tetraoxadamantene **130** have been prepared by Marx *et al.* by the reaction of arsenic(III) oxide with propionic acid–propionic anhydride and butyric acid–butyric anhydride, respectively (Scheme 38) <1996ZFA1097>.

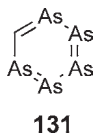


Scheme 38

9.17.5.2 Rings with Five Arsenic Atoms

9.17.5.2.1 Pentaarsinines

The electronic structure and properties of pentaarsinine **131** have been investigated by Ghiasi using hybrid DFT B3LYP <2005JOM(690)4761>. It is claimed that the magnetic aromaticity of arsabenzenes decreases with increasing number of As-atoms, whereas the stability of arsabenzenes increases with the number of As-atoms.



9.17.6 Six-Membered Rings with Six Heteroatoms

9.17.6.1 Rings with One Arsenic, Two Sulfur, and Three Phosphorus Atoms

9.17.6.1.1 2,6,7-Trithia-1,3,4-triphospha-5-arsabicyclo[2.2.1]heptanes

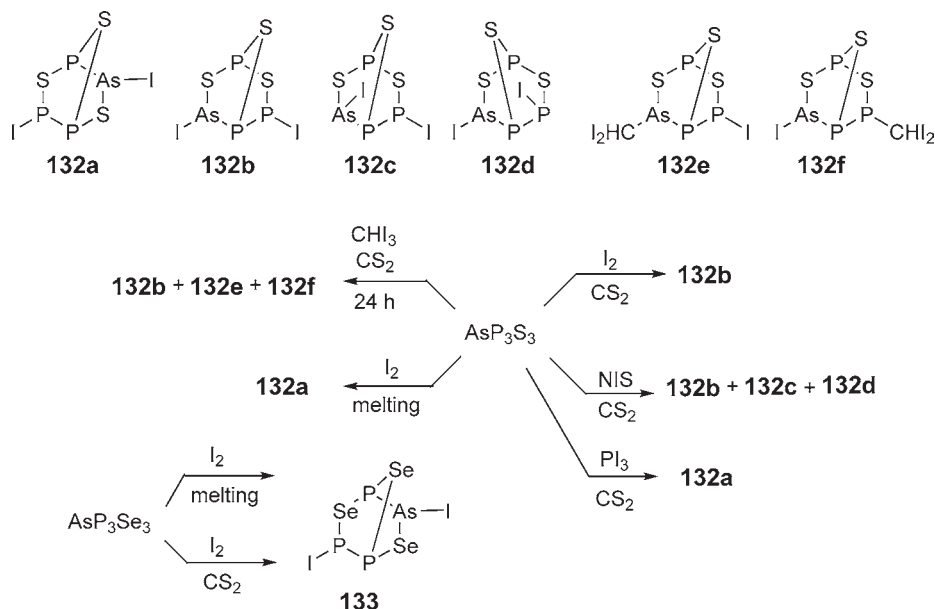
The reaction of AsP_3S_3 and AsP_3Se_3 with several iodine-containing compounds, such as CHI_3 , PI_3 , NIS , and I_2 , were carried out in the melt or in CS_2 solution by Blachnik and Neto <1997ZFA1043>. The 2,6,7-trithia-1,3,4-triphospha-5-arsabicyclo[2.2.1]heptanes **132a–132f** and 3,6-diiodo-2,5,7-triseleno-1,4,6-triphospha-3-arsabicyclo[2.2.1]heptane **133** obtained were investigated by ^{31}P NMR spectroscopy (Scheme 39).

9.17.6.2 Rings with One Arsenic and Five Selenium Atoms

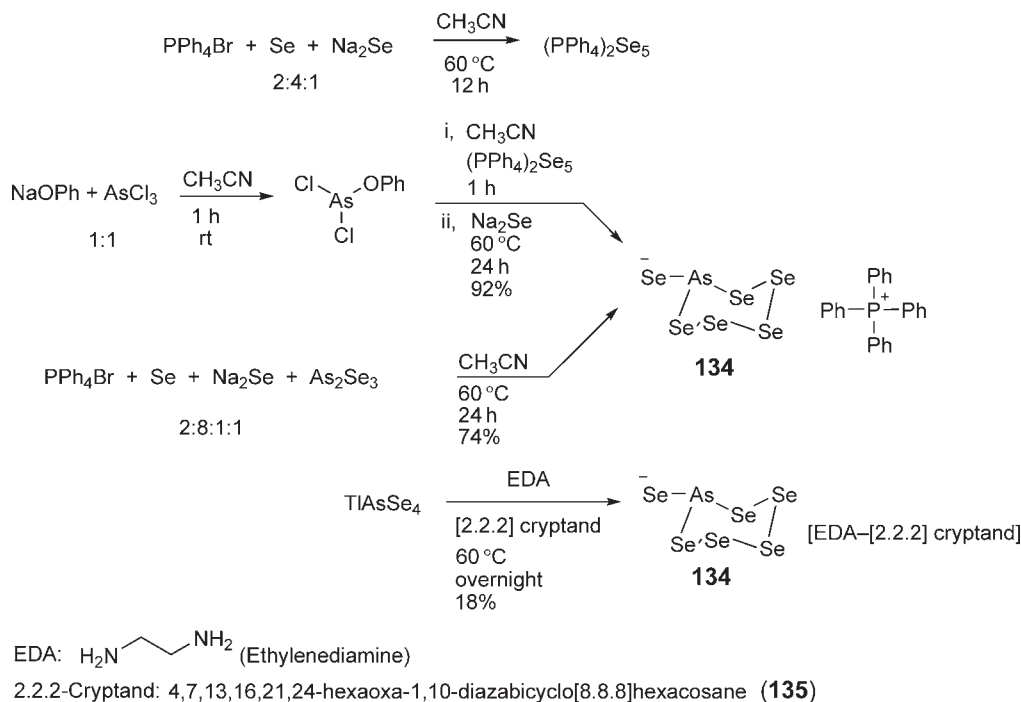
9.17.6.2.1 1,2,3,4,5,6-Pentaselenarsinane-6-selenolate

Sodium phenoxide and AsCl_3 in acetonitrile formed Cl_2AsOPh , which was then reacted with $(\text{PPh}_4)_2\text{Se}_5$ and finally with Na_2Se to yield $\text{PPh}_4[\text{Se}_5\text{AsSe}]$, tetraphenylphosphonium 1,2,3,4,5,6-pentaselenarsinane-6-selenolate **134**. The

latter was also obtained from As_2Se_3 , Se, Na_2Se , and PPh_4Br in a 74% yield (Scheme 40) <1998ZFA239>. The Se_5AsSe anion **134** consists of a six-membered AsSe_5 ring in a chair conformation, with an additional terminal Se atom attached to the As-atom. The $[\text{Se}_5\text{AsSe}]$ anion in an ethylenediamine[2.2.2] cryptand was obtained in 18% yield by Smith *et al.*, who reacted TiAsSe_4 with ethylenediamine (EDA), followed by the [2.2.2] cryptand, 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane **135** (Scheme 40) <1998IC2340>.



Scheme 39

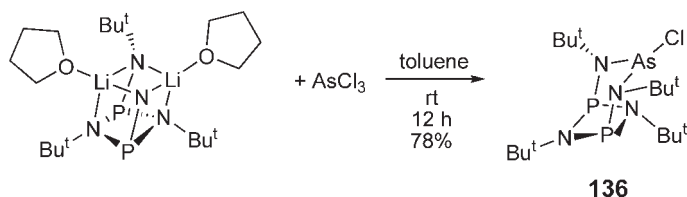


Scheme 40

9.17.6.3 Rings with One Arsenic, Two Phosphorus, and Three Nitrogen Atoms

9.17.6.3.1 2,4,6,7-Tetraaza-1,5-diphospha-3-arsabicyclo[3.1.1]heptane

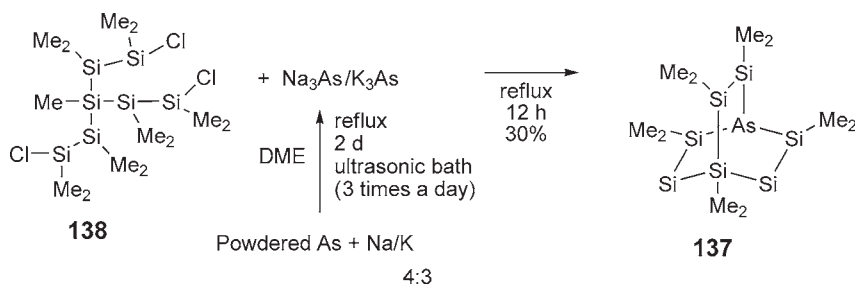
The synthesis and single crystal X-ray diffraction studies of a heterobicyclic cyclodiphosphazane, 2,4,6,7-tetra-tert-butyl-3-chloro-2,4,6,7-tetraaza-1,5-diphospha-3-arsabicyclo[3.1.1]heptane **136**, having a central arsenic(III) atom were described by Schranz *et al.* <2000IC3037>.



9.17.6.4 Rings with One Arsenic and Five Silicon Atoms

9.17.6.4.1 1-Arsa-2,3,4,5,6,7,8-heptasilabicyclo[2.2.2]octane

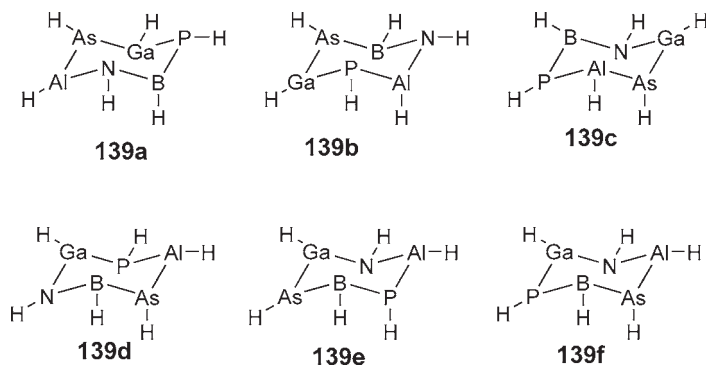
The synthesis of 2,2,3,3,4,5,5,6,6,7,7,8-tridecamethyl-1-arsa-2,3,4,5,6,7,8-heptasilabicyclo[2.2.2]octane **137** was accomplished by Hassler *et al.* from the reaction of 1,5-dichloro-3-(2-chloro-1,1,2,2-tetramethyldisilyl)-1,1,2,2,3,4,4,5,5-nonamethylpentasilane **138** with As-Na-K alloy (Scheme 41) <1997JOM(533)51>.



Scheme 41

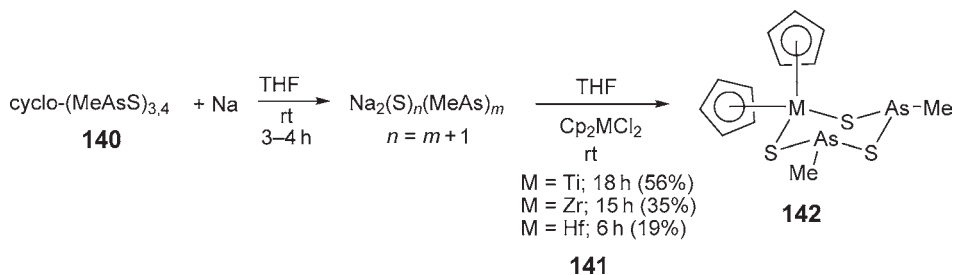
9.17.6.5 Rings with One Arsenic, One Phosphorus, One Nitrogen, One Boron, One Aluminium, and One Gallium Atom

The relative energies of the [BAlGaNPAs]H₆ isomers **139** have been calculated at the B3LYP/TZVP level of theory by Timoshkin (TZVP = triple-zeta valence polarization) <2003IC60>. All isomers have nonplanar structures. The nitrogen and group 13 centers exhibit a tendency toward planar coordination, while the P- and As-centers are pyramidal. The most stable isomer among them is **139a**.



9.17.6.6 Rings with Two Arsenic, One Group 4 Atom, and Three Sulfur Atoms

The sodium-reduced form of the mixed trimer and tetramer of cyclo-methylarsathiane **140** in THF reacted with the metallocene dichlorides **141** of group 4 elements to give the metallacycle complexes **142** (Scheme 42) <1997OM5142>. The structures **142** are isomorphous, consisting of a cyclohexane-like six-membered MS_3As_2 ring in a chair conformation with two η^5 -Cp rings on the metal atoms in pseudoequatorial and -axial positions and the methyl groups on arsenic in equatorial positions.

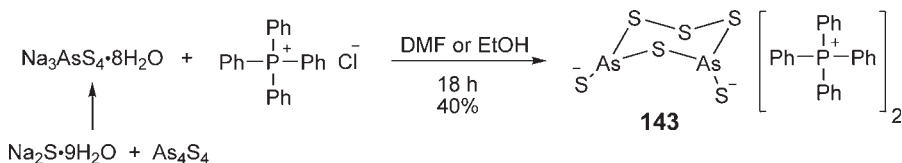


Scheme 42

9.17.6.7 Rings with Two Arsenic and Four Sulfur Atoms

9.17.6.7.1 1,2,3,5,4,6-Tetrathiadiarsinane-4,6-dimercapto dianion

The reaction of Na_3AsS_4 , obtained from Na_2S and As_4S_4 , with tetraphenylphosphonium chloride in EtOH or DMF proceeds via an intramolecular redox reaction to yield 1,2,3,5,4,6-tetrathiadiarsinane-bis(tetraphenylphosphonium) 4,6-dimercapto ion $[(\text{PPh}_4)_2\text{As}_2\text{S}_6]$ **143** in 40% yield (Scheme 43) <1995ZFA979>. According to X-ray crystal structure analysis, the dianion consists of a six-membered ring of two arsenic atoms and four sulfur atoms in a chair conformation. The arsenic atoms occupy the ring positions 1 and 3, and each of them has an additional terminal sulfur atom.



Scheme 43

9.17.6.8 Rings with Two Arsenic and Four Selenium Atoms

9.17.6.8.1 1,2,4,5,3,6-Tetraselenadiarsinane-3,6-bis(selenolate)

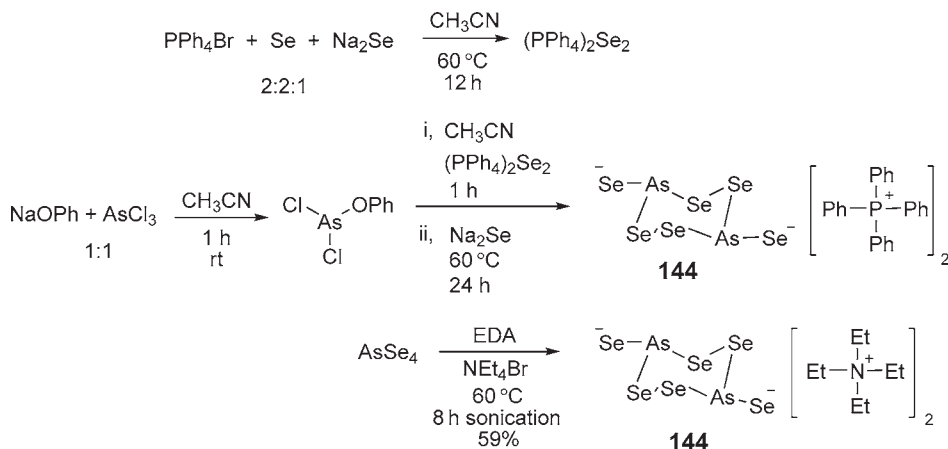
The reaction of Cl_2AsOPh , obtained from NaOPh and AsCl_3 , with $(\text{PPh}_4)_2\text{Se}_2$ and finally with Na_2Se produced $[(\text{PPh}_4)_2[1,4\text{-As}_2\text{Se}_6]]$ di-(tetraphenylphosphonium)-1,2,4,5,3,6-tetraselenadiarsinane-3,6-bis(selenolate) **144**. The As_2Se_6 anion has a six-membered ring structure in a chair conformation, with two arsenic atoms at positions 1 and 4 (Scheme 44) <1998ZFA239>. The tetraethylammonium salt of anion As_2Se_6 **144** was also prepared from the extraction of AsSe_4 in EDA, followed by treatment with NEt_4Br <1998IC2340>.

9.17.6.9 Rings with Two Arsenic and Four Silicon Atoms

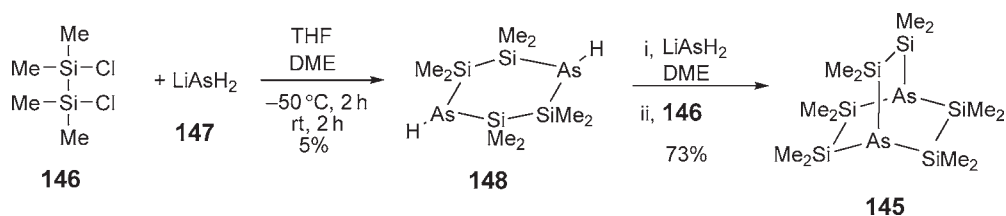
9.17.6.9.1 1,4-Diarsa-2,3,5,6,7,8-hexasila-bicyclo[2.2.2]octane

2,2,3,3,5,5,6,6,7,7,8,8-Dodecamethyl-1,4-diarsa-2,3,5,6,7,8-hexasila-bicyclo[2.2.2]octane **145** was obtained readily in 73% yield by the cyclocondensation reaction of 1,2-dichloro-1,1,2,2-tetramethyldisilane **146** with the lithium pnictides **147** $[\text{LiAsH}_2(\text{DME})]$ (DME = 1,2-dimethoxyethane). The reaction proceeds via the formation of

2,2,3,3,5,5,6,6-octamethyl-1,4,2,3,5,6-diarsatetrasilane **148**, which is isolated in the form of air- and water-sensitive colorless crystals by fractional crystallization from the reaction mixture subsequent to the synthesis of **145** (Scheme 45) <1997CEJ874>.



Scheme 44

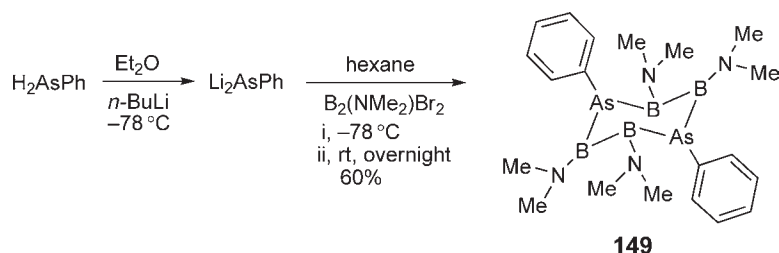


Scheme 45

9.17.6.10 Rings with Two Arsenic and Four Boron Atoms

9.17.6.10.1 1,4,2,3,5,6-Diarsatetraborinane

The reaction of Li_2AsPh , obtained from phenylarsine, with the diborane derivative $\text{B}_2(\text{NMe}_2)_2\text{Br}_2$, which is a stable 1,2-dihalodiborane precursor, afforded $N^2,N^2,N^3,N^3,N^5,N^5,N^6,N^6$ -octamethyl-1,4-diphenyl-1,4,2,3,5,6-diarsatetraborinane-2,3,5,6-tetraamine **149** having the six-membered ring in a chair conformation (60%) (Scheme 46) <1995ZFA1933>.

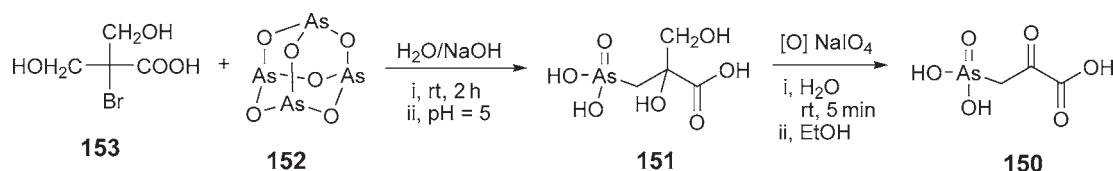


Scheme 46

9.17.6.11 Rings with Three Arsenic and Three Oxygen Atoms

9.17.6.11.1 2,4,6,8,9,10-Hexaoxa-1,3,5,7-tetrarsatricyclo[3.3.1.1^{3,7}] and 1,3,5,2,4,6-trioxatriarsinane-2,4,6-triol

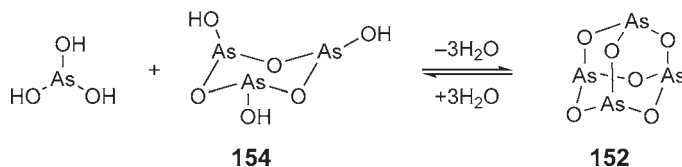
The 3-arsenopyruvic acid (3-arsono-2-oxopropanoic acid) **150** was prepared via the oxidation of 3-arsono-2-hydroxy-2-(hydroxymethyl)propanoic acid **151**, which was obtained from the treatment of As₄O₆ (arsenolite, arsenic(III) oxide, 2,4,6,8,9,10-hexaoxa-1,3,5,7-tetrarsatricyclo[3.3.1.1^{3,7}]decane **152**) with 2-bromo-3-hydroxy-2-(hydroxymethyl)propanoic acid **153** (Scheme 47) <1995BJ931>.



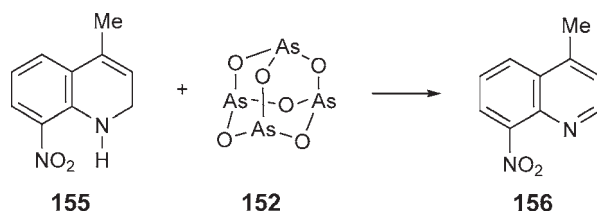
Scheme 47

A complete *ab initio* theoretical study of As₄O₆ **152** has been carried out by Jensen *et al.* at HF, MP2, and DFT/B3LYP levels of theory using the 6-311G^{*} basis set. The normal mode frequencies intensities and the corresponding vibrational assignments of As₄O₆ **152** in *T_d* symmetry were calculated <2003JMT(664)145>. A semi-empirical quantum-chemical study for As₄O₆ **152** was performed also by Pankratov and Uchaeva to test the thermodynamic and molecular properties of **152** <2000JMT(498)247>. In addition, theoretical studies on **152** in minerals and in aqueous solution were carried out by Tossell to calculate the frequencies and intensities of infrared (IR) absorptions <1997MI1613>. UV absorption spectra have been calculated for 1,3,5,2,4,6-trioxatriarsinane-2,4,6-triol **154** and arsenolite **152** in aqueous solution at configuration interaction singles (CIS) and time-dependent (TD) B3LYP levels of theory using the 6-311+G(2d,p) basis set <2001MI239>.

The polymerization of 1,3,5,2,4,6-trioxatriarsinane-2,4,6-triol **154** and dissolution reaction of As₄O₆ **152** was also investigated by Tossell (Scheme 48) <1997MI1613>. The complete Raman spectrum of arsenolite **152** has been reported by Gilliam *et al.* <2003MI54>. The thermodynamics of sublimation of As₄O₆ **152** was studied at 375–415 K using a combination of the Knudsen method and high-temperature mass spectrometry. Partial pressures, formation enthalpies, and atomization of **152** have been determined <1997MI31>. Pyrolysis–gas chromatography–mass spectrometry (PY–GC–MS) studies for As₄O₆ **152** and As₄S₆ **157** were performed by Chiavari *et al.* <1995RCM559>. Arsenolite **152** was used as an oxidizing agent by Pomeranc *et al.* to convert 4-methyl-8-nitro-1,2-dihydroquinoline **155** to 4-methyl-8-nitroquinoline **156** (Scheme 49) <2001CRC197>.

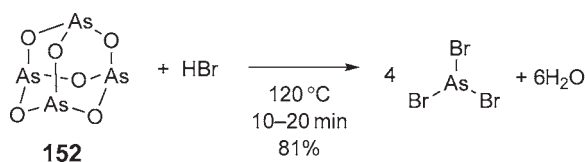


Scheme 48



Scheme 49

Pure arsenic(III) bromide could be prepared by the treatment of As_4O_6 **152** with HBr in high yield (81%). However, the yield is reduced if the evacuation is prolonged after removal of the extraction solvent (hexane), since the vapor pressure of AsBr_3 is significant, although AsBr_3 is a colorless crystalline solid that melts at 32°C (Scheme 50) <2002IS(33)203>.

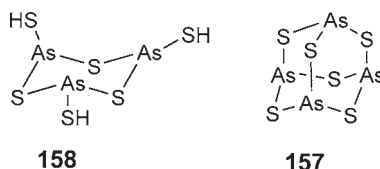


Scheme 50

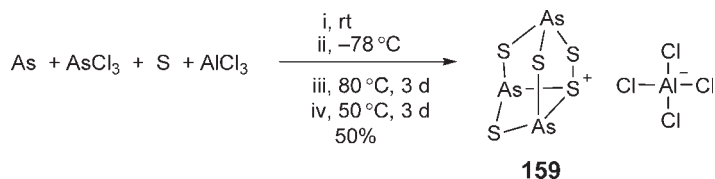
9.17.6.12 Rings with Three Arsenic and Three Sulfur Atoms

9.17.6.12.1 1,3,5,2,4,6-Trithiatriarsinane-2,4,6-trithiol, arsenic(III) sulfide, and pararealgar

UV absorption spectra have been calculated for 1,3,5,2,4,6-trithiatriarsinane-2,4,6-trithiol **158** and arsenic(III) sulfide (orpiment, As_4S_6) **157** in aqueous solution at CIS and TD B3LYP levels of theory using the 6-311+G(2d,p) basis set <2001MI239>. The bond distances, vibrational frequencies, gas-phase energetics, and proton affinity of **158** have been estimated by means of MO theory <1995MI4591>.

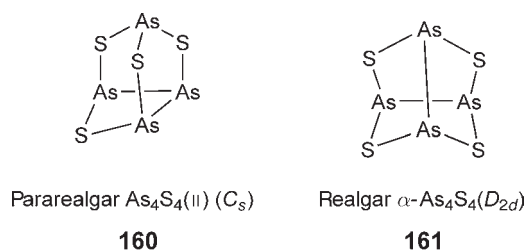


The reaction of arsenic, AsCl_3 , and AlCl_3 with sulfur in a closed ampoule led to the pentathiatrarsabicyclo cation **159** in 50% yield (Scheme 51) <2005ZFA2450>.



Scheme 51

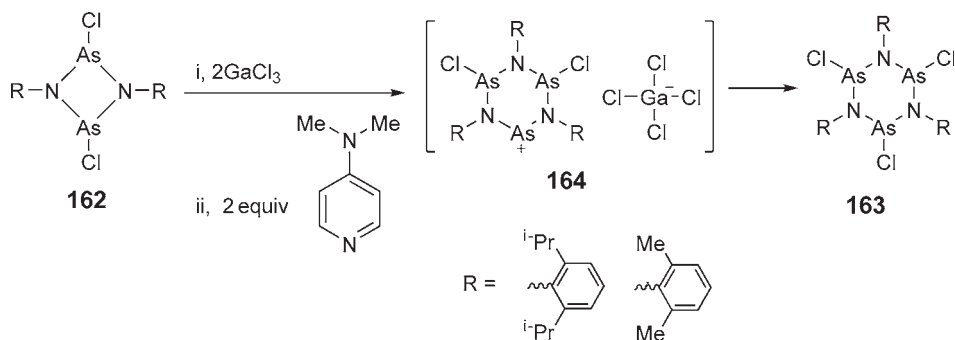
Pararealgar **160**, a polymorph of realgar **161**, crystallizes in the monoclinic space group. The characterization of tetraarsenic(III) tetrasulfide (pararealgar) **160** by means of Raman spectroscopy was performed by Trentelman and Stodulski <1996ANC1755>. Valence and core-level binding energy shifts of pararealgar **160** have been determined by Bullen *et al.* using X-ray photoelectron studies <2003MI319>. The crystal structure of pararealgar **160** was investigated by Bonazzi *et al.* <1995MI400, 1996MI874, 2003MI1463> and Kyono *et al.* <2005MI1563>. A single crystal of pararealgar was obtained by light exposure of realgar **161**. The realgar **161** is transformed into pararealgar and produces the As_4S_5 molecule if oxygen is present. The additional S-atom contributes to anisotropic expansion. An S-atom in the As_4S_5 molecule is released from one of the equivalent As-S-As linkages in As_4S_5 , which becomes the As_4S_4 molecule of pararealgar. After the As_4S_5 molecule is divided into a S-atom (radical) and the As_4S_4 pararealgar molecule, the free S-atom is reattached to another As_4S_4 realgar molecule, and reproduces an As_4S_5 molecule <2003MI1463>. The structure **160** consists of discrete covalently bonded As_4S_4 molecules, which are held together by van der Waals forces.



9.17.6.13 Rings with Three Arsenic and Three Nitrogen Atoms

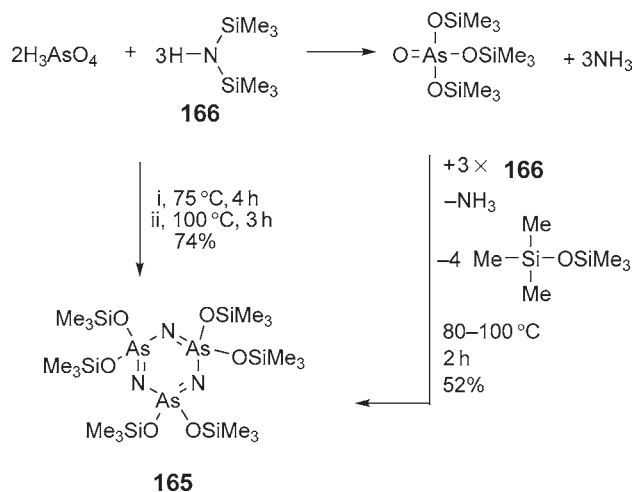
9.17.6.13.1 1,3,5,2,4,6-Triazatriarsinanes and 1,3,5,2,4,6-triazatriarsinines

2,4-Dichloro-1,3-diaryl-1,3,2,4-diazadiarsetidines **162** have been transformed into the corresponding 2,4,6-trichloro-1,3,5-triaryl-1,3,5,2,4,6-triazatriarsinanes **163** upon reaction with GaCl_3 followed by 4-(dimethylamino)pyridine (**Scheme 52**) <2005IC5897>. This ring-expansion, disproportionation reaction is initiated by chloride ion abstraction. The intermediate 2,4-dichloro-1,3,5-tris(2,6-diisopropylphenyl)cyclo-2,4-diarsa-1,3,5-triazane-6-arsenium tetrachlorogallate **164** could be isolated and structurally characterized. Subsequent reaction with 4-(dimethylamino)pyridine effects release of chloride ion from the gallate anion and consequent formation of a covalent As–Cl bond.



Scheme 52

Baier *et al.* prepared hexakis[trimethylsilyloxy]triarsa(v)azane **165** in moderate to good yield by treating H_3AsO_4 with hexamethyldisilazane **166** (**Scheme 53**) <1993CBR351>.

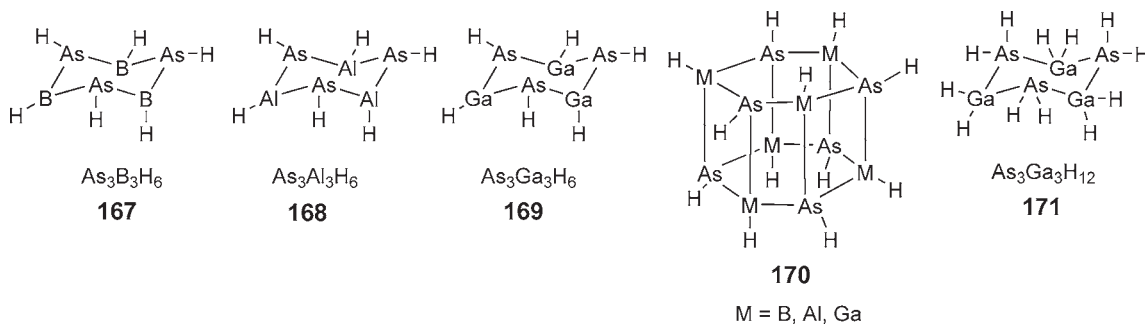


Scheme 53

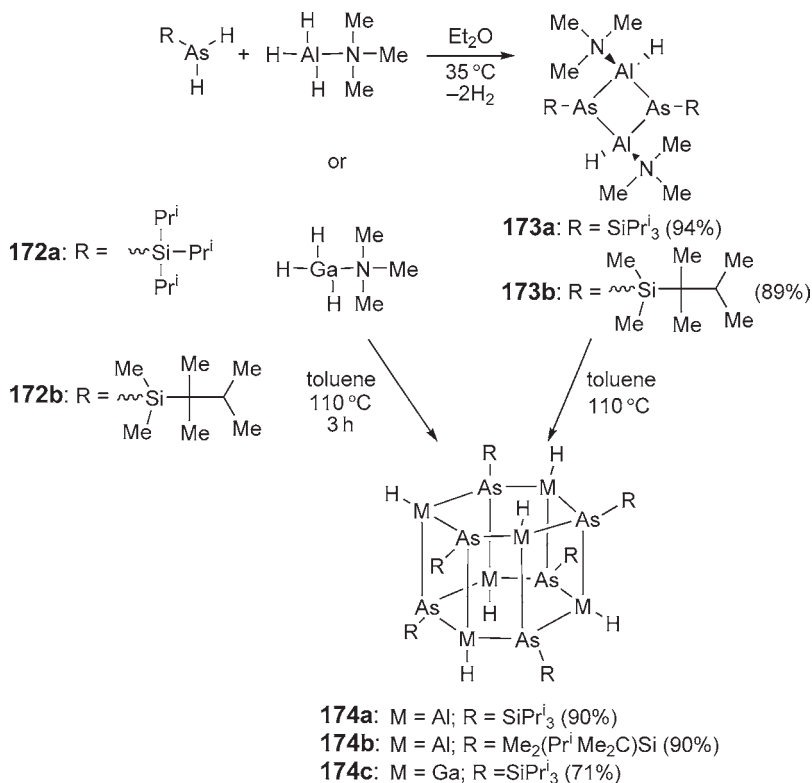
9.17.6.14 Rings with Three Arsenic and Three Boron, or Three Aluminium, or Three Gallium Atoms

9.17.6.14.1 1,3,5,2,4,6-Triarsatriborinane

Theoretical calculations on $\text{As}_3\text{B}_3\text{H}_6$, $\text{As}_3\text{Al}_3\text{H}_6$, $\text{As}_3\text{Ga}_3\text{H}_6$, and their dimers, viz. **167–170**, were reported by Timoshkin at the B3LYP/TZVP level of theory <2003IC60>. Korambath *et al.* also performed a theoretical study for $\text{As}_3\text{Ga}_3\text{H}_{12}$ **171** by means of *ab initio* MO theory <2000IJQ563>. The structure **171** is unique in the sense that each heavy atom is bonded to heavy atoms and two hydrogen atoms, forming a ring structure. Compound **171** has two conformations, viz. a boat and a chair, which are almost degenerate at the HF level of calculations.



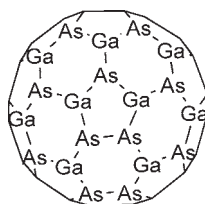
The cyclocondensation reaction of the primary silylarsanes, RAsH_2 , **172** with AlH_3NMe_3 in Et_2O led to the four-membered 1,3-diarsa-2,4-dialuminetanes **173a** and **173b**. Upon heating of **173a** and **173b** in toluene, the NMe_3 groups at the Al-centers were cleaved readily and the resulting unsolvated Al_2As_2 rings trimerized, affording the hexagonal prismatic Al_6As_6 cluster compounds **174**. Reaction of the silylarsane **172a** with AlH_3NMe_3 or GaH_3NMe_3 in toluene produced directly the hexameric Al_6As_6 and Ga_6As_6 arsagallane clusters **174a** and **174c**, respectively (Scheme 54) <1998CEJ1628>.



Scheme 54

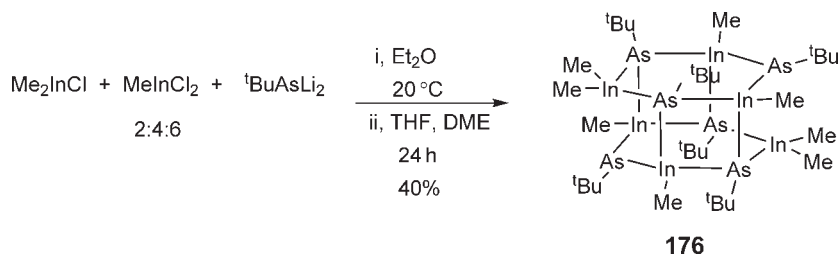
9.17.6.14.2 Gallia[5,6]fullerenes

Extensive theoretical calculations of the geometric and electronic properties of the neutral and ionized GaAs fullerene-like clusters (gallia[5,6]fullerenes **175** $\text{As}_{12}\text{Ga}_{16}$, $\text{As}_{14}\text{Ga}_{18}$, $\text{As}_{16}\text{Ga}_{12}$, $\text{As}_{18}\text{Ga}_{14}$, $\text{As}_{18}\text{Ga}_{22}$, $\text{As}_{24}\text{Ga}_{28}$) have been performed on the basis of DFT <2001PCB12477>. The heterofullerene clusters studied are less spherical than those formed by carbon atoms. The correlation between the calculated binding energy per atom of the heterofullerene clusters and the inverse nuclearity was also investigated.

**175**

9.17.6.15 Rings with Three Arsenic and Three Indium Atoms

The reaction of Me_2InCl , MeInCl_2 , and *tert*- BuAsLi_2 in a molar ratio of 2:4:6 led to the formation of an anionic In–As skeleton which consists of $[\text{Li}(\text{DME})_3]_2[(\text{InMe}_2)_2(\text{InMe})_4(\text{tert-BuAs})_6] \cdot 2\text{DME}$ **176** (Scheme 55) <2003ZFA1136>.

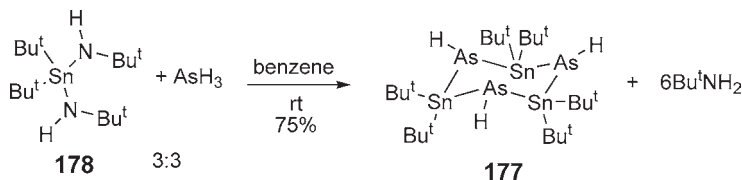
**176**

Scheme 55

9.17.6.16 Rings with Three Arsenic and Three Tin Atoms

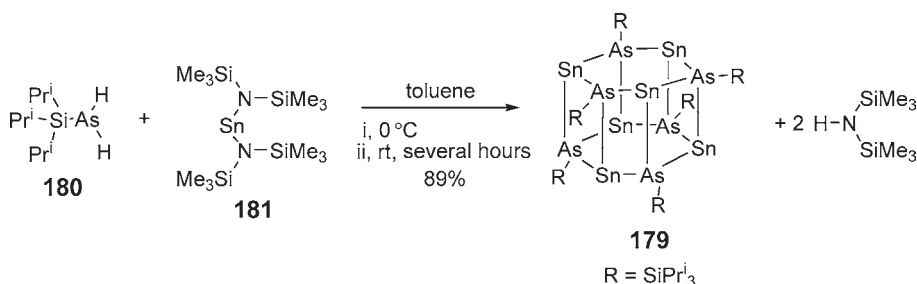
9.17.6.16.1 1,3,5,2,4,6-Triarsatristanninanes

The oligomeric, six-membered heterocycle, 2,2,4,4,6,6-hexa-*tert*-butyl-1,3,5,2,4,6-triarsatristanninane **177**, has been prepared in 75% yield by the reaction of *N,N'*-1,1-tetra-*tert*-butylstannanediamine **178** with AsH_3 (Scheme 56) <1998ZFA1202>.

**177**

Scheme 56

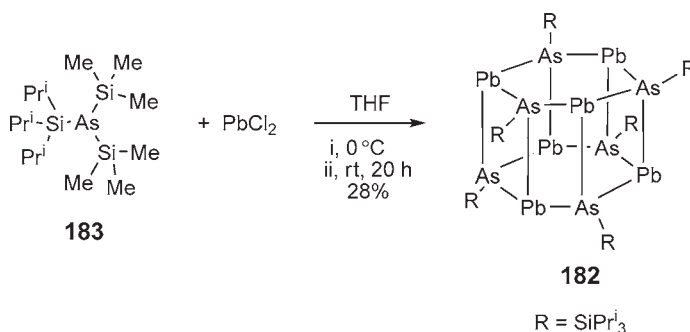
Westerhausen *et al.* synthesized the hexamer Sn_6As_6 **179** by the treatment of (triisopropylsilyl)arsine **180** with tin(II) bis[bis(trimethylsilyl)amide] **181** in 89% yield. The structure of the compound was determined by X-ray crystallography (Scheme 57) <2000JOM70>.



Scheme 57

9.17.6.17 Rings with Three Arsenic and Three Lead Atoms

Compound **182**, which was obtained from (triisopropylsilyl)bis(trimethylsilyl) arsine **183** and PbCl_2 , is the first structurally characterized compound with chemical bonds between lead and arsenic (Scheme 58) <2004ZFA345>.



Scheme 58

9.17.6.18 Rings with Four Arsenic and Two Sulfur Atoms

9.17.6.18.1 2,6,7-Trithia-1,3,4,5-tetraarsabicyclo[2.2.1]heptanes

The reaction of $\text{Cp}_2\text{Co}_2(\text{CO})_2$ **184** with a mixture of $\beta\text{-As}_4\text{S}_4[\text{Cr}(\text{CO})_5]_n$ ($n = 1, 2$) **185** in toluene afforded cobalt complexes of 2,6,7-trithia-1,3,4,5-tetraarsabicyclo[2.2.1]heptane **186**, hexarsinane **187**, and 7-thia-1,2,3,4,5,6-hexaarsa-bicyclo[2.2.1]hepta-2,5-diene **188** (Scheme 59) <1997OM4954>. When $\text{Cp}_2\text{Co}_2(\text{CO})_2$ **184** was reacted with only realgar **161** in toluene at 80°C , compound **189** was formed in very low yield (<1%) <1996CBR657>. Treatment of $\text{Cp}_2\text{Co}_2(\text{CO})_2$ **184** with As_4S_3 **190** in toluene produced compound **186** in 3% yield <1996CBR657>.

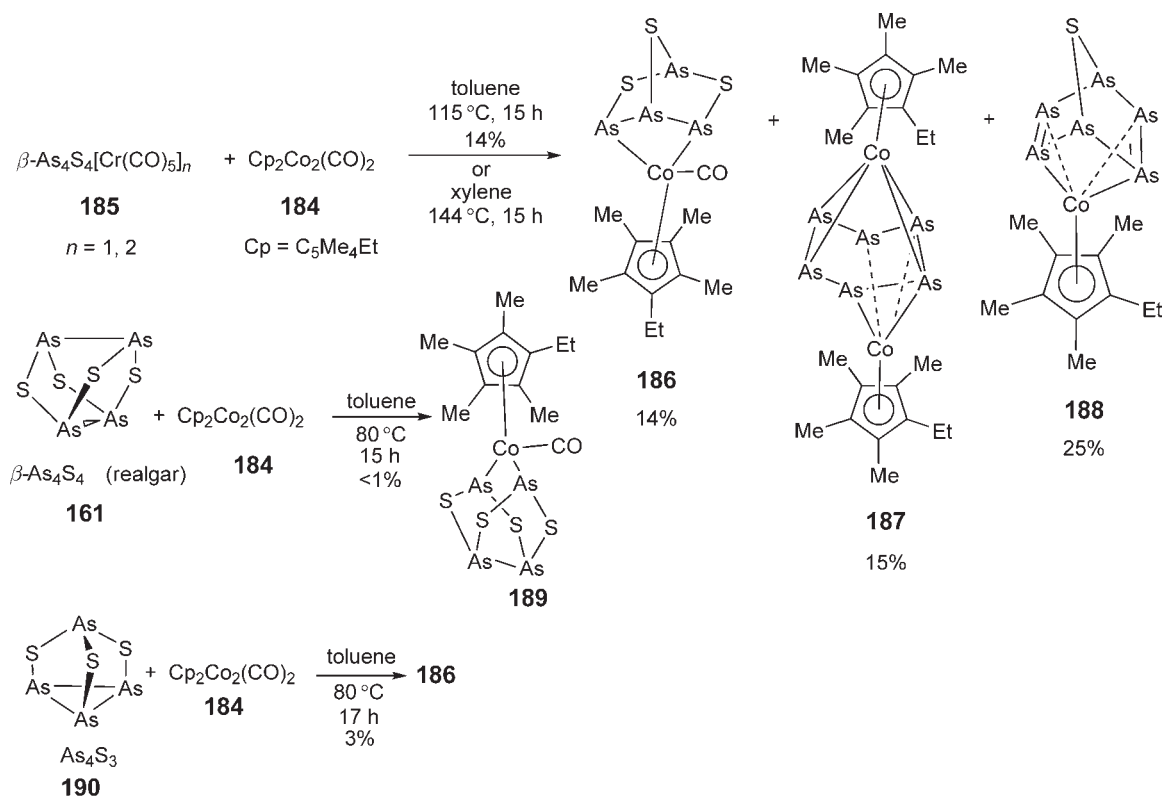
9.17.6.19 Rings with Six Arsenic Atoms

9.17.6.19.1 Hexarsinanes, hexarsinines, 1,2,3,4,5,6-hexaarsabicyclo[2.2.1]hepta-2,5-dienes, and arsa[5,6]fullerenes

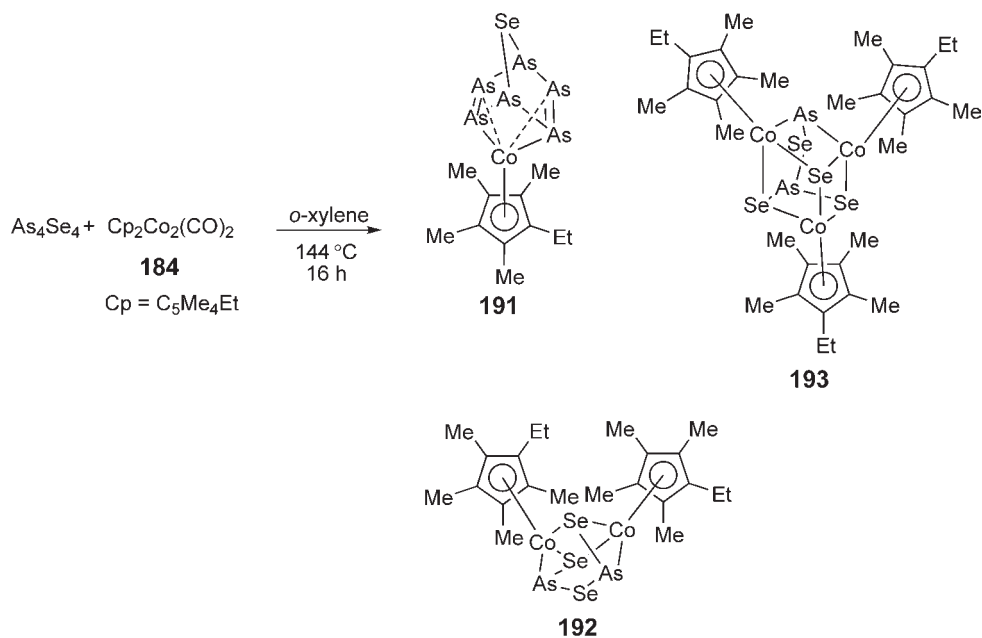
Cobalt complexes of 7-thia-1,2,3,4,5,6-hexaarsa-bicyclo[2.2.1]hepta-2,5-diene and hexarsinine have been discussed in Section 9.17.6.18.1.

The reaction of $\text{Cp}_2\text{Co}_2(\text{CO})_2$ **184** with an equimolar amount of As_4Se_4 was investigated at different temperatures and compared to the reaction of $\text{Cp}_2\text{Co}_2(\text{CO})_2$ with As_4S_4 . In boiling toluene, the formation of **192** and **193** was observed, whereas, in boiling xylene, in addition to **192** and **193** the cobalt complex of 7-selena-1,2,3,4,5,6-hexaarsa-bicyclo[2.2.1]hept-2,5-diene **191** was formed in 4% yield (Scheme 60) <1999POL347>.

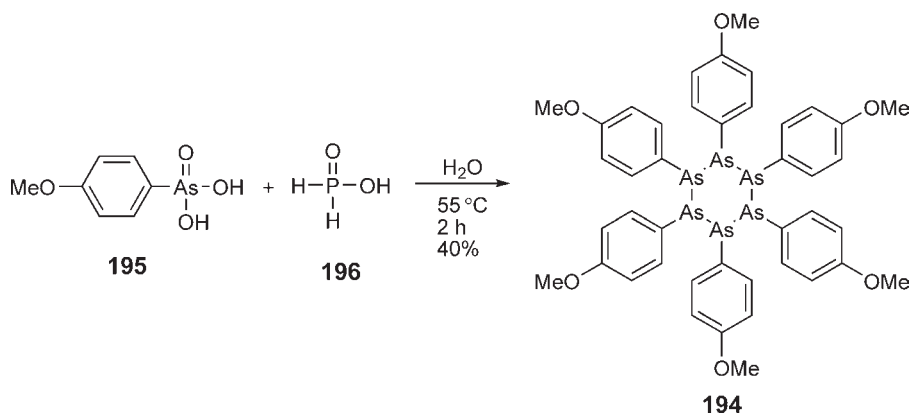
1,2,3,4,5,6-Hexakis(4-methoxyphenyl)hexarsinine **194** was synthesized in 40% yield by Marx *et al.* by the treatment of 4-methoxyphenylarsonic acid **195** with phosphinic acid (hypophosphorus acid) **196** (Scheme 61) <1997ZFA75>.



Scheme 59

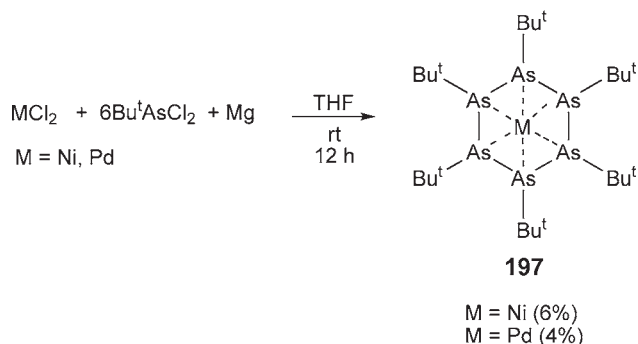


Scheme 60



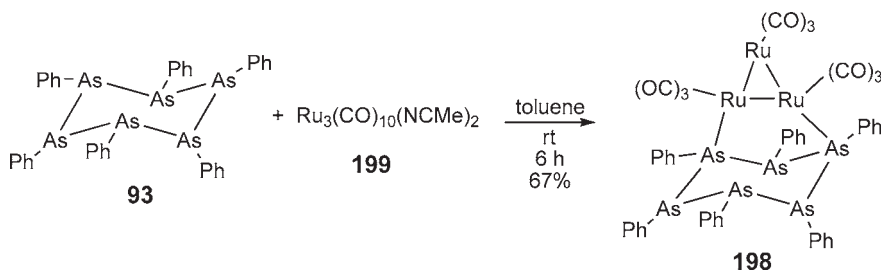
Scheme 61

The reaction of *tert*-BuAsCl₂ with magnesium in the presence of NiCl₂ or PdCl₂ gave the Ni- and Pd-complexes [Ni(*tert*-BuAs)₆] and [Pd(*tert*-BuAs)₆] of 1,2,3,4,5,6-hexa-*tert*-butylhexarsinane **197** in low yields (Scheme 62) <1996ZFA689>. The compounds obtained consist of a six-membered ring in a chair conformation with the nickel or palladium in the center of the ring.



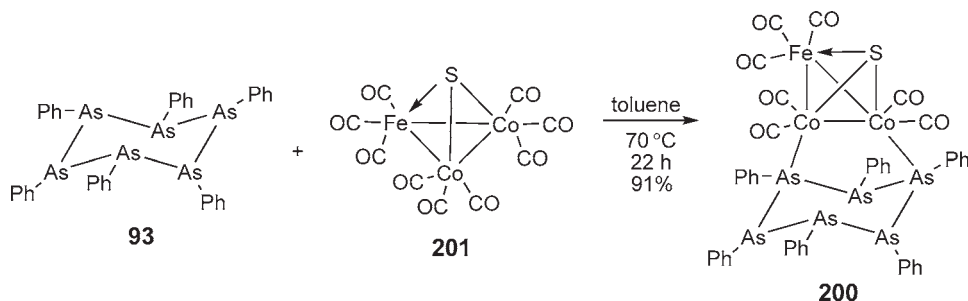
Scheme 62

The ruthenium complex of 1,2,3,4,5,6-hexaphenylhexarsinane, viz. **198**, was prepared in 67% yield by De Silva *et al.* by the reaction of [Ru₃(CO)₁₀(NCMe)₂] **199** with 1,2,3,4,5,6-hexaphenylhexarsinane **93** at room temperature (Scheme 63) <2002JOM(664)27>.



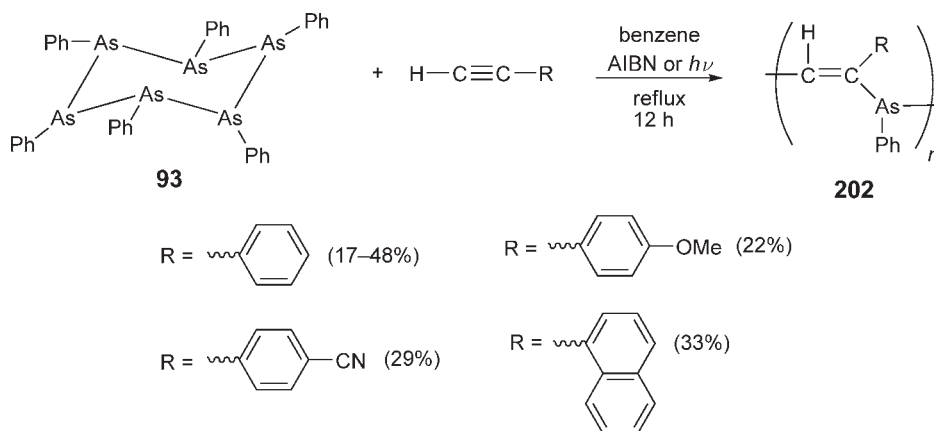
Scheme 63

The dicobalt–iron complex of 1,2,3,4,5,6-hexaphenylhexarsinane, viz. **200**, was prepared by De Silva *et al.* as the only product in 91% yield by the reaction of 1,2,3,4,5,6-hexaphenylhexarsinane **93** with **201** (Scheme 64) <2002JOM(642)237>.



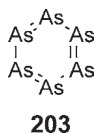
Scheme 64

The polymerization reaction of 1,2,3,4,5,6-hexaphenylhexarsinane **93** with phenylacetylene <2002JA6600> and arylacetylenes <2004MM1271> in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) in benzene afforded the corresponding poly(vinylenearsine)s **202** in moderate yield (Scheme 65). The number-average molecular weight of the polymer was found to be ~4000. The electronic structures of the polymers were investigated also by ultraviolet–visible (UV–Vis) spectroscopy. The UV–Vis absorption spectrum of polymer **202** (R = Ph) in CHCl₃ showed a small absorption in the UV region. The lower-energy absorption edge was located at 550 nm. It is assumed that this lower-energy absorption results from a delocalized n–π* transition in the main chain.

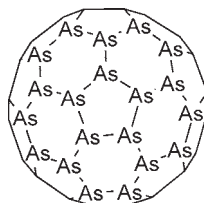


Scheme 65

The electronic structure and properties of hexarsinine **203** have been investigated by the use of hybrid DFT B3LYP <2005JOM(690)4761>. The vertical ionization potentials, atomization energy, and bond lengths of hexarsinine have been determined in valence-only *ab initio* calculations by using energy-adjusted pseudopotentials <1994MI413>. The data obtained from these calculations were compared with experimental values where it was possible.



The electronic structure, vibrational modes, polarizabilities, and IR and Raman spectra of fullerene-like arsa[5,6]-fullerenes **204**, -As₂₈, -As₃₂, -As₃₆, -As₆₀, which consist of five- and six-membered rings with only arsenic atoms, were studied by DFT <2004CPL(387)476>.



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9.18

Six-membered Rings with Two or More Heteroatoms with at least One Silicon to Lead

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9.18.1 Introduction

This chapter follows the same format as that used in CHEC-II(1996) <1996CHEC-II(6)1119>; about 150 ring systems are described.

There is no equivalent chapter in CHEC(1984). Clearly, it is impossible to be comprehensive even in listing the various classes of rings under this chapter heading in such a short article and the format of this chapter is different from many others for this reason. Instead of a comprehensive approach to a small number of ring systems, this chapter will give a relatively brief survey of as wide a range of rings as possible. For many ring systems there is little information available and the variety of rings in this area means that only a small number of representative syntheses will be given, and leading references for many rings will be found only in the various tables in [Sections 9.18.2.1, 9.18.3.1, and 9.18.4.1](#). It is hoped that this wide-ranging approach will be of more use to those searching for information about unusual rings than an in-depth discussion of a small number of rings. In general, compounds containing hypercoordinate group 14 elements in chelate ring complexes have been omitted.

9.18.2 Monocyclic Compounds

This chapter has been split into four main sections. The first deals with monocyclic compounds and this is followed by sections dealing with bi-, tri-, and polycyclic compounds.

9.18.2.1 Survey of Ring Systems

This section aims to provide the reader with leading references to as wide a range as possible of ring systems. The rings are arranged in order of increasing number of heteroatoms, from two to five in [Tables 1–4](#). In many instances, the only references to a ring in this chapter will be found in these tables.

Table 1 Rings containing two heteroatoms^a

Ring type	References
<i>1,2-Substituted rings</i>	
	
E = N; M = Si	Prep.: 1999OM5103, 2004HCA1681, 2004JOC3008
E = O; M = Si	Prep.: 2006OL483, 2005S3389, 2004TL4329, 2004PS955, 2003OL4231, 1996TL6781 Reacts. 2001JA6957, Prep. reacts. 2000TL9281, 1999JOC1843, 1998CC2745, 1997JOC4206 Polymers 1997JAP1081
Hex-3-ene	Prep.: 2005JA10028, Struct. reacts. calcs.: 2004PCA4694
Hex-4-ene	Prep.: 2002JMO9, 2001ASC184
Hex-5-ene	Prep.: 1996OM1524
E = S; M = Si	Calcs.: 2005JPO35
E = Si; M = Si	Reactions: 2006JOM(691)2440, 2005CL56, 2005OM156, 1997OM5223; X-ray, reactions, metal complexes: 2003OM2517; photochemistry: 2003OM1766, prep.: 2001OM3718, prep.: 1999TL7777
Hex-4-ene	Prep.: 2003JA3414
Hex-1-ene	Prep.: 2002CL22
Hexa-3,5-diene	Prep.: 1995OM5695
Disilabenzene	Calcs.: 2002OM4823, 2003OM5556
E = Ge; M = Ge	
Hex-4-ene	2000OM3379, 2000JOM(601)324
<i>1,3-Substituted rings</i>	
	
E = N; M = Si	Prep.: 2001RJC1874
E = O; M = Si	Prep. react.: 1996JOC2441
E = S; M = Si	Prep.: 1997RJC1449, reacts.: 2006JGU103, 2003RJC321, calcs.: 2005JPO35, 2004JA11456, struct.: 1997RJC1728
E = Si; M = Si	Prep. X-ray, calcs.: 2004AGE1543, calcs.: 2000AGE3074, prep. X-ray: 1997OM5048, prep.: 1996MM5306
Disilabenzene	Calcs.: 2002OM4823
<i>1,4-Substituted rings</i>	
	
E = N; M = Si	Prep. struct.: 2005JOM(690)33, prep. reacts.: 2004OBC3006, 2001RJC1874 2004OM4468, 2004OM361, 2003OM916
Biological activity	
E = P; M = Si	Prep. reacts.: 2003OL2671, 1997IC1867
E = S; M = Si	Reacts.: 2006JGU103, calcs.: 2005IJQ(105)313, 2005JOM(690)4103, 2005IJQ(101)40, 2005JPO35
E = M = Si	Prep.: 1999RCB1712, conformation: 1998T13181, reacts.: 1998TL3197, 1996CL683, prep. struct.: 1998OM2018, prep.: 1996MM5306, Prep. X-ray struct.: 1995OM2556
Hex-2-ene	Prep.: 1995OM2556, prep. struct.: 2001OM5537
Hexa-2,5-diene	Reactions, struct.: 2001OM1195, prep. struct.: 1998OM2018
Disilabenzene	Calcs.: 2002OM4823
E = Pt; M = Si	Prep. struct.: 2001OM4451
Hexa-2,5-diene	Prep. reacts.: 2004CEJ416, 2003OM373

^aUnless otherwise stated, all rings are saturated.

Table 2 Rings containing three heteroatoms^a

<i>Ring type</i>	<i>References</i>
<i>1,2,3-substituted rings</i>	
	
E = X = N; M = Si Hex-4-ene	Prep.: 1998EJI1967, 2004JCD1083 Prep., reacts.: 2006JA9628
E = X = O; M = Si	Prep. 2003JOC9050, 2001JOC8666, 2006JA2258, 2004TL4533
E = O; X = N; M = Si	Prep. reacts.: 2003JA9596, 1997T15011
E = X = Si; M = N	Prep. reacts. calcs.: 1999MM1, 1995IC4840, prep.: 1997IC4360, reacts.: 1996ZNB1707, 1995JOM(489)201
E = X = Si; M = O	Prep.: 2003OBC4017, 2001OM1204, reacts.: 1999JA5413, 1996JA8501, 1995MI135
E = X = O; M = Sn	Prep. reacts.: 1998MAC273
E = X = S; M = Sn	Reacts.: 2004BMC975, prep. polym.: 2000PSA3656 prep. calcs.: 2000JOM(605)82, preps. reacts.: 1998MAC273
E = X = Sn; M = O	Prep. struct.: 2001CHE1405, 1999JOM(574)176
E = X = Sn; M = S	Prep. struct.: 1995JOM(492)145
<i>1,2,4-substituted rings</i>	
	
E = X = Si; M = O	Prep.: 2006T3103, 2001OM5537, 1995OM2556
<i>1,3,5-substituted rings</i>	
	
E = O; M = O; X = Si	Reacts.: 2004RCB2029, 1998RCB2445, prep.: 1996TA69
E = X = P; M = Si	Struct.: 1998AXC1449
E = M = N; X = Si	Prep.: 1997CB1777, 1996CB483
E = X = M = Si	Prep.: 1998TL3193, prep. reacts.: 2005AGE2107, 2003SCI266, 2003ZFA951, 2001JOM(621)10, struct.: 2001JST(598)245, NMR: 1999ZFA97, 1998ZFA1973, reacts.: 1996AGE324
Trisilabenzene E = X = M = Ge	1995JMT(358)1 Struct.: 2005CEJ1375

^aUnless otherwise stated, all rings are saturated.

9.18.2.2 Theoretical Methods

The relative energies of a wide range of isomers of disilabenzene, C₄Si₂H₆, have been studied by density functional theory (DFT) methods <2002OM4823>. Sixty-one minimum-energy structures were found on the C₄Si₂H₆ potential energy surface which include the expected planar structures such as **1–3** together with nonplanar, or hydrogen-bridged, structures such as **4** and **5**.

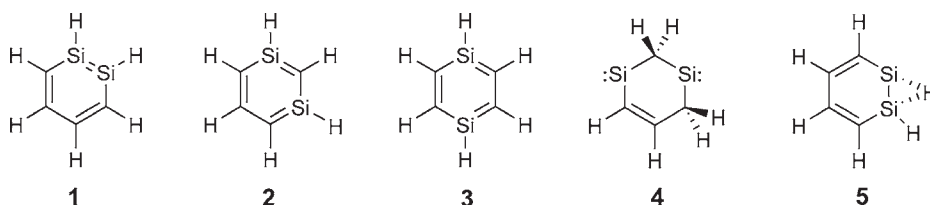
Table 3 Rings containing four heteroatoms^a

<i>Ring type</i>	<i>References</i>
<i>1,2,3,4-substituted rings</i>	
	
A = D = Si; B = C = N	Calcs. prep.: 1995IC4840
A = C = O; B = D = Si	Prep. reacts.: 2005CEJ2954, 2003OL1119, 1998JA1930
A = B = C = Si; D = O	Prep.: 1997OM2413
A = B = C = D = Si	Calcs.: 2004PNA10517, 2002PCA2369, 1997PCA4759, 1997CPL(270)500, prep. reacts.: 1996OM3606
Hex-5-ene	Prep. reacts.: 1996OM3606
<i>1,2,3,5-substituted</i>	
	
A = B = C = D = Si	Prep.: 1998TL3193
A = C = D = Si; B = O	Prep.: 1998TL3193
<i>1,2,4,5-substituted</i>	
	
A = B = C = D = Si	Prep. reacts.: 2000JOM(611)12

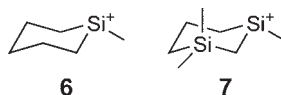
^aUnless otherwise stated, all rings are saturated.**Table 4** Rings containing five heteroatoms^a

<i>Ring type</i>	<i>References</i>
	
A = E = Si; B = D = N; C = Al	Prep., X-ray: 1998OM3135
A = B = C = D = Si; E = O	Prep.: 2001CL1220
A = C = E = Si; B = D = O	Prep.: 2004CC2672, 1999RCB114
A = C = E = Si; B = D = S	Prep.: 2003MI77
A = C = E = Si; B = D = Se	Prep.: 2003MI77
A = C = E = Si; B = D = Te	Prep.: 2003MI77
A = E = Si; C = Ge; B = D = S	Prep.: 2003MI77
A = E = Si; C = Ge; B = D = Se	Prep.: 2003MI77
A = E = Si; C = Ge; B = D = Te	Prep.: 2003MI77
A = E = Si; C = Sn; B = D = S	Prep.: 2003MI77
A = E = Si; C = Sn; B = D = Se	Prep.: 2003MI77
A = E = Si; C = Sn; B = D = Te	Prep.: 2003MI77

^aAll rings are saturated.



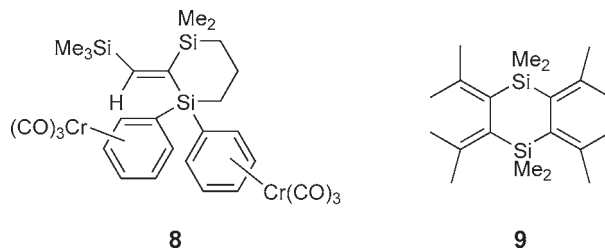
The geometries, relative stabilities, and ^{29}Si nuclear magnetic resonance (NMR) chemical shifts for the pair of silacyclohexane derivatives **6** and **7** have been calculated by DFT methods [<2003JOC1827>](#). It is found that the introduction of the β -SiMe group stabilizes the cation by $6.7 \text{ kcal mol}^{-1}$ in a manner similar to the well-known β -Si stabilization of carbenium ions, and slightly increases the degree of pyramidalization at the Si^+ center.



9.18.2.3 Experimental Structural Methods

The very wide range of ring systems covered in this chapter has meant that there is insufficient space to describe most of the structural information available here. Instead, the discussion will concentrate on a small number of compounds that have been fully characterized structurally, mainly by X-ray crystallography. References to further structural studies can be found in [Tables 1–4](#).

The structure of the vinyl cation **74** (counter anion = $[\text{CB}_{11}\text{H}_6\text{Br}_6]^-$) in [Scheme 25](#) (Section 9.18.3.4.2) has been determined by X-ray crystallography, which shows the ring to adopt a chair conformation and to have unusually long Si-C_β bonds, indicative of β -Si-C hyperconjugation [<2004AGE1543>](#). A second 1,3-disilacyclohexane derivative **8** has been characterized structurally in order to determine the nature of the product arising from an intermolecular hydrosilylation [<1997OM5048>](#). In this case, the Si-C bond lengths are all normal. The structure of the 1,4-disilacyclohexane derivative **9** has also been determined by X-ray crystallography [<1995OM2556>](#). There are relatively few structural studies on rings with more than two heteroatoms under this chapter heading; references to them can be found in [Tables 2–4](#).

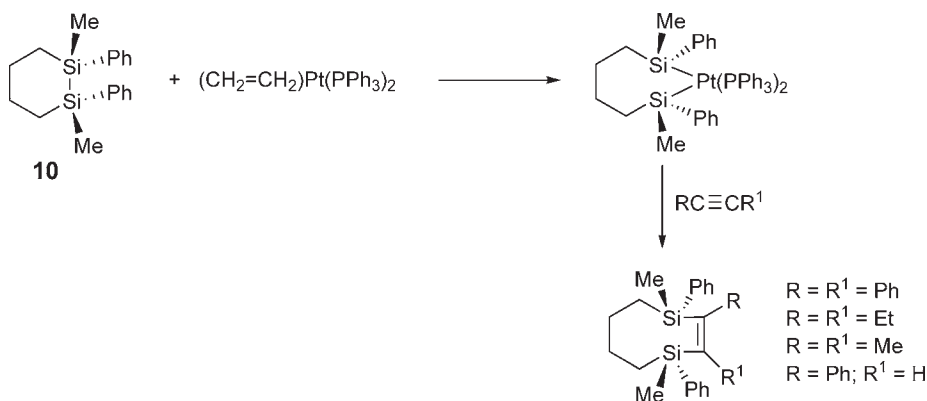


The zwitterion **32**, [Equation \(3\)](#), has an unusual structure in the solid state in which a cationic tetrahedral Al(III) center and a planar carbanion are both part of a six-membered ring [<1998OM3135>](#). NMR spectroscopy suggests that this unusual structure is retained in solution. The X-ray crystal structure of **33** ($\text{M} = \text{Si}$) shows the heterocycle to be almost planar with the tin atoms being inequivalent. This inequivalence is also seen in the solid-state ^{119}Sn NMR spectrum [<2000OM3272>](#).

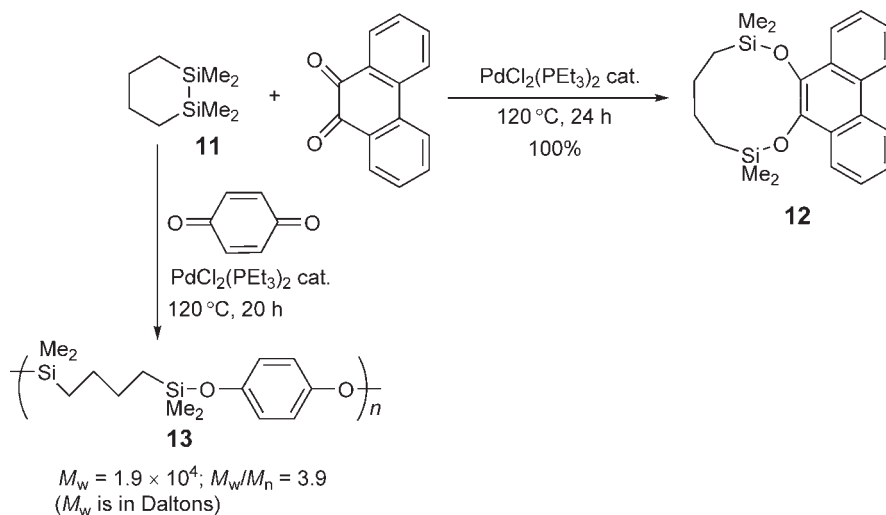
9.18.2.4 Reactivity of Nonconjugated Rings

The pure *cis*- and *trans*-1,2-disilacyclohexanes **10** each undergo platinum-catalyzed stereoselective insertion reactions with alkynes. Products from reactions of the *cis*-isomer are shown in [Scheme 1](#) [<2001OM3718>](#).

The palladium-catalyzed reaction of disilacyclohexane derivative **11** with quinones gives different products depending on the nature of the quinone. With 9,10-phenanthraquinone a 10-membered ring product **12**, arising from an insertion reaction, forms, but with *p*-benzoquinone a ring-opening copolymerization occurs to give **13** ([Scheme 2](#)) [<1997OM5223>](#).



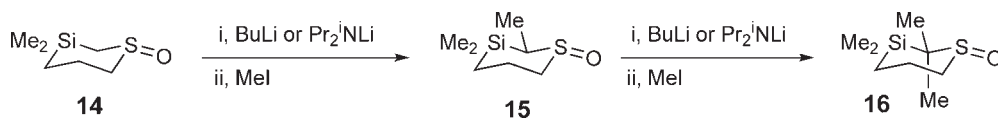
Scheme 1



Scheme 2

9.18.2.5 Reactivity of Substituents Attached to Ring Carbon Atoms

The stabilization of an anion with an α -Si or a sulfur substituent is well known and this can be seen readily in the metallation reactions of the thiasilinine **14** which undergoes sequential metallations to give first the trimethyl derivative **15** followed by the tetramethyl derivative **16** (Scheme 3) <2006JGU103>. Similar reactions occur for the 1,4-thiasilinine isomer of **14** to give a product in which both the carbons α to the sulfoxide group have been monomethylated to afford a pair of stereoisomers <2006JGU103>.



Scheme 3

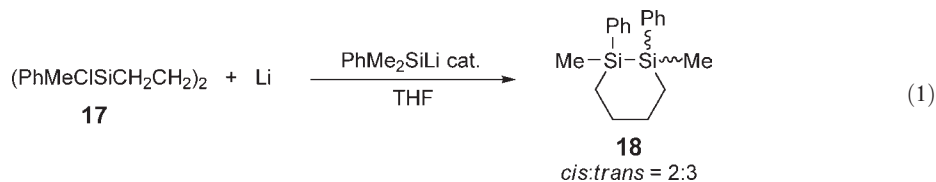
9.18.2.6 Ring Syntheses

9.18.2.6.1 Rings containing two heteroatoms

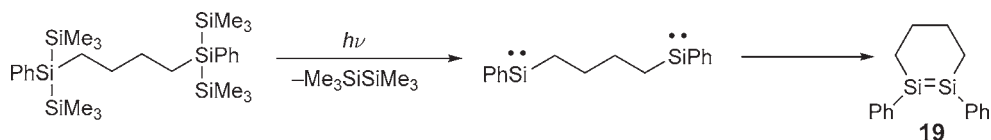
Many different rings relevant to this chapter containing two heteroatoms are known; the syntheses of selected examples are given here while references to many more examples than can be described in detail below are given in Table 1.

9.18.2.6.1(i) 1,2-Heteroatoms

A mixture of *meso*- and *dl*-silylbutanes **17** gives, upon Wurtz-type coupling with lithium metal and a catalytic amount of Me₂PhSiLi, a mixture of *cis*- and *trans*-1,2-disilacyclohexanes **18** (Equation 1). The isomers can be separated by fractional distillation <2001OM3718>. Ring closure occurs when the dipotassio reagent [K(SiMe₃)₂SiCH₂CH₂]₂ reacts with (BrCH₂)₂ to give a 1,2-disilacyclohexane <2000CL494>.

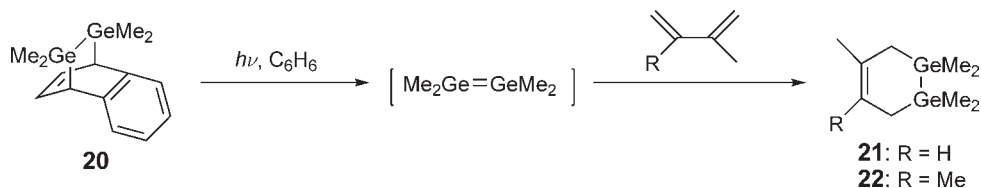


The novel cyclic disilene **19** is formed via intramolecular dimerization of two silylene centers (**Scheme 4**), but it has not been isolated, its presence being inferred from the results of trapping experiments [<2002CL22>](#).



Scheme 4

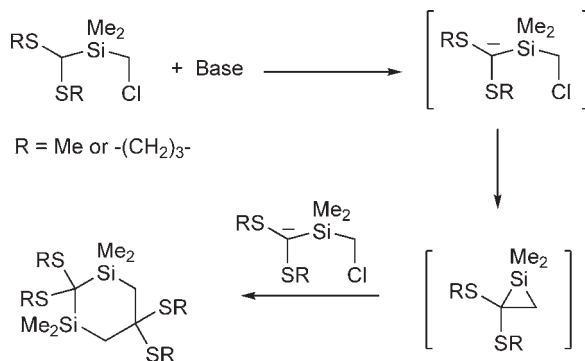
The trapping of highly reactive, unsaturated group 14 multiply bonded species has been found incidentally to give a synthetic route to 1,2-substituted heterocycles. For example, photolysis of the tricyclic species **20** in the presence of a large excess of butadienes gives **21** and **22** in 29% and 22% yields, respectively (**Scheme 5**), presumably via trapping of the reactive digermene $\text{Me}_2\text{Ge}=\text{GeMe}_2$ [<2000OM3379, 2000JOM\(601\)324>](#).



Scheme 5

9.18.2.6.1(ii) 1,3-Heteroatoms

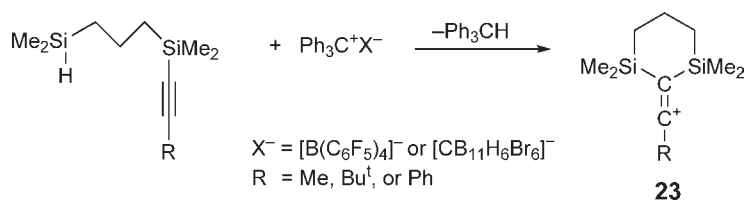
A novel synthesis of 1,3-disilacyclohexanes can be achieved via the method shown in [Scheme 6](#) [<1999ICA\(296\)231, 1996CL1083>](#). The mechanism is thought to involve initial deprotonation of the bis(alkylthio)methyl group by the base,



Scheme 6

followed by formation of a silacyclopropane and subsequent attack by a second equivalent of bis(alkylthio)methyl anion. The yield is dependent on the choice of the base which may be either BuLi or lithium diisopropylamide (LDA).

The vinyl cations **23** are stabilized by the two β -Si atoms in the 1,3-disilacyclohexane ring and can be isolated from the reaction shown in [Scheme 7](#) <2004AGE1543, 2000AGE3074>.



Scheme 7

9.18.2.6.1(iii) 1,4-Heteroatoms

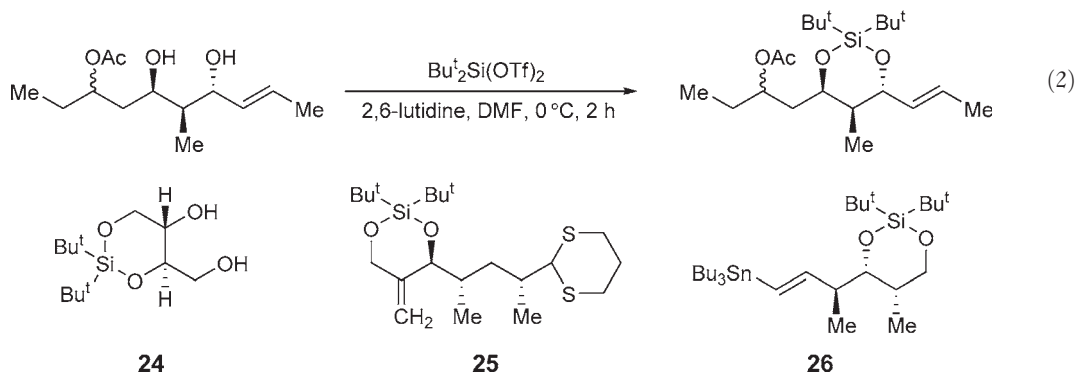
The diphenylsilyldiethylene or DPSide group has been proposed as a new protecting group for primary amines and is introduced using $\text{Ph}_2\text{Si}(\text{CH}_2\text{CH}_2\text{OTos})_2$. This method of protection naturally gives rise to 1,4-azasilacyclohexanes <1999TL5333>.

9.18.2.6.2 Rings containing three heteroatoms

There is a wide variety of rings containing three heteroatoms, many of which are referred to only in [Table 2](#). Some of the more important ring systems are, however, described in more detail below.

9.18.2.6.2(i) 1,2,3-Substituted rings

The synthesis of heterocyclic rings containing the O–Si–O linkage has increased dramatically since the introduction of the Bu^t_2Si group for the protection of diols. This usually involves the reaction between a suitable diol <2002SOS(4)269> or bis(tetrahydropyranyl) precursor <1996SL523> and $\text{Bu}^t_2\text{Si}(\text{OSO}_2\text{CF}_3)_2$ or $\text{Bu}^t_2\text{SiCl}_2$ in the presence of an organic base; a typical reaction is shown in [Equation \(2\)](#) <2001JOC1708>. Most of the compounds formed in this way are intermediates, incidental to a multistep procedure. Examples of such compounds are the erythritol derivative **24**, <2001JOC8666>, an intermediate **25**, in the synthesis of azaspiracid-1 <2006JA2258>, and an intermediate **26**, in the synthesis of bafilomycin A1 <2004TL4533>.

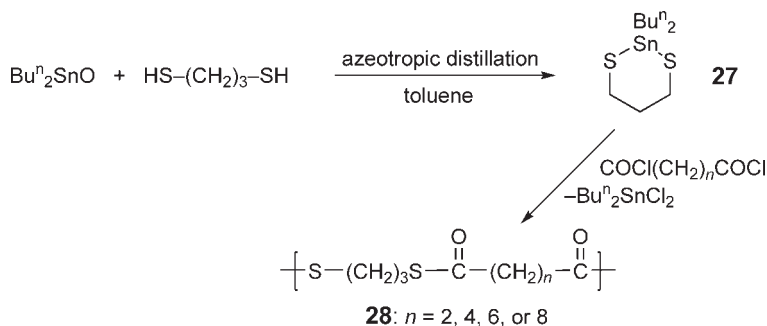


The reaction between dibutyltin oxide and bis-thiols leads to cyclic products including the six-membered ring product **27** ([Scheme 8](#)) <2000PSA3656>. Reaction of **27** with bis-acid chlorides affords the polymers **28**.

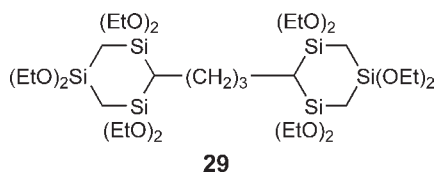
9.18.2.6.2(ii) 1,3,5-Substituted rings

The structures of a range of 1,3,5-trisilacyclohexane derivatives have been determined by gas-phase electron diffraction, ^1H , ^{13}C , and ^{29}Si NMR spectroscopy, and computationally <2001JST(598)245, 2001JMT(544)61, 1999ZFA97, 1998ZFA1973, 1998ZFA65, 1998JMT(454)91>. The unsubstituted 1,3,5-trisilacyclohexane is relatively flat and has a lower energy difference between the chair and twist boat conformers than does cyclohexane. The

bis-1,3,5-trisilacyclohexane derivative **29** can be prepared by metallation of $[\text{CH}_2\text{Si}(\text{OEt})_2]_3$ followed by reaction with $\text{Br}(\text{CH}_2)_3\text{Br}$ and can be used as a precursor to a periodic mesoporous organosilica <2005AGE2107, 2003SCI266>.



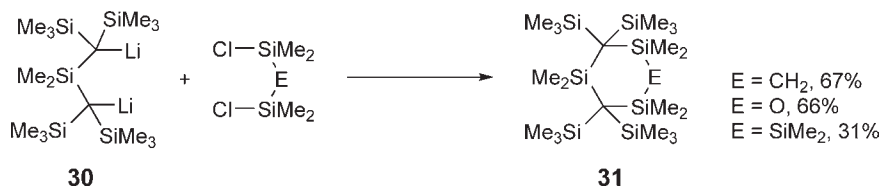
Scheme 8



9.18.2.6.3 Rings containing four heteroatoms

References to many rings containing four heteroatoms are given in [Table 3](#). Their syntheses are often similar to those for the three heteroatom cases, that is, by trapping of low-coordinate or unsaturated group 14 species, or by insertion into group 14 M–M bonds.

The dilithium reagent **30** reacts ([Scheme 9](#)) with a variety of bis-chlorosilanes to give products of type **31** <1998TL3193>. The dilithium reagent could, no doubt, be used as a precursor to an even wider range of compounds by metathesis reactions with metal halides.

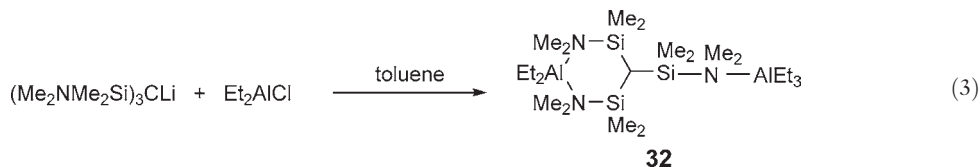


Scheme 9

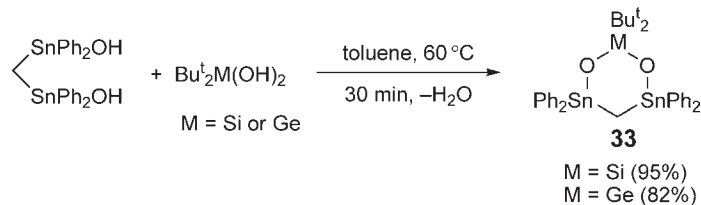
9.18.2.6.4 Rings containing five heteroatoms

Relatively few six-membered rings containing a carbon and five heteroatoms have been prepared; in fact, they have often resulted as unexpected products from reactions of unstable intermediates. Examples of heterocycles in which all of the atoms in the six-membered ring are different appear to be extremely rare. References to five heteroatom rings are given in [Table 4](#).

An unusual zwitterion **32** is formed in 30% yield in the metathesis reaction involving the very bulky lithium reagent $(\text{Me}_2\text{NMe}_2\text{Si})_3\text{CLi}$ ([Equation 3](#)). Reaction of the same lithium reagent with AlCl_3 , however, affords a four-membered ring product <1998OM3135> (see Chapter 2.11).



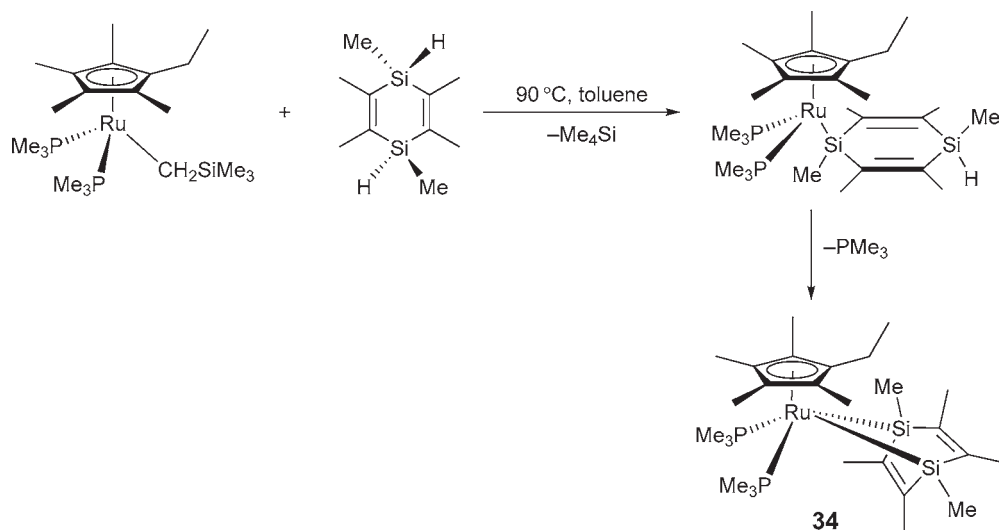
Neutral, six-membered rings **33** containing five heteroatoms can be prepared also in the condensation reaction shown in **Scheme 10** <2000OM3272>.



Scheme 10

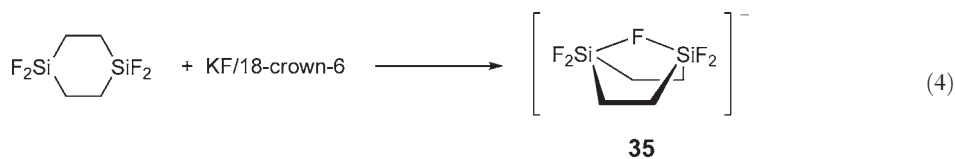
9.18.2.7 Reactivity of Substituents Attached to Ring Heteroatoms

An attempt to prepare a ruthenium complex containing a disilabenzene ligand (**Scheme 11**) led instead to the complex **34**, which is best described as a metallodisilanorbornadiene <2001OM1195>.



Scheme 11

Attempts to difluorinate 1,1,4,4-tetrafluoro-1,4-disilacyclohexane using KF lead only to monofluorination to give an anion which can undergo intramolecular exchange of fluorine between the two silicon atoms via the bridged structure **35** (Equation 4) <1996CL683>.



9.18.2.8 Important Compounds and Applications

Few of the compounds described in **Section 9.18.2.1** have any significant applications but one area of recent growth is that of the preparation of 'sila-drugs', compounds that are silicon analogues of known heterocyclic organic drugs. For

example, compounds such as sila-haloperidol and sila-niguldipine have been prepared and shown to have biological activity <2004OM4468, 2004OM361, 2003OM916>. A second related area involves the use of $R_2Si(OH)_2$ species to act as protease inhibitors. These compounds often contain sila-heterocycles as intermediates <2004JOC3008>.

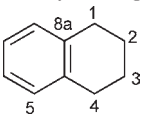
9.18.3 Bicyclic Compounds

A large number of polycyclic heterocycles containing two or more six-membered rings that share two or more carbon atoms are known. For the majority of these systems, only one of the six-membered rings contains the heteroatoms and the other rings are fused carbocyclic rings such as cyclohexane, benzene, naphthalene, and, in rare examples, anthracene. Systems in which more than one of the six-membered rings contain heteroatoms are also briefly discussed; these include spirocyclic compounds and substituted naphthalenes.

9.18.3.1 Survey of Ring Systems

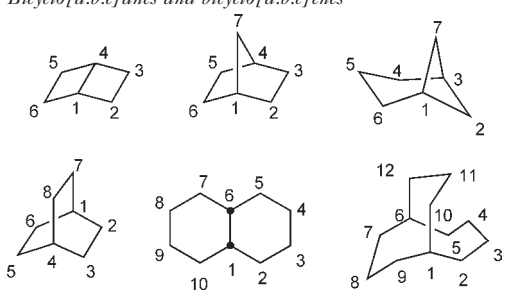
Compounds in which the heteroatoms are at bridgeheads of fused rings and pyridino- or pyrano-fused polycyclics are not mentioned as they are the subjects of other volumes in this series. **Table 5** lists the various parent ring systems found, being arranged with increasing number of rings and heteroatoms, with miscellaneous systems completing the section. In many cases the only references to a ring system will be found in **Table 5**.

Table 5 Bicyclic compounds

<i>Ring system</i>	<i>Heteroatoms^a</i>	<i>References</i>
<i>Benzo-fused rings</i>		
		
<i>Containing two heteroatoms</i>		
3,1-Benzazasiline	E = N; M = Si	Prep. toxicity: 2005CHE613
1,3-Benzazasiline	E = N; M = Si	Prep.: 2005CEJ3805
2 <i>H</i> -1,2-Benzoxasilin	E = O; M = Si	Prep.: 2005CEJ280
2 <i>H</i> -1,4-Benzoxasilin	E = O; M = Si	Prep.: 2005JPH29
1 <i>H</i> -2,1-Benzoxasilin	E = O; M = Si	Prep. struct.: 2006JOM(691)229
1 <i>H</i> -2,3-Benzoxasilin	E = O; M = Si	Prep.: 2004TL8647, 1998OM2942
1 <i>H</i> -3,2-Benzoxasilin	E = O; M = Si	Prep.: 2006OL483
1,4-Benzothiasilin	E = S; M = Si	Prep.: 1997JOC7142
1,2-Disilanaphthalene	E = Si; M = Si	Prep. and struct.: 2005JA10174
1,3-Disilanaphthalene	E = Si; M = Si	Prep. and biological activity: 2003CHE813
1,4-Disilanaphthalene	E = Si; M = Si	Prep.: 1998OM4267, 1997JOM(547)149
1,4-Dioxa-2,3-disilanaphthalene		Prep. struct.: 1995CB935
<i>Containing three heteroatoms</i>		
1,4,2-Benzodiazasiline	E = N; E = N; M = Si	Prep.: 2005JCD2945
<i>Containing four heteroatoms</i>		
1,2,3,4-Tetrasilanaphthalene	M = Si; M = Si; M = Si; M = Si	Prep.: 1996T4995, Reactions: 1997OM2746
1,2,3,4-Tetragermanaphthalene	M = Ge; M = Ge; M = Ge; M = Ge	Prep.: 1996T4995

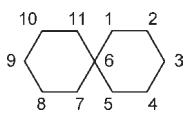
(Continued)

Table 5 (Continued)

Ring system	Heteroatoms ^a	References
<i>Bicyclo[a.b.c]anes and bicyclo[a.b.c]enes</i>		
		
1,4-Digermabicyclo[2.2.0]hexane		Prep.: 1997OM4956; X-ray: 1996OM3103
1,4-Digermabicyclo[2.2.0]hex-2-ene		Prep.: 1997OM4956
1,3-Disilabicyclo[2.2.1]heptane		Stability, NMR calcs.: 2003JOC1827
2,3,4,6,7-Pentasila[3.1.1]heptane		Prep.: 1999SL1772
1,5-Diphospha-3-sila[3.1.1]heptane		Prep. struct.: 2002JOM(645)256
2,3-Disilabicyclo[2.2.1]hept-5-ene		Prep. X-ray: 1995OM5695
1,4-Disilabicyclo[2.2.2]propellane		Stability calcs.: 2005CEJ5067
1,4-Digermabicyclo[2.2.2]propellane		Stability calcs.: 2005CEJ5067
1,4-Distannabicyclo[2.2.2]propellane		Stability calcs.: 2005CEJ5067;
1,4-Disilabicyclo[2.2.2]octane		NMR, hyperconjugation calcs.: 2003JOC1827
1,4-Phosphasilabicyclo[2.2.2]octane		2006CL294, 2003OL2671
1-Sila-2,6,7-trioxa[2.2.2]octane		Calcs.: 2001OM927
7,8-Disilabicyclo[2.2.2]octa-2,5-diene		Photolysis: 1999TL1133
2,3,4,6,7,8-Hexasilabicyclo[3.2.1]octane		Prep.: 1999SL1772
2,3,5,6,7,8-Hexasilabicyclo[2.2.2]octane		Calcs.: 2005TL5567, prep. struct.: 2000JOM(611)12
2,3,5,6,7,8-Hexagermabicyclo[2.2.2]octane		Calcs.: 2005TL5567
2,3,5,6,7,8-Hexastannabicyclo[2.2.2]octane		Calcs.: 2005TL5567
2,3,5,6,7,8-Hexaplumbabicyclo[2.2.2]octane		Calcs.: 2005TL5567
2,4,7-Trioxa-3-silabicyclo[4.4.0]decane		Prep.: 2005T8589
2,4,6,7-Tetrasila-3,5,8-trithiabicyclo[2.2.2]octane		Prep. struct.: 2002JOM(660)27
2,4,6,7-Tetrasila-3,5,8-triselenobicyclo[2.2.2]octane		Prep. struct.: 2002JOM(660)27
2,6,7-Trisila-4-germa-3,5,8-trithiabicyclo[2.2.2]octane		Prep.: 2002JOM(660)27
2,6,7-Trisila-4-germa-3,5,8-triselenobicyclo[2.2.2]octane		Prep.: 2002JOM(660)27
2,6,7-Trisila-4-stanna-3,5,8-trithiabicyclo[2.2.2]octane		Prep.: 2002JOM(660)27
2,6,7-Trisila-4-stanna-3,5,8-triselenobicyclo[2.2.2]octane		Prep.: 2002JOM(660)27
1,4-Digermabicyclo[2.2.2]octane		Stability calcs.: 2005CEJ5067
1,4-Distannabicyclo[2.2.2]octane		Stability calcs.: 2005CEJ5067
2,3-Disilabicyclo[2.2.2]octa-5,7-diene		Reactions: 2001JOM(636)63
1,6-Disilabicyclo[4.4.0]decane		Reactions, struct.: 2001CHE1369
1,6-Disilabicyclo[4.4.0]dec-3-ene		Prep.: 2002CL22
2,3-Oxasilabicyclo[4.4.0]decane		Prep.: 2005JA10028
Hex-3-ene		Prep.: 2005JA10028
2,4,7-Trioxa-3-silabicyclo[4.4.0]dec-8-ene		Prep.: 2001JOC8666, 2005JOC3988, 2003OBC3772
2,4,9-Trioxa-3-silabicyclo[4.4.0]decane		Prep.: 2005JA528
2,4,7,9-Tetraoxa-3-silabicyclo[4.4.0]decane		Prep.: 2001JOC8666
1,6-Diaza-2,5,7,10-tetrasilabicyclo[4.4.0]decane		Calcs.: 1995IC4840
1,2,3,4,5,6,7,8-Octasila-9,12-dioxabicyclo[4.3.3]dodec-10-ene		Prep.: 2005JA15376

(Continued)

Table 5 (Continued)

Ring system	Heteroatoms ^a	References
<i>Spiro</i> [5.5]undecanes		
		
1,5-Disilaspiro[5.5]undecane		Structure, NMR, and stability calcs.: 2002CEJ1163
1,5,7,11-Tetraza-6-silaspiro[5.5]undecane		Prep.: 1998EJI1967
2,4,8,10-Tetraaza-6-silaspiro[5.5]undecane		Prep.: 1996CB483
3,9-Diphospha-6-silaspiro[5.5]undecane		Prep. conformation: 1997IC1867

^aThe ordering of the heteroatoms is as indicated in the ring system name.

9.18.3.2 Benzo-Fused Systems

This is the largest class of compounds in this category. The heterocyclic ring can contain from two to four heteroatoms. Many types of derivatives of the parent compounds found in [Table 5](#) are known in which functional groups such as carbonyl and carboxylic groups, for example, extend from the heterocycle and/or the aromatic ring. In addition, the heterocyclic ring may be partially conjugated. This is true for all the polycyclic compounds described and, due to the great number, the derivatives are not generally mentioned by name but can be found in the references cited.

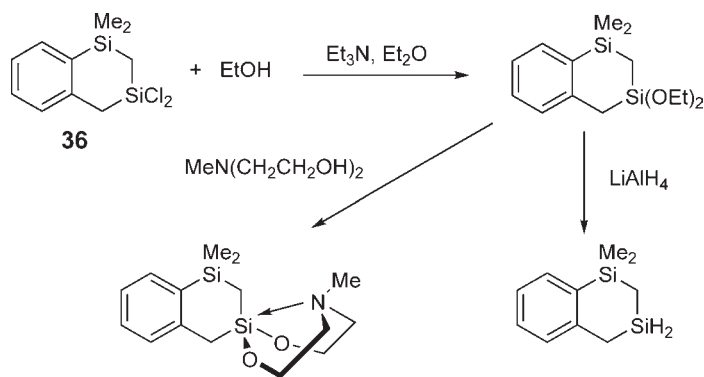
9.18.3.2.1 Experimental structural methods

The compounds described in this section have all been characterized by a variety of techniques such as NMR, infrared (IR), electronic spectroscopy, or mass spectrometry. In addition, several X-ray crystallographic studies have been carried out; references to these are given in [Table 5](#).

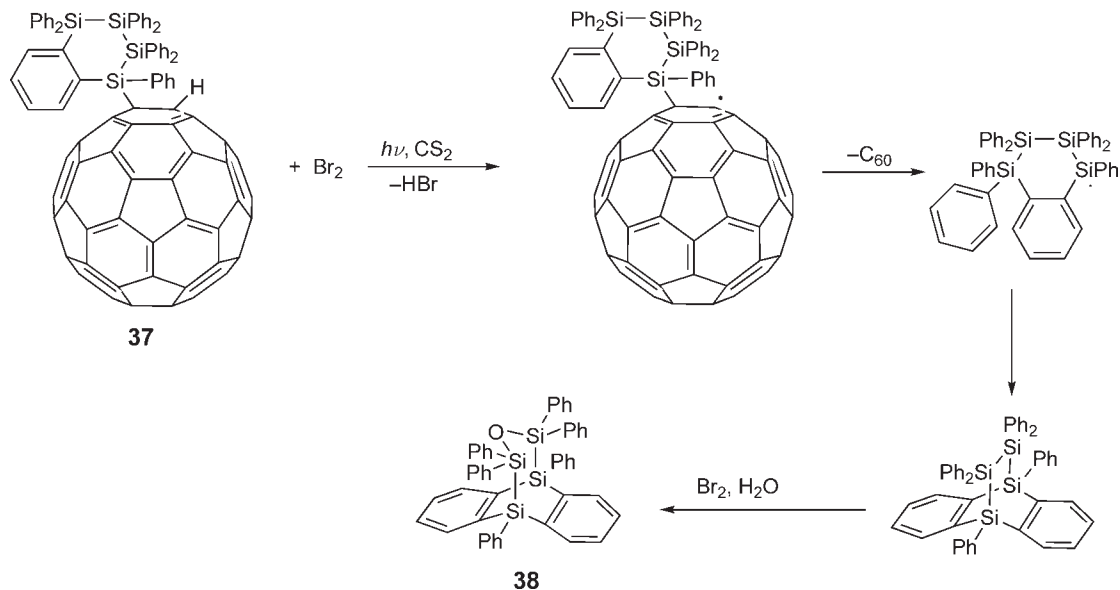
The structure of the silyl zirconium complex **45** ([Section 9.18.3.2.3](#)) shows that the majority of the material formed in its production is the *l,l*-diastereomer [<2005JA10174>](#).

9.18.3.2.2 Reactivity of rings

Several reactions have been carried out ([Scheme 12](#)), at the functional silicon atom in the benzo-fused 1,3-disilacyclohexane **36** (formed in [Scheme 17](#), [Section 9.18.3.2.3](#)). The psychotropic effects of these compounds have been studied and they are found to have a sedative effect [<2003CHE813>](#).

**Scheme 12**

The advances in fullerene chemistry have included the synthesis and reactivity of several silyl derivatives of C_{60} . Treatment of the benzo-tetrasilacyclohexane derivative of C_{60} , **37**, with bromine leads to cleavage of the heterocycle from the C_{60} and ultimate formation of tetracyclic product **38** (Scheme 13) <1997OM2746>.

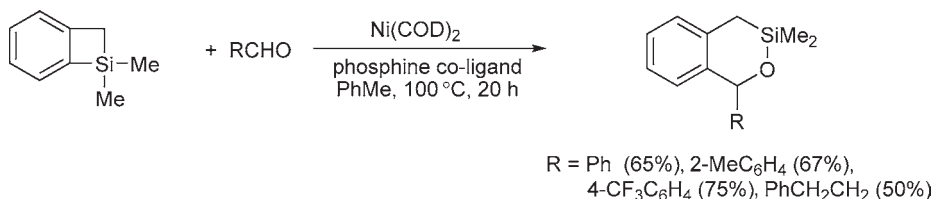


Scheme 13

9.18.3.2.3 Synthesis of rings

The great number of ring systems covered in this chapter prevents a detailed discussion of all their syntheses, but a few of the synthetic routes employed in their preparation are described in detail. Some of the more general synthetic methods will be discussed briefly and Table 5 provides more comprehensive references, which should be consulted for further information.

The nickel-catalyzed ring opening of silacyclobutanes in the presence of aldehydes affords good yields of oxasilacyclohexanes (Scheme 14), <2006OL483>. Further examples of benzo-fused and related ring systems containing an Si–O bond can be found in Section 9.18.3.5.

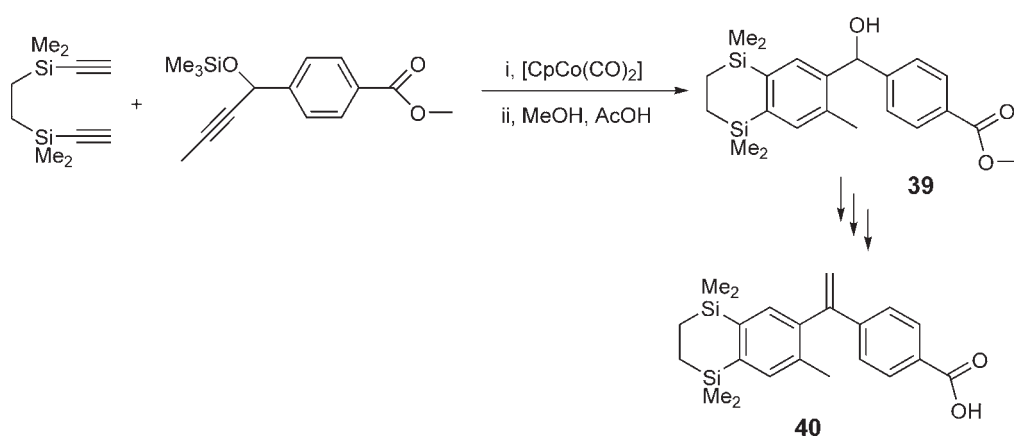


Scheme 14

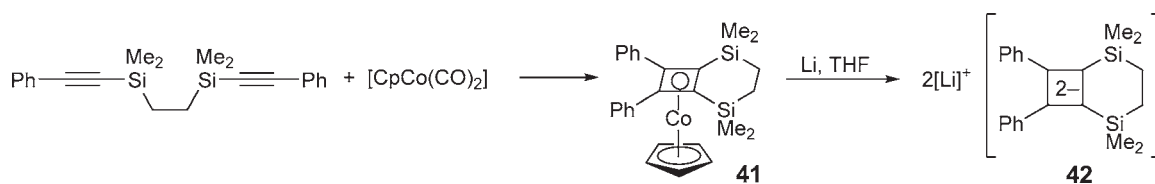
The cobalt-catalyzed Vollhardt cyclization shown in Scheme 15 gives rise to the 1,4-disilacyclohexane derivative **39**, which can then be further transformed to give the disila analogue **40** of bexarotene, which is in use for treatment of cutaneous T-cell lymphoma <2005OM3192>.

A related intramolecular cyclization occurs to give the cyclobutadiene complex **41**, which on treatment with lithium gave the dilithium species **42** (Scheme 16). The latter could be isolated and characterized by crystallography <2000CL896>.

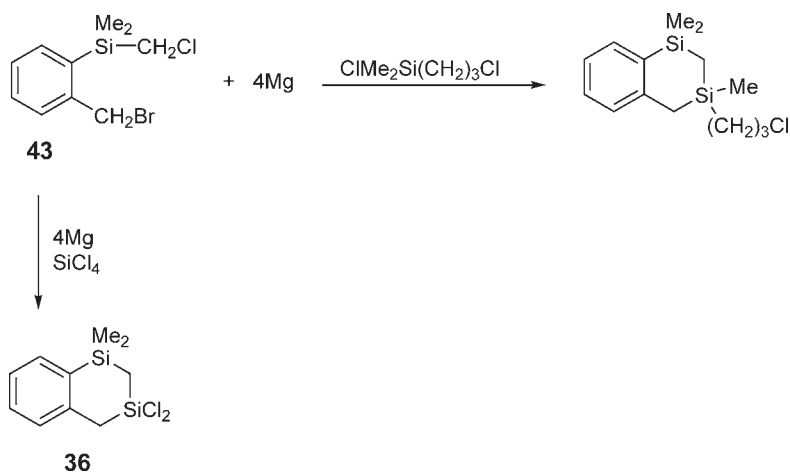
Reduction of the bis-halomethyl compound **43** results in ring closure and formation of benzo-fused 1,3-disilacyclohexane derivatives (Scheme 17) <2003CHE813>.



Scheme 15

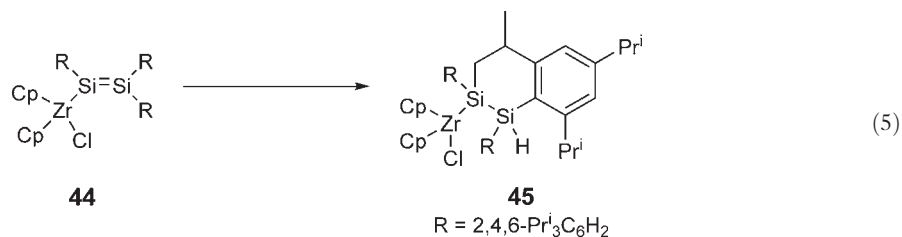


Scheme 16

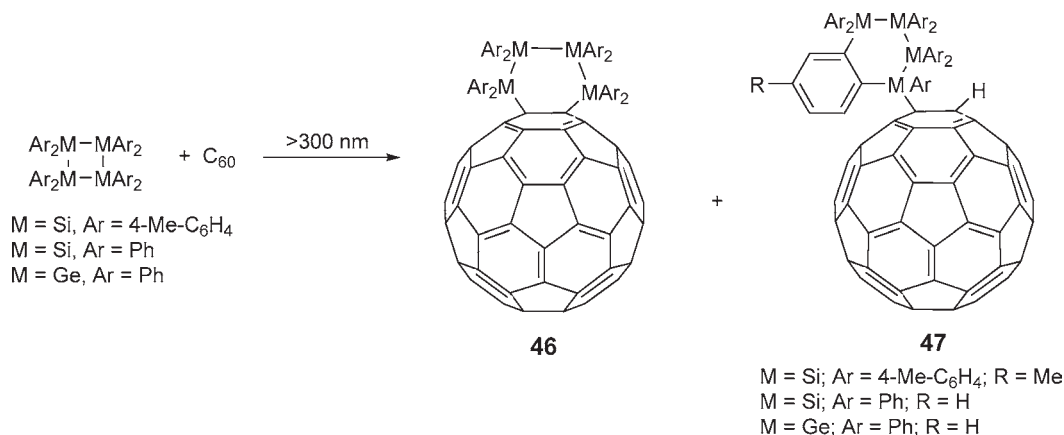


Scheme 17

The novel η^1 -disilene zirconium complex **44** is highly reactive and undergoes ready rearrangement via addition of a methyl C–H bond to the $\text{Si}=\text{Si}$ bond to give the silyl zirconium complex **45**, as a mixture of diastereoisomers, shown in Equation (5) [\[2005JA10174\]](#).



Photolysis of cyclotetrasilane and cyclotetragermane derivatives in the presence of C_{60} gives rise to a mixture of products **46** and **47**, via the free radical addition of a diradical formed on the initial cleavage of the four-membered rings (Scheme 18) <1996T4995, 1995OM2142>.



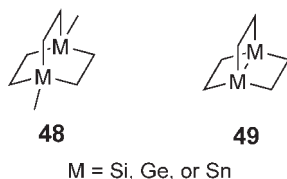
Scheme 18

9.18.3.3 Bicyclo[*a.b.c*]anes, Bicyclo[*a.b.c*]propellanes, and Bicyclo[*a.b.c*]enes

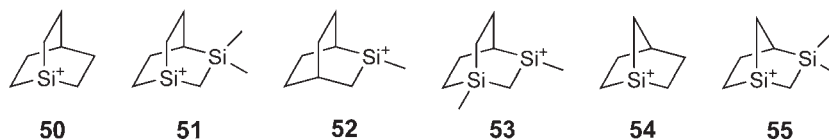
As the name suggests, these compounds contain two rings that share two atoms as bridgeheads. The [*a.b.c*] represents the number of atoms in each bridge. References to these compounds may be found in Table 5.

9.18.3.3.1 Theoretical studies

The stabilities of a series of dimetallabicyclo[2.2.2]alkanes and dimetallabicyclo[2.2.2]propellanes **48** and **49** have been calculated using B3LYP and MP2 methods <2005CEJ5067>. The bicyclooctanes have D_3 symmetry, show little increase in strain as the size of the heteroatom increases, and are structurally similar to 9,10-dimetallatryptycenes. The dimetallapropellanes are calculated to have biradical groundstates with no M–M bond, are prone to dimerization, and are unlikely to be available for experimental study at room temperature <2005CEJ5067>.



The structures, stabilities, and ^{29}Si NMR chemical shifts for pairs of silabicyclo[2.2.2]octyl and a pair of silanorbornyl derivatives, **50/51**, **52/53**, and **54/55**, all show that introduction of the β -SiMe group stabilizes the cation and decreases pyramidalization at the cation center, consistent with the well-known stability of β -silyl versus β -alkyl carbenium ions <2003JOC1827>.

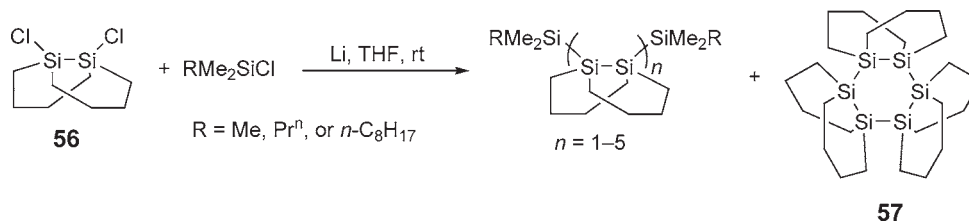


9.18.3.3.2 Experimental structural methods

The structure of the bis-disilabicyclo[4.4.0]decane compound **60** shows that the configuration of both of the disilane units is *syn*, implying that the configuration of the precursor dilithium reagent is also *syn* <2001CHE1369>.

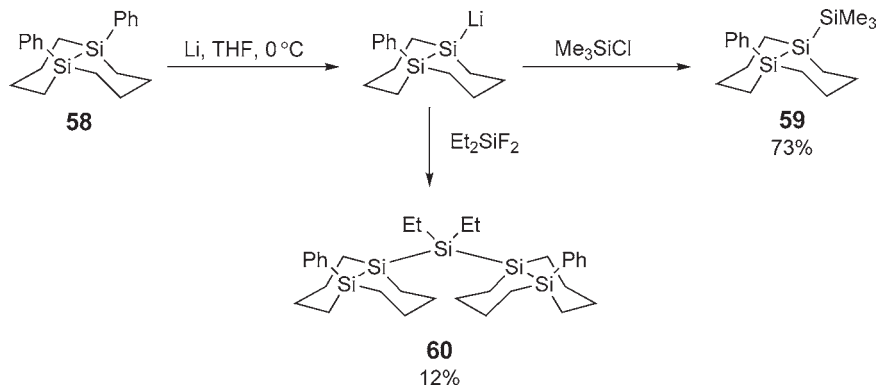
9.18.3.3.3 Reactivity of nonconjugated rings

Treatment of the bicyclic chlorosilane **56** with Li in the presence of a second chlorosilane leads to Wurtz-type reductive coupling and the formation of mixtures of oligosilanes as shown in **Scheme 19** <2004OM1639, 2003JA7486>. The yields of each oligomer are variable and depend on the substituent R, and the ratio of the two chlorosilane starting materials. The cyclohexasilane **57** is formed in 4–11% yield under all the conditions used. Lithiation at one of the bridgehead carbon atoms in **71** can be achieved using the superbase BuLi-*t*-BuOK. The lithium derivative reacts with Me₃SiCl to give a silylated bridgehead species <2000JOM(611)12>.



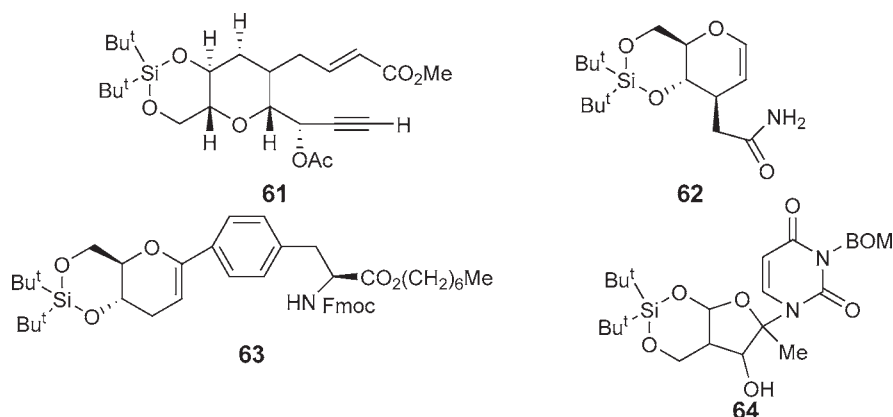
Scheme 19

The Si–Ph bond in the disilabicyclo[4.4.0]decane derivative **58** can be cleaved by metallic lithium to give a silyllithium reagent which retains its Si–Si bond largely intact. This can then be quenched with halosilanes to give polysilyl species **59** and **60** (**Scheme 20**) <2001CHE1369>.

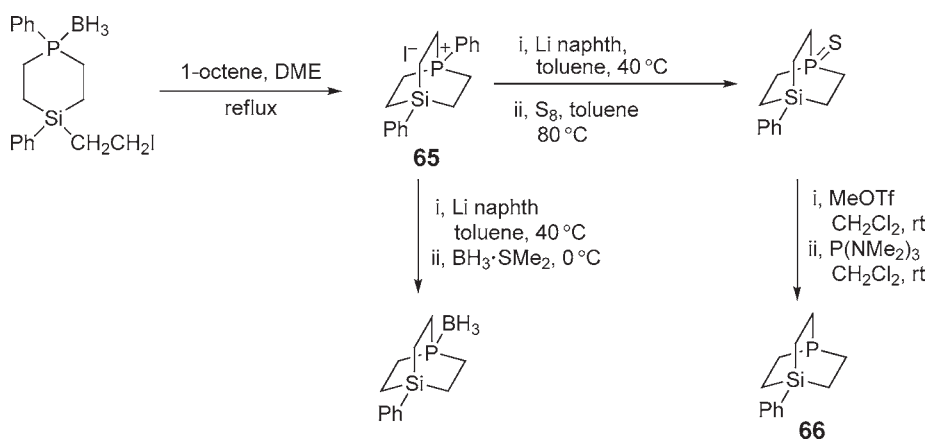


Scheme 20

The use of the Bu^t₂Si protecting group for diols has resulted in the synthesis of many bicyclic compounds containing the O–Si–O linkage, in much the same way as monocyclic cyclic siloxanes have been formed, that is, by the reaction of Bu^t₂Si(OSO₂CF₃)₂ and a diol in the presence of a base. As for the case of the monocyclic compounds, the bicyclic O–Si–O compounds are usually intermediates in a complicated synthetic procedure and are rarely studied as ring systems in their own right. Examples of these bicyclic compounds, illustrating the range of ring types available, include the tetrahydropyran precursor **61** <2005T8589>, the mannosamine intermediate **62** <2005JOC3988>, the phenylalanine derivative **63** <2003SL1834>, and the nucleoside **64** <2002MI17>. The utility of the Bu^t₂Si protecting group within these heterocycles is that it is stable toward ring-opening reactions in the presence of a wide range of reagents. This allows the elaboration of complicated structures while retaining the protected diol intact. Deprotection causes ring opening with formation of a diol and this can be achieved readily for a range of compounds using Bu₄NF/THF or HF/pyridine (THF = tetrahydrofuran); see, for example <2005CEC803> and <2003COR1461>.



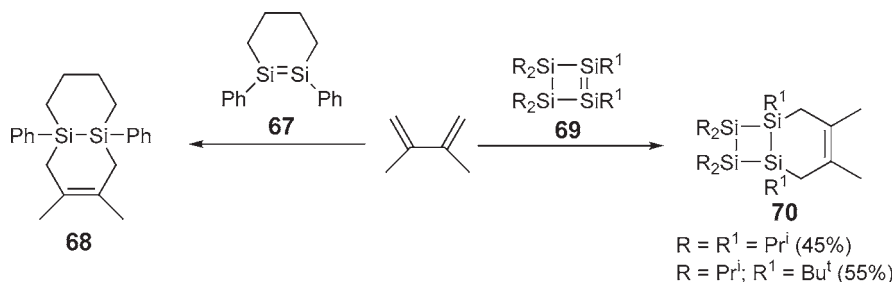
The unusual bicyclic phosphonium salt **65**, formed as shown in [Scheme 21](#), has been shown to undergo a range of reactions at the phosphorus atom, including the preparation of the neutral phosphine **66**, which can be used as a Lewis base in various complexes ([Scheme 21](#)) <2003OL2671>.



Scheme 21

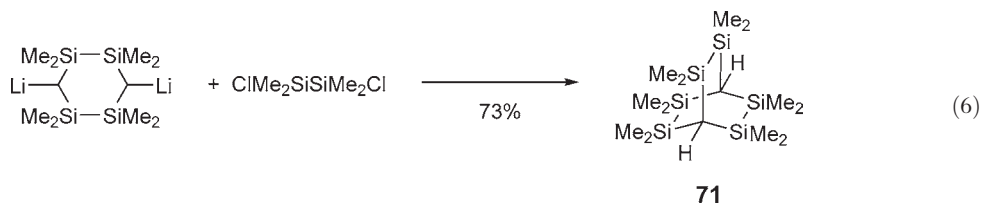
9.18.3.3.4 Synthesis of rings

The trapping of reactive unsaturated group 14 species via cycloadditions continues to be a popular method of investigating the chemistry of unstable intermediates and many of these reactions give rise to six-membered sila-heterocycles. For example, the novel cyclic disilene **67** reacts with 2,3-dimethylbutadiene to give the bicyclic product **68** ([Scheme 22](#)) <2002CL22> and the cyclotetrasilene **69** gives **70** ([Scheme 22](#)) <2000CL494>.

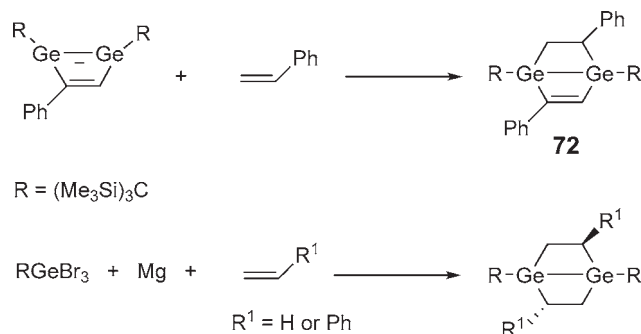


Scheme 22

The 2,3,5,6,7,8-hexasilabicyclo[2.2.2]octane derivative **71** can be prepared by quenching a monocyclic 1,4-dilithium reagent with $(\text{ClMe}_2\text{Si})_2$, as shown in Equation (6) <2000JOM(611)12>.



The steric protection afforded by the very bulky $(\text{Me}_3\text{Si})_3\text{C}$ group enables a reactive digermene to be formed which reacts with styrene to give the digermabicyclo[2.2.0]hexene derivative **72** in 64% yield (Scheme 23) <1997OM4956>. Related digermabicyclo[2.2.0]hexanes are formed on the reduction of $(\text{Me}_3\text{Si})_3\text{CGeX}_3$, to give germylenes $(\text{Me}_3\text{Si})_3\text{CGeX}$ ($\text{X} = \text{Cl}$ or Br), in the presence of an alkene (Scheme 23) <1996OM3103, 1997OM4956>.



Scheme 23

A range of bicyclic species **73** containing three chalcogen atoms have been prepared via the route shown in Scheme 24 <2002JOM(660)27>. The yields for these reactions are about 45–65% and, presumably, this route could be used to prepare a range of similar compounds.



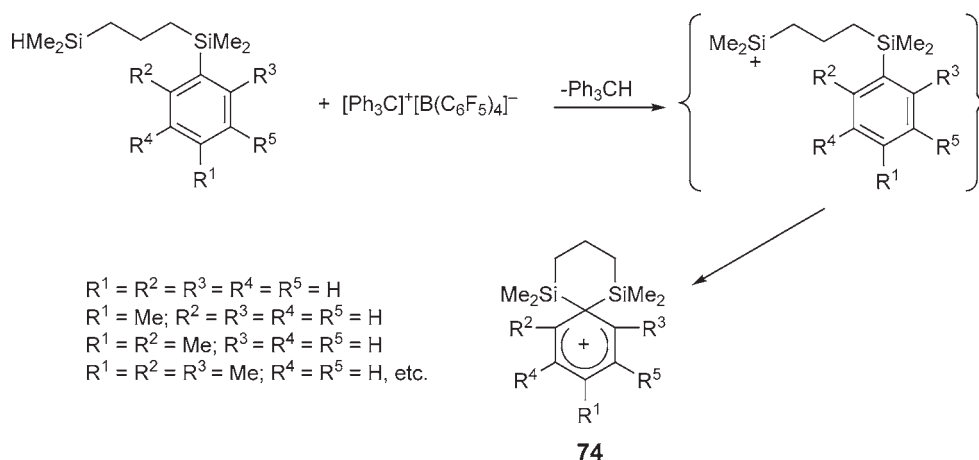
Scheme 24

9.18.3.4 Spirocyclic Systems

9.18.3.4.1 Theoretical methods

As the name implies, these ring systems are spirocyclic, that is, the six-membered ring shares a common carbon atom with a second ring (see Table 5).

The interest in cationic silicon compounds has been considerable in the last 10 years and they have been pursued vigorously by both synthetic methods (see below) and computationally. The structures of a series of bis-silylated arenium ions **74** (see Scheme 25) have been calculated and their ^{29}Si NMR chemical shifts calculated for comparison with experimental values <2002CEJ1163>. The stability of the cations is attributed to the thermodynamic stabilization of the arenium ion by the two β -silyl substituents.

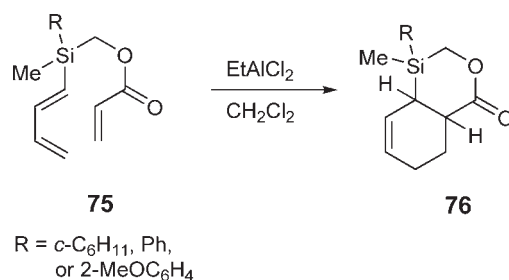


Scheme 25

9.18.3.4.2 Synthesis of rings

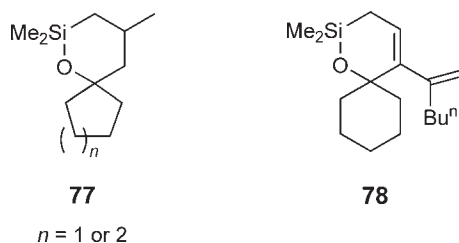
A series of bis-silylated arenium ions **74** have been prepared as reactive intermediates by hydride abstraction from silanes (Scheme 25) <2002CEJ1163>. The success of the synthetic route can be attributed to the use of non-coordinating hydrocarbon solvents and a very weakly coordinating anion, $[\text{B}(\text{C}_6\text{F}_5)_4]^-$; addition of a stronger nucleophile such as MeCN results in desilylation of the arenium ion.

The EtAlCl_2 -catalyzed intramolecular Diels–Alder reaction of trienes **75** affords a variety of bicyclic species such as **76** in good yield (Scheme 26). For the case of **76** ($\text{R} = 2\text{-MeOC}_6\text{H}_4$), one diastereomer is formed in 90% yield <2003T2451, 2000EJO3039>.



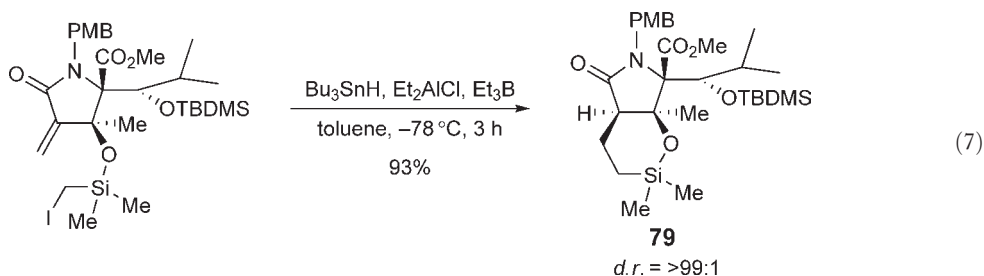
Scheme 26

The rings **77** are available via intramolecular free radical cyclizations catalyzed by Bu^n_3SnH <2005T2037>, while **78** is available in good yield via a ruthenium-catalyzed cyclisation of an enyne <2002JMO9>.

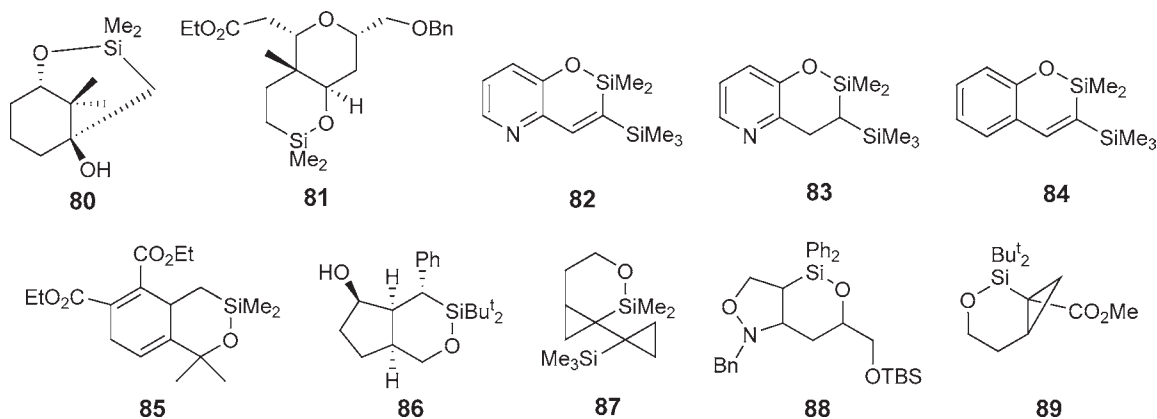


9.18.3.5 Miscellaneous Bicyclic Systems

The ring closure shown in Equation (7) gives the bicyclic species **79** in 93% chemical yield and with almost complete stereoselectivity <2005JA8974, 2005OL2699>. This compound can be used as a precursor to omuralide salinosporamide-type proteasome inhibitors.



The increasing use of the silicon-tether strategy in organic synthesis has generated many new cyclic siloxane species as useful synthetic intermediates. Some of these, together with a range of other cyclic siloxanes, are described here to give an overview of the ring systems of this type currently available. The bicyclic species **80** has been prepared as a precursor in the synthesis of Taxol <2004TL8647> and the bicyclic **81** is a precursor to (–)-lasonolide A <2003JOC8080>. The species **82–84** are produced via photochemical intramolecular ring closures of pentamethyldisilanylethyne derivatives <2003JPH15, 2001JPH167> and **85** is formed via the Diels–Alder reaction between a 1,2-oxasilacyclohex-4-ene and $\text{EtO}_2\text{CC}\equiv\text{CCO}_2\text{Et}$ <2001ASC184>. The bicyclic siloxane **86** forms by hydrolysis of a carbonate precursor <2001JOC1966> and the cyclopropyl species **87** is formed in 78% yield from a palladium-catalyzed reaction of a pentamethyldisilanyloxy precursor <2000OL3877>. A range of bicyclic[4.3.0] species, for example **88**, is formed via intramolecular nitron addition reactions <2000JA7633>. The bicyclic[4.1.0] species **89** is formed thermally or photochemically from an α -diazoacetate precursor <1999EJO1939>.

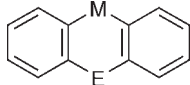
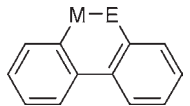
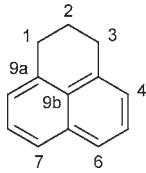
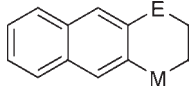


9.18.4 Tricyclic Systems

9.18.4.1 Survey of Ring Systems

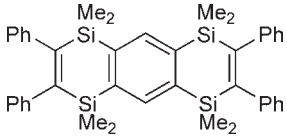
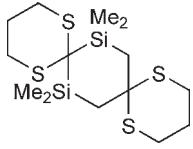
There are a large number of tricyclic compounds containing heavier group 14 heteroatoms and in recent years there has been considerable interest in species in which silicon-containing heterocycles bridge between aromatic or potentially aromatic five- or six-membered rings (see Chapter 14.19). Such compounds have interesting electronic properties and can be used in transition metal complexes to make useful catalysts. There is also significant interest in heteroadamantanes, especially on the effect that the introduction of the heteroatoms has on the nature of the carbon framework. Detailed references to many of these compounds can be found in Table 6.

Table 6 Tricyclic compounds

Ring system	Heteroatoms ^a	References
<i>Dibenzo-fused rings</i>		
		
Phenazasiline	E = N; M = Si	Prep. reacts.: 2006OM3974, 2003AGE921, 2001POJ498, props.: 2005POJ52, polymers: 2002POJ400
Phenophosphasilin	E = P; M = Si	Prep.: 2006CL758
1 <i>H</i> -Phenoxasilin	E = O; M = Si	Prep. reacts.: 2006OM3974, 2006SL745, 1996J(P2)1843
1 <i>H</i> -Phenothiasilin	E = S; M = Si	Prep. reacts.: 1996J(P2)1843
Silanthrene	E = Si; M = Si	Reacts.: 2001JOM(629)44, 2001JOM(626)32, 1998JOC1327, 1997CL293, 1996J(P2)1843, 1995TL3897, Reacts. struct.: 1999CL1183, prep. struct.: 1997OM3800, prep.: 1996T4995
Phenosilastannin	E = Sn; M = Si	Reacts.: 1996J(P2)1843
Stannanthrene	E = Sn; M = Sn	Reacts. struct.: 2005CL1018, Prep. react.: 2004PS957, Prep. react. struct.: 2004EJI743, 2001PS249, 2001OM749
		
9,10-Oxasilaphenanthrene	E = O; M = Si	Reacts.: 1997RCB1487, 2004RJC1513, 2002JAP9
9,10-Disilaphenanthrene	E = Si; M = Si	Prep.: 2003JA6638, reacts. 2005CL56, 2005OM156
<i>Naphtho-fused rings</i>		
		
1 <i>H</i> -Naphth[1,8- <i>cd</i>][1,3]disiline	M = M = Si	Prep. struct.: 1996CB495
1 <i>H</i> -Naphth[1,8- <i>cd</i>][2,1]azasiline	E = N; M = Si	Prep. struct.: 1996MC229
1 <i>H</i> -Naphth[1,8- <i>cd</i>][1,3]phosphasiline	E = P; M = Si	Prep.: 2002PS1409, 2001JA9210
1 <i>H</i> -Naphth[1,8- <i>cd</i>][2,1,3]azadisiline	E = N; M = M = Si	Prep. struct.: 1996CB495
1 <i>H</i> -Naphth[1,8- <i>cd</i>][2,1,3]phosphadisiline	E = P; M = M = Si	Prep. struct.: 1996CB495
1 <i>H</i> -Naphth[1,8- <i>cd</i>][2,1,3]oxadisiline	E = O; M = M = Si	Prep.: 1996CB495
1 <i>H</i> -Naphth[1,8- <i>cd</i>][2,1,3]thiadisiline	E = S; M = M = Si	Prep.: 1996CB495
Naphth[1,8- <i>de</i>]-1,3,2-diazasilin	E = N; E = N; M = Si	Prep. reacts.: 2004ZFA2090, 2001JCD3179, 1998EJI1967
Naphth[1,8- <i>de</i>]-1,3,2-diazaastannin	E = N; E = N; M = Sn	Prep. struct.: 2004ZFA2090
		
Disilaanthracene	E = M = Si	Prep.: 2003CL1104

(Continued)

Table 6 (Continued)

Ring system	Heteroatoms ^a	References
<i>Miscellaneous rings</i>		
		
1,4,5,8-Tetrasilaanthracene	M = Si; M = Si; M = Si; M = Si	Prep. struct.: 1999ICC510
		
2,6,10,14-Tetrathia-7, 16-disilaspiro[5.2.5.2]hexadecane		Prep. struct.: 1999ICA(296)231

^aThe ordering of the heteroatoms is as indicated in the ring system name.

9.18.4.2 Dibenzo and Related Fused Systems

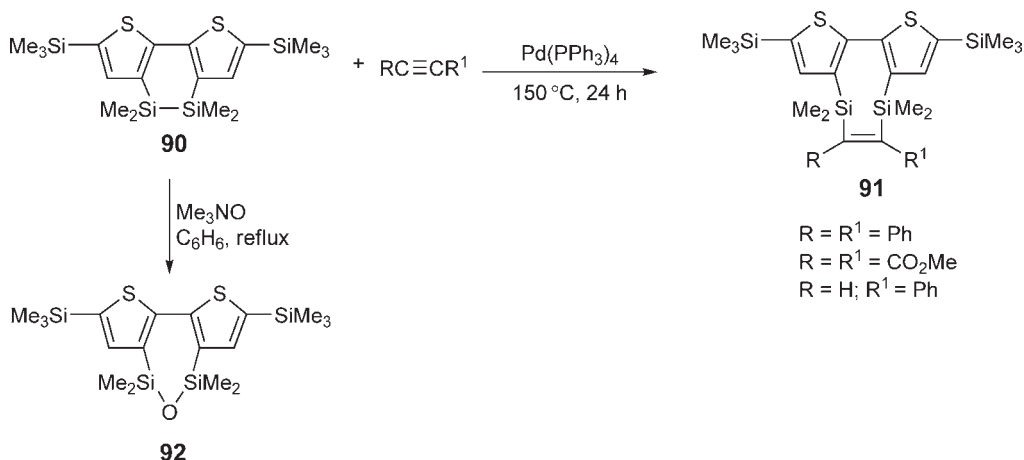
In CHEC-II(1996), most of the interest in compounds under this heading was in compounds consisting of two simple aryl rings flanking the heterocycle. More recently, work on similar compounds has extended to species where the aromatic flanking groups are cyclopentadienyl, indenyl, or thiophene, as these have potential in transition metal chemistry as ligands in catalysts. Most of the work on these compounds has centered on theoretical studies of the electronic structures and aromatic properties of these heterocycles and their transition metal complexes; references are given in [Table 6](#).

9.18.4.2.1 Experimental structural methods

The structures of the bithiophene derivatives **97** ($R = R^1 = \text{Me}$, and *trans* $R = \text{Ph}$, $R^1 = \text{Me}$) have been determined by X-ray crystallography [\(<1999OM1453>](#). Both compounds exhibit a twisted bithiophene system with a twist angle of about 20° between the thiophene rings and the bond angles and lengths suggest that there is little strain in the tricyclic system. The X-ray structure of the related thiophene derivative **98** ($E = \text{Si}$, $R^1 = \text{SiMe}_3$, $R^2 = R^3 = \text{Ph}$) shows that the molecule is slightly folded about the $\text{Si} \cdots \text{S}$ vector, the two planes making an angle of 171° [\(<2004OM5365>](#) while **98** ($E = \text{Ge}$, $R^1 = \text{H}$, $R^2 = R^3 = \text{Ph}$) has the heterocyclic ring in a slight boat conformation [\(<2000ICA\(305\)46>](#). The structures of a large number of transition metal complexes containing the bridged bis-cyclopentadienyl ligand **102** and its substituted analogues have been determined by X-ray crystallography. The ligand may coordinate to a single metal with one Cp ring, chelate with both Cp rings, or bridge to form polymetallic species [\(<2001IC7014, 2001JA11494, 2001OM3035, 2001OM534, 2001OM534, 1999JOM\(583\)86, 1998ICA\(280\)226, 1998ICA\(280\)1, 1998POL1081, 1998JOC1327, 1997OM1553, 1997AGE387, 1996OM4063>](#) (see [Section 9.18.4.2.4](#) for further references and some representative structures).

9.18.4.2.2 Reactivity of rings

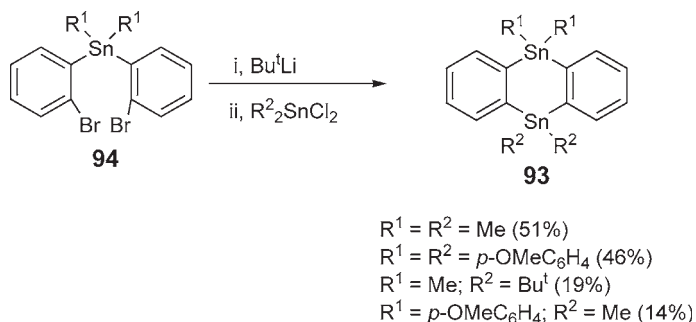
The sulfur in the six-membered ring in species **98** ([Scheme 31](#)) can be oxidized in good yield to both the monoxide and dioxide by use of *m*-chloroperbenzoic acid (MCPBA) [\(<2004OM5365>](#). The dithienodisilacyclohexadiene derivative **90** undergoes palladium-catalyzed insertion reactions with alkynes to give **91** and with Me_3NO to give a disiloxane product **92** ([Scheme 27](#)) [\(<2006OM48>](#). Similar palladium-catalyzed insertion reactions in the Si–Si bond occur when 1,1,2,2-tetramethyl-1,2-(1,8-naphthylene)disilane reacts with arynes [\(<2005OM156, 2005CL56, 2003JA6638>](#).



Scheme 27

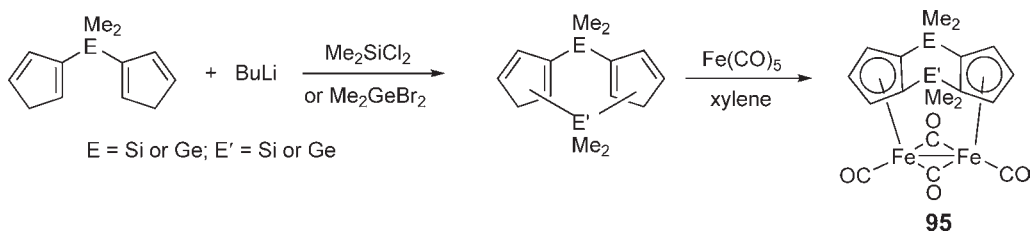
9.18.4.2.3 Synthesis of rings

An improved route to 9,10-distannanthracene derivatives **93** has been developed and involves lithiation of arylbromides **94**, followed by quenching with a tin dichloride (Scheme 28) <2004EJI743, 2001PS249, 2001OM749>.



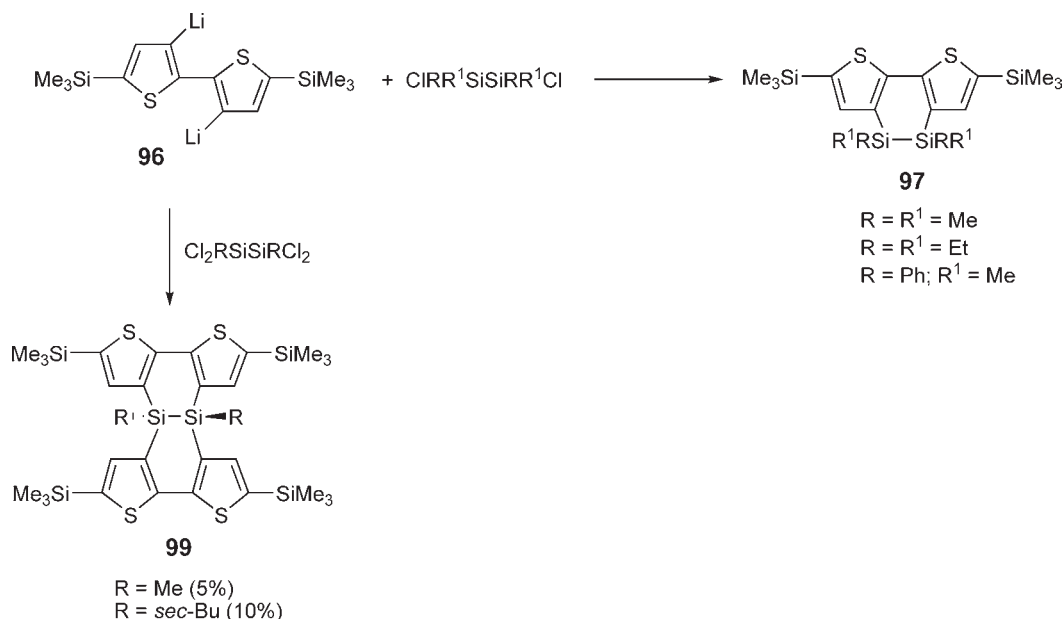
Scheme 28

A series of iron complexes **95** containing group 14 bridged cyclopentadienyl ligands can be prepared in low yield according to Scheme 29 <2001JOM(626)186>. The digerma-substituted compound is relatively unstable and loss of one of the germyl groups gives a more stable product.

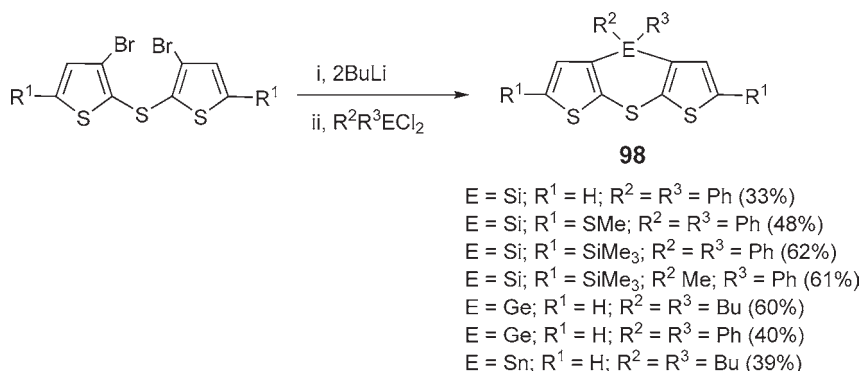


Scheme 29

Treatment of the dilithium reagent **96** with dichlorodisilanes gives a series of silicon bridged bithiophenes **97** in about 30% yield (Scheme 30) <1999OM1453>. Tricyclic species **98** containing thiophene rings can be prepared also according to the method shown in Scheme 31 in which an intermediate dilithium species reacts with a group 14 element dichloride <2004OM5365, 2000ICA(305)46>. The reaction of **96** with tetrachlorodisilanes gives low yields of the hexacyclic species **99** (Scheme 30) <2002JOM(642)137>.



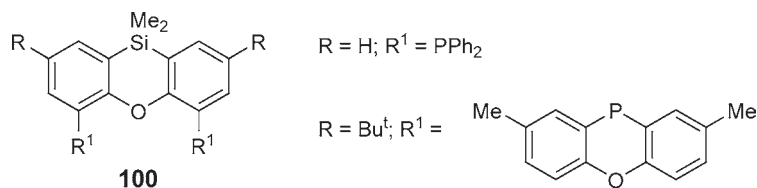
Scheme 30



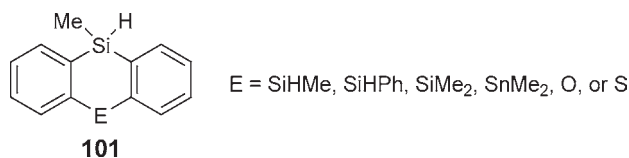
Scheme 31

9.18.4.2.4 Important compounds and applications

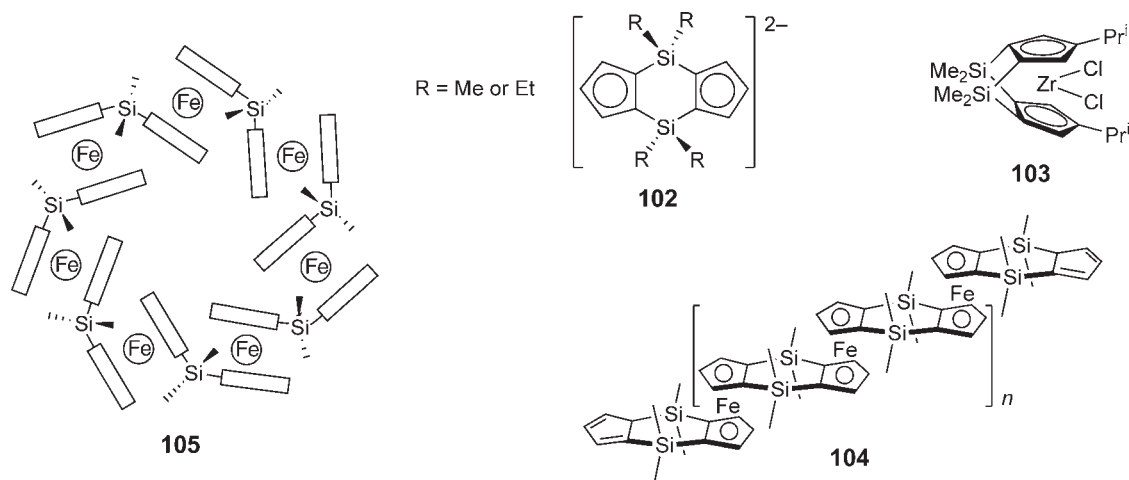
The bulky phenoxaphosphino ligands **100**, containing a bridging SiMe_2 group, have been used as wide-bite-angle ligands in Rh-complexes for hydroformylation reactions <2003OM5358, 2003IC2859, 2000OM872, 1997CC373, 1995OM3081>, Pd-complexes <2002JCD2308, 2001EJI837, 2001CEJ475, 1999EJI1237, 1998EJI155, 1998EJI25, 1997JCD1839>, Pt/Sn-complexes <1998JOM(551)165>, and Ni-complexes <1995CC2177>.



A series of 9-sila-10-heteroanthracenes **101** have been prepared and their reducing abilities under free radical conditions studied <1996J(P2)1843>. The 9,10-disilaanthracene derivative was found to be the most active of the compounds and cyclic compounds **101** were found to be more active than acyclic analogues.



A variety of bridged cyclopentadienyl ligands such as **102** (or analogues with alkyl substituents on the Cp rings) react with a range of transition metal complexes to give new complexes in which the ligand may bind to a single metal or bridge metal centers so as to form monomeric or polymeric organometallic materials, such as **103–105** <2004OM5662, 2004JA8216, 2003OM3691, 2003OM188, 2003OM172, 2002OM3292, 2002OM1235, 2002OM617, 2002PSA3249, 2002JOM(658)266, 2002JA9525, 2002CEJ5219, 2001OM691, 1997JOM(548)157>. The interest in these compounds has been considerable and centers on their ability to act as polymerization catalysts for olefins.



The bridged thiophene species, **97**, have high-electron-transporting properties and can be used to fabricate triple-layer electroluminescent devices <2003SM(137)1007>. Transition metal complexes containing ligands of the type shown in iron complexes **95**, but having $E = \text{Si}$, $E' = \text{P}$ or B , have been prepared and used as catalysts in olefin polymerization <2005WO2005073242>.

9.18.4.3 Naphtho-Fused Systems

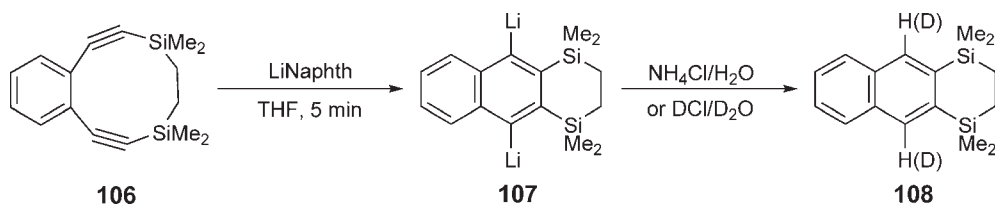
The naphthalene part of the molecule in these compounds has been prepared fused to the heterocycle in two different ways, indicated in **Table 6**.

9.18.4.3.1 Experimental structural methods

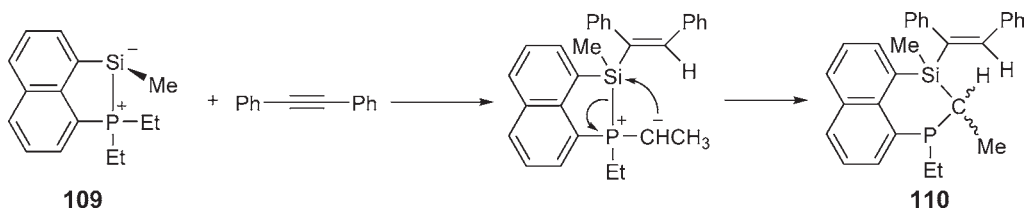
The structures of several related naphtho-fused ring systems have been determined by X-ray crystallography. Thus, the cyclic silazane **112** ($R = \text{Ph}$) is planar at the nitrogen atom and all the rings lie almost coplanar, while the related compound **112** ($R = \text{Bu}^t$ but with an anisyl group attached to one of the silicon atoms) has the silicon atoms out of the plane of the tricyclic system, and the ylide **113** has the heterocyclic ring in an envelope conformation and the ylidic carbon is pyramidal and not planar <1996CB495> (see **Section 9.18.4.3.2**).

9.18.4.3.2 Synthesis of rings

The intramolecular reductive cyclization of the 1,2-bis(silylethynyl)benzene derivative **106** can be effected under a range of conditions, via the dilithium derivative **107**, to give the tricyclic species **108** (**Scheme 32**) <2003CL1104>. The best yield is obtained when using 4 equiv of LiNaphth at room temperature. The sila-ylide (which can be considered also as a base-coordinated silylene) **109** reacts with diphenylacetylene to give the naphtho-fused ring system **110** (**Scheme 33**) in 78% yield <2002PS1409, 2001JA9210>.

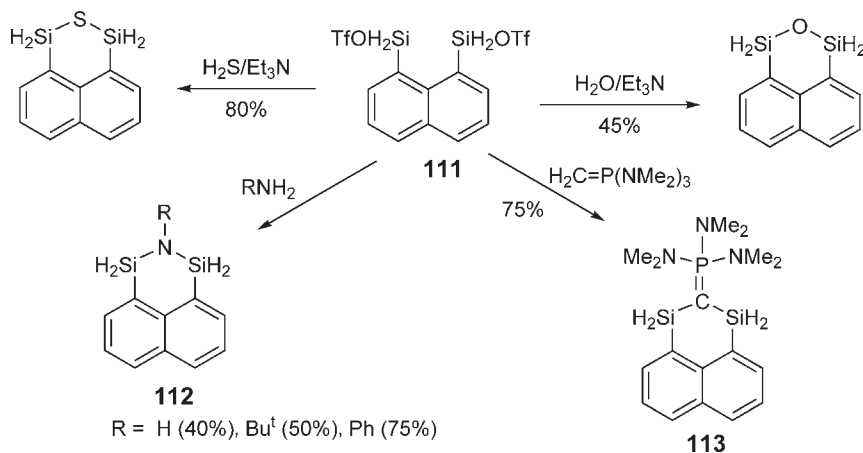


Scheme 32



Scheme 33

A series of heterocycles derived from 1,8-disilylnaphthalene, **111**, has been prepared utilizing the high reactivity of the Si–H groups present (Scheme 34) <1996CB495>. These reactions proceed in good yield and this route could, no doubt, be used to prepare further novel heterocycles.

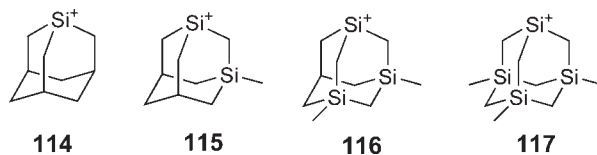


Scheme 34

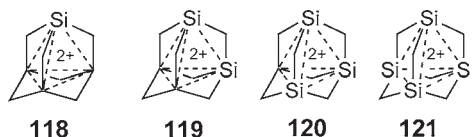
9.18.4.4 Miscellaneous Tricyclic Systems

9.18.4.4.1 Theoretical methods

The structures, stabilities, and ²⁹Si NMR chemical shifts for a series of neutral and cationic sila-adamantanes, for example **114–117**, have been calculated <2003JOC1827, 1998JMT(432)105>. Successive introductions of β-SiMe groups lead to stabilizations of 8.2, 15.1, and 21.5 kcal mol^{−1} on going from cations **114** to **117** and the degree of pyramidalization at the silylium center also decreases on going from **114** to **117**. The changes are consistent with the β-silyl effect being greater than the β-alkyl effect in the sila-adamantyl cations and with the well-known stability of β-silyl versus β-alkyl carbenium ions.

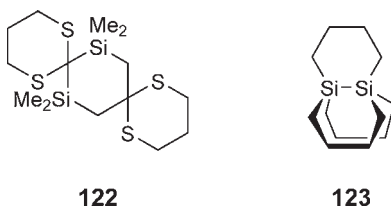


The structures and NMR chemical shift properties of a series of 1,3-dehydro-sila-adamantane dications, **118–121**, have been calculated by DFT methods <2003JA15507, 2002JOC8721>. The cations are found to exhibit three-dimensional heteroaromaticity and indicate that there is significant positive charge at the Si centers. Related results have been obtained for the germanium analogue of **121** <2003JA15507>.



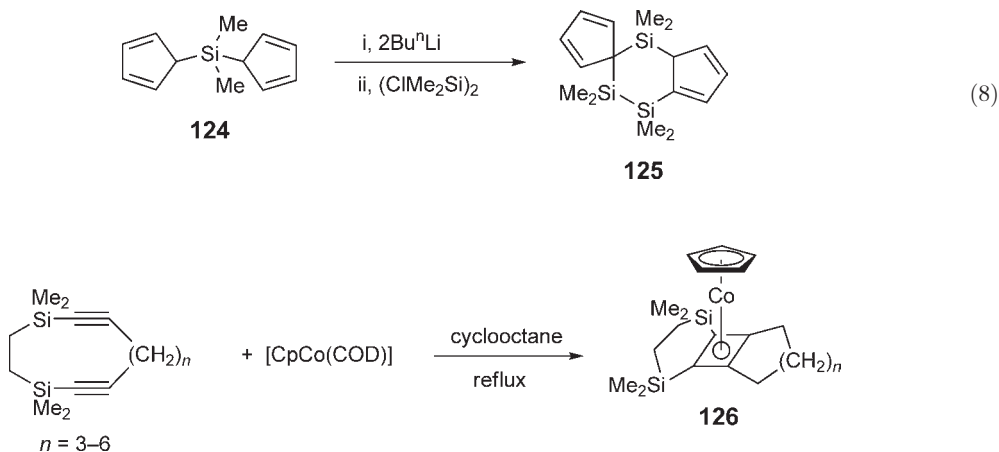
9.18.4.4.2 Experimental structural methods

The structure of the 7,16-disilaspiro[5.2.5.2]hexadecane derivative **122** has been determined <1999ICA(296)231>. The central ring has a chair conformation and has an essentially strain-free, cyclohexane-like structure. The structure of another tricyclic species with 1,3-Si atoms, **128**, shows the vicinal methyl groups to be in a *trans*-equatorial arrangement and the six-membered rings to have twisted chair conformations <1998AXC1473>. The electronic structure of the disila[3.3.3]propellane **123** has been probed by photoelectron spectroscopy, magnetic circular dichroism, and electronic spectroscopy which show that the lowest energy electronic absorption band is a doubly degenerate $\sigma_{\text{SiSi}}(\text{HOMO}) \rightarrow \pi^*_{\text{SiC}}(\text{LUMO})$ transition (HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital) <2003PCA3559>. The solid-state structure of the dimeric tin compound **146** shows it to have distorted trigonal bipyramidal geometry at tin and that the triflate anions are only weakly coordinated to the tin <2004OM6150>.



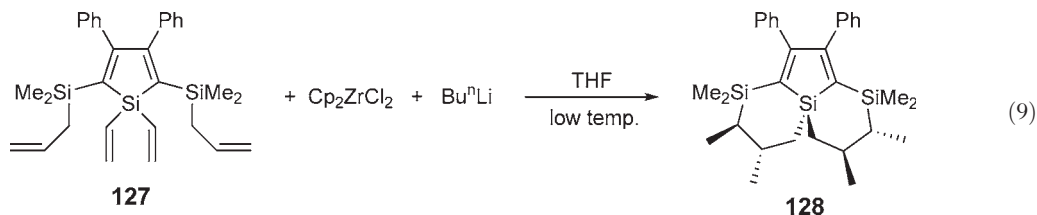
9.18.4.4.3 Synthesis of rings

In a metallation reminiscent of those described in Section 9.18.4.2.3 (Equation 8), treatment of the biscyclopentadienyl compound **124** with $(\text{ClMe}_2\text{Si})_2$ gives the trisilaheterocycle **125** in 69% yield <1997JOM(541)9>. The cobalt cyclobutadiene complexes **126** are formed via intramolecular cyclizations in 56–70% yield. This demonstrates that silaheterocycles can be formed at a metal center to form complexes as well as being preformed and then added to a suitable metal center to give metal derivatives (Scheme 35) <1997OM646>.

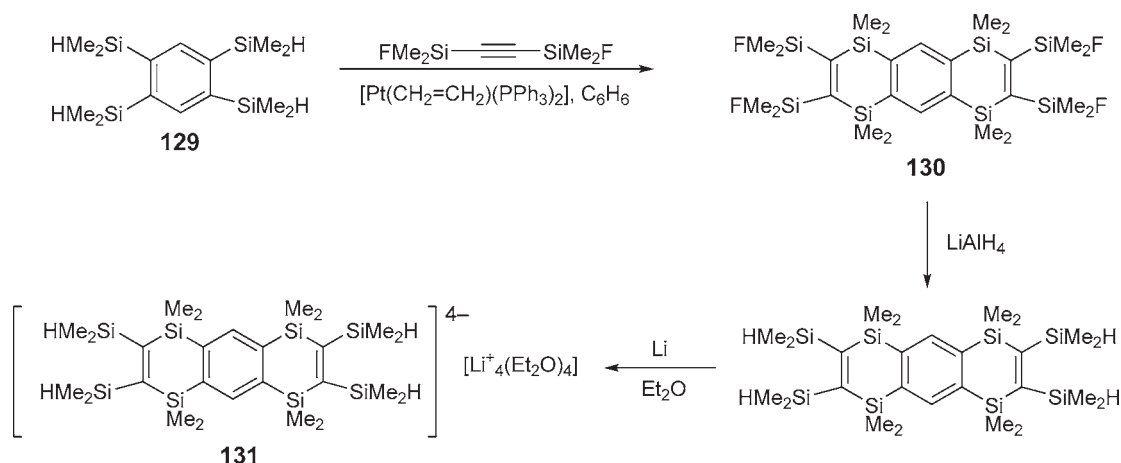


Scheme 35

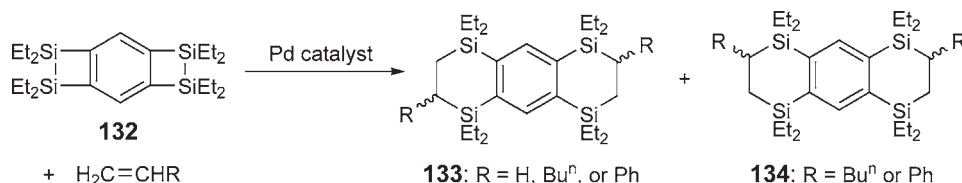
The reaction of silole **127** with BuLi in the presence of a threefold excess of Cp_2ZrCl_2 causes intramolecular cyclization and the formation of two six-membered rings, compound **128**, in 45% yield (Equation 9). If the amount of Zr-complex is reduced, then a bicyclic product is favored <1997T12979>.



The tetrasilylbenzene derivative **129** undergoes platinum-catalyzed reaction with bis(fluorodimethylsilyl)acetylene to give the tricyclic product **130**, which, after reduction with LiAlH_4 , reacts with lithium to afford the tetranion **131** (which has a twisted structure due to SiH–Li interactions; Scheme 36) <1999ICC510>. In a related reaction, the strained tetrasilylbenzene derivative **132** undergoes palladium-catalyzed reaction with alkenes to give tricyclic species **133** and **134** (Scheme 37) <1999JOM(587)1>.



Scheme 36

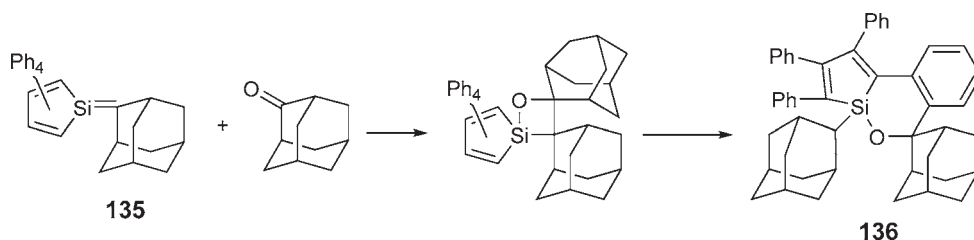


Scheme 37

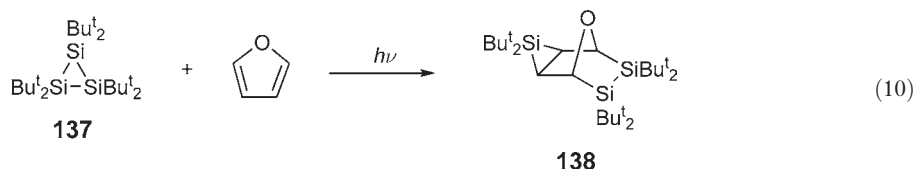
The synthetic route to simple 1,3-disilacyclohexanes shown in Scheme 6 also affords a 7,16-disilaspiro[5.2.5.2]-hexadecane derivative, the structure of which, **122**, is shown in Section 9.18.4.4.2 <1999ICA(296)231>.

Unsaturated organosilicon compounds continue to be a rich source of precursors to unusual heterocyclic compounds. Thus, the silene **135** reacts with adamantanone to give the highly sterically hindered polycyclic species **136** in 31% yield, presumably via a strained 1,2-siloxetane intermediate (Scheme 38) <2004JA5336>.

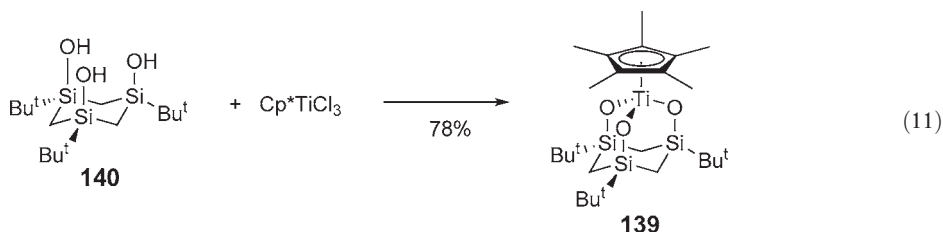
The photolysis of cyclotrisilane **137** in the presence of furan gives an unusual tricyclic product **138** (among other products), presumably by reaction of furan with both the disilene $\text{Bu}^t_2\text{Si}=\text{SiBu}^t_2$ and the silylene Bu^t_2Si : generated by the photolysis of **137** (Equation 10) <1995OM5695>.



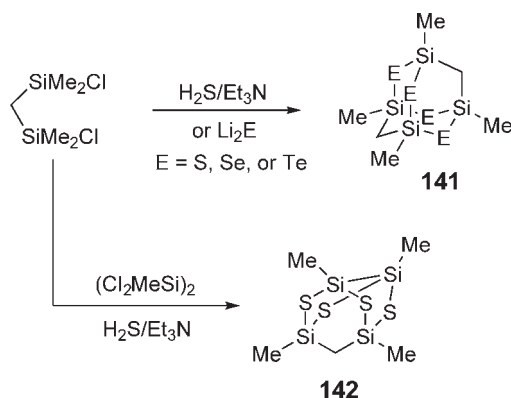
Scheme 38



An unusual metalla-adamantane derivative **139** can be prepared using the reactivity of the *cis,cis*-triol **140**; this precursor could be useful in the preparation of related metalla-adamantanes (Equation 11) <2003ZFA951>.

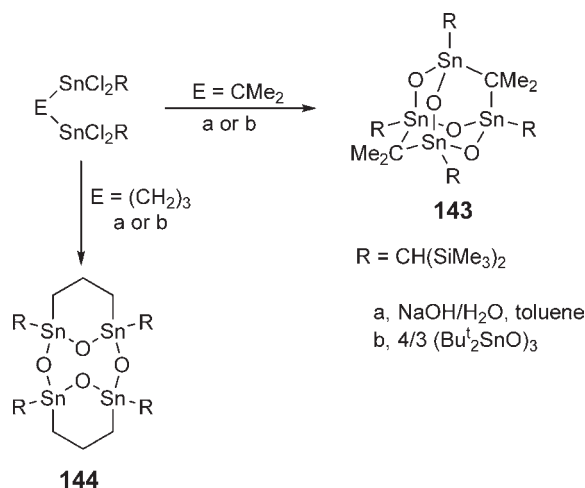


A series of chalcogen-containing adamantanes **141** have been prepared using the route shown in Scheme 39 <2001JOM(628)133> and the noradamantane **142** can be prepared in a similar way if $(\text{Cl}_2\text{MeSi})_2$ is added as a reagent.

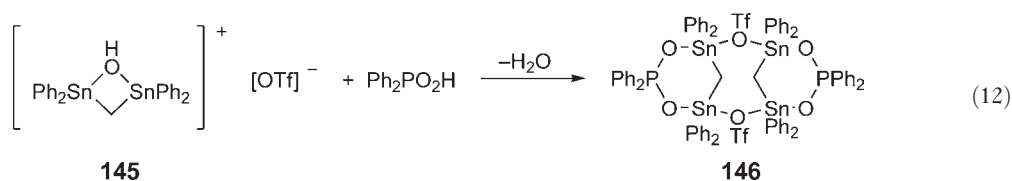


Scheme 39

Unusual tin heterocycles **143** and **144** are formed according to Scheme 40; apparently the product is determined by the length of the alkyl group in the precursor <1998OM4096>. The hydroxyl-bridged tin cation **145** reacts with HO_2PPh_2 to give a dimeric triflate-bridged species **146** in 56% yield which contains two CO_2PSn_2 rings (Equation 12) <2004OM6150>.



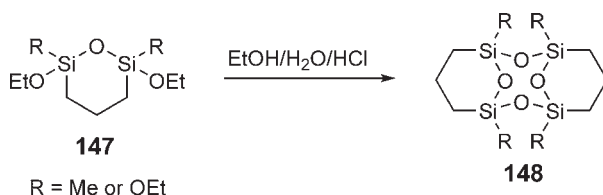
Scheme 40



9.18.4.4.4 Reactivity of nonconjugated rings

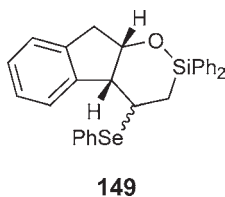
A range of triflate derivatives of sila-adamantanes have been prepared from methylsilyladamantanes by cleaving the Si–Me bond with ICl/AgOTf. These compounds have been used then as precursors to cationic sila-adamantanes <2002JOM(658)141>. Various C-chlorinated and C-brominated tetrasiladadamantanes have also been prepared and their chemistry explored <2000CJC1388, 1995BSF585>.

Acid hydrolysis of the ethoxysiloxanes **147** affords the tricyclic species **148**, presumably via silanol intermediates that condense to form siloxane linkages (Scheme 41) <1999JA5413>.



Scheme 41

Selenium-substituted tricyclic siloxanes such as **149** react via free-radical mechanisms with Buⁿ₃SnH/AIBN to give a variety of products (AIBN = 2,2'-azobisisobutyronitrile) <2000JA1343, 1997JOC5676>.



9.18.5 Higher Cyclic Rings

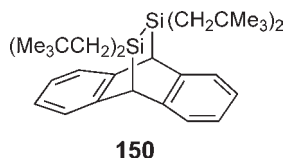
There are many examples of tetracyclic and higher cyclic compounds containing the lower group 14 elements, some of which will be briefly mentioned here. There are many synthetic routes to these compounds, metathetical and photochemical methods being some of the most useful.

9.18.5.1 Theoretical Methods

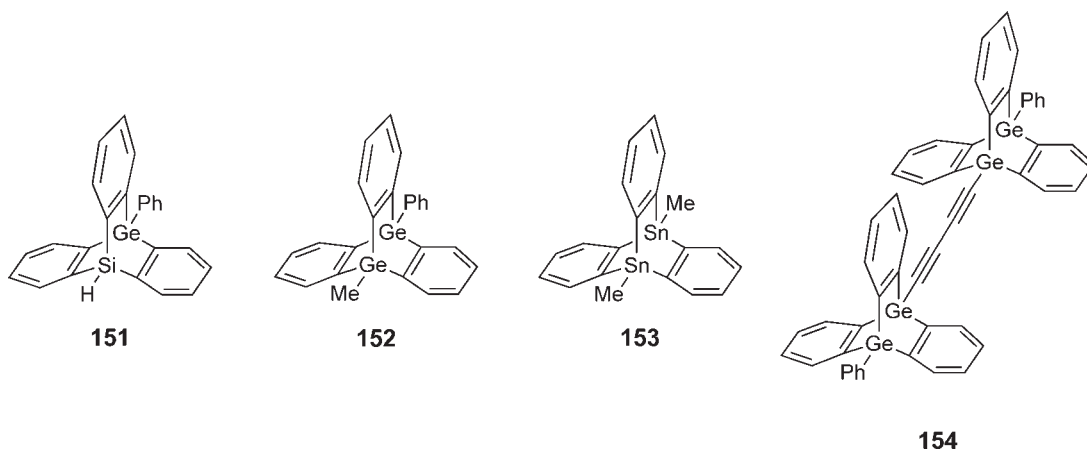
The increasing importance of fullerene chemistry has prompted computational work to investigate if silicon, germanium, tin, and other elements may be incorporated into carbon polyhedra (see Chapter 1.09). DFT provides evidence that a variety of heterofullerenes such as $C_{58}Si_2$, $C_{48}Si_{12}$, $C_{40}Si_{20}$, $C_{36}Si_{24}$, and $C_{30}Si_{30}$ have some stability; some of the structural isomers possible contain a range of six-membered rings containing two or more silicon or other heteroatoms <2005JCP204323, 2005PCA4415, 2005CMS237, 2005JCP084304, 2003JPO726, 2003JCP1127, 2002PRB085422, 2002PRB045405, 2001PRB085411, 2000IJQ(80)220, 1998ICA(280)219>.

9.18.5.2 Experimental Structural Methods

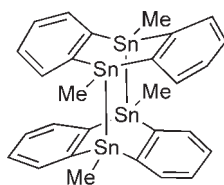
The first X-ray structural analysis of a dibenzodisilabicyclo[2.2.2]octa-2,5-diene was carried out on compound **150** and showed that the Si–Si bond and the Si–C bonds are all elongated, presumably due to steric repulsion by the bulky neopentyl groups <1996JOM(510)121>. The structure of the indenyl derivative **178** has also been determined; the three all-carbon rings are essentially coplanar while the sp^3 -silyl groups sit away from their plane <2004TL9029>. The X-ray structure of the disilabinaphthyl **181** shows it to be a rare example of an optically pure silaheterocycle <2002TA2167>.



The solid-state structures of triptycenes **151**, **152** <1998JOM(550)347>, and **153** <1996CEJ1139> all show significant distortions away from ideal tetrahedral values at the bridgehead positions, imposed by the polycyclic structure. The structure of the novel triptycene dimer **154** shows an unusually short nonbonded Ge···Ge distance of 3.044 Å <1998OM1762>.

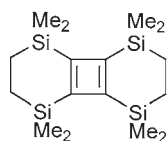


The structure of the 9,10-distannaanthracene **155** has been determined by X-ray crystallography and shows that the six-membered stannacycles have a boat conformation and that each half of the molecule has a butterfly conformation. The Sn–Sn bond length of 2.7836(5) Å is in the normal range <2005CL1018>.

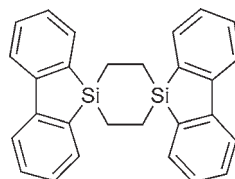


155

The structure of the first fulvene dianion derivative, **183** ($X = CH_2$), has been determined by X-ray crystallography <1999BCJ1115, 1998OM3143>. In the solid state, the dianion is monomeric with one Li-atom coordinated to the central five-membered ring in an η^5 -fashion and the second coordinated to an exocyclic carbon. In solution, the molecule is fluxional, the lithiums migrating between the two coordination sites. The X-ray structure of the spirocyclic species **188** ($R = Bu^t$) <1996JOM(512)225> confirms the *ipso*-substituted position of the silyl groups in the tetracyclic mixture formed in Scheme 48. The dynamic structure of the neutral indacene precursor to **102** ($R = Me$; see Section 9.18.4.2.4) in solution has been studied in detail <1997RCB1228>. Two isomers are present which interconvert via two silatropic pathways. The novel cyclobutadiene derivative **156** has been characterized by X-ray crystallography, which shows that the four-membered ring has a planar rectangular geometry and that the double bonds are localized <2001AGE1675>. The structure of the heptacyclic 1,4-disilacyclohexane derivative **157** has been determined by X-ray crystallography and shows the molecule to have crystallographic C_2 symmetry with the 1,4-disilacyclohexane ring adopting a perfect chair conformation <2002JA49>.

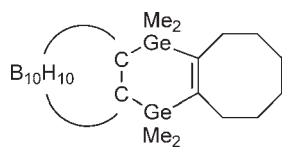


156

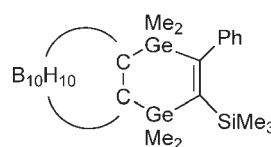


157

The X-ray structures of carborane derivatives **158** and **159** have been determined <2002OM3922> and show nonplanar six-membered rings but no surprising structural features. The bis-carborane-substituted species **199** (Scheme 51) has a boat conformation for the six-membered ring and a dihedral angle of 158° for the tricyclic framework <2002IC3084>.



158



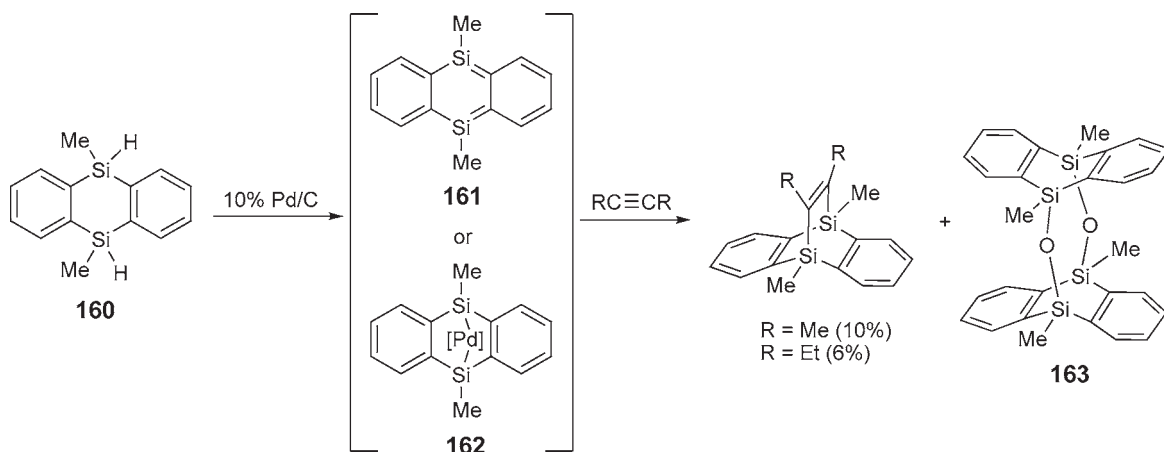
159

9.18.5.3 Reactivity of Nonconjugated Rings

The Si–Si bond in the chiral disilabinaphthyl derivative **181** is cleaved by iodine in quantitative yield to give an optically active bis-iodosilyl species that can be used as a catalyst in Diels–Alder reactions <2002TA2167>. The Si–Si bond in **181** is also cleaved by $LiAlH_4$ to give a bis-SiMe₂H product <2000OM3170>.

9.18.5.4 Reactivity of Substituents Attached to Ring Heteroatoms

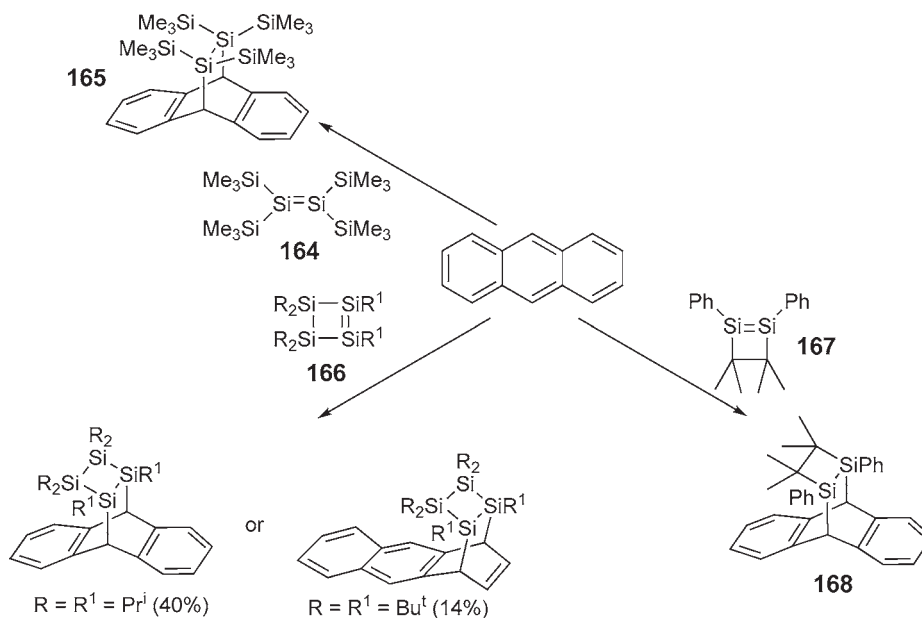
The disilanthracene derivative **160** undergoes palladium-catalyzed reactions with alkynes to give products that could be the result of a formal Diels–Alder reaction with the silaaromatic **161**, or with the palladacycle **162** (Scheme 42). The siloxane product **163** forms in the absence of alkyne, possibly as a result of oxygen addition to the aromatic intermediate <2001JOM(629)44>.



Scheme 42

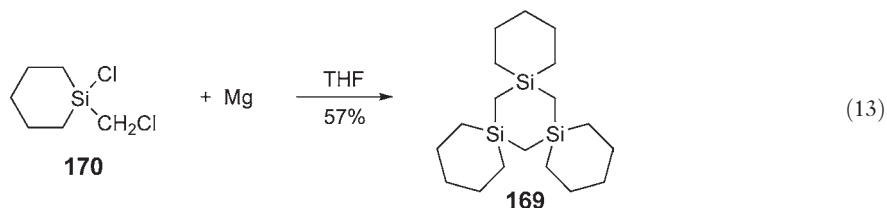
9.18.5.5 Synthesis of Rings

The trapping of reactive, unsaturated group 14 compounds has continued to be a source of heterocyclic compounds. Thus the disilene **164** reacts with anthracene to give the tetracyclic **165** in 56% yield as colorless crystals (Scheme 43) <2003JA3414>. Similarly, the cyclotetrasilene **166** reacts with anthracene (for a related reaction, see Scheme 22) to give two isomeric products from addition across either the central ring or one of the outer rings (Scheme 43) <2000CL494>. In a similar addition, cyclodisilene **167** reacts with anthracene to give **168** in 85% yield (Scheme 43) <1997JA3629>.

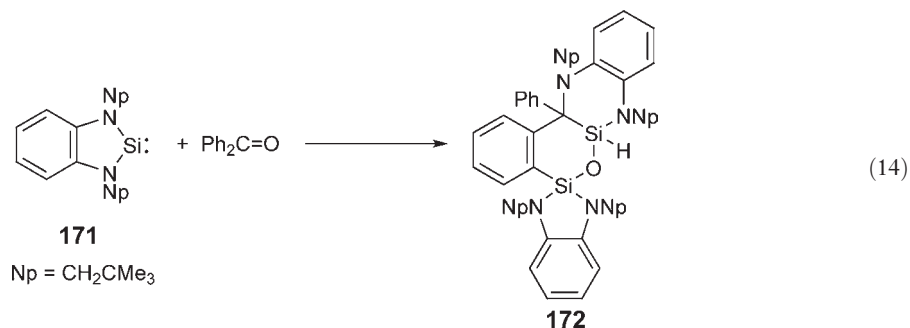


Scheme 43

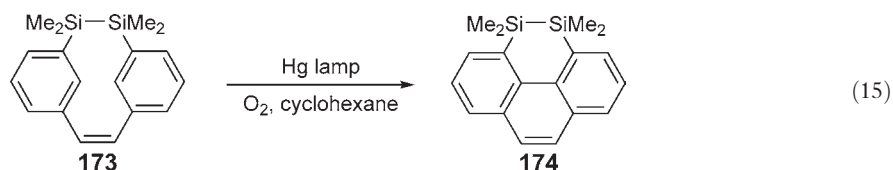
An unsaturated silicon intermediate may also be involved in the synthesis of the tetracyclic product **169** from the dichloride precursor **170** (Equation 13) <1996POL1545>.



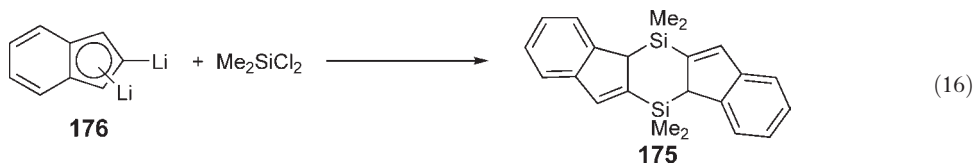
The divalent silicon species **171** is stable toward self-reaction but it reacts via a multistep pathway with benzophenone to give the polycyclic species **172**, containing both siloxane and silazane rings (Equation 14) <1998POL999, 1997OM4861>.



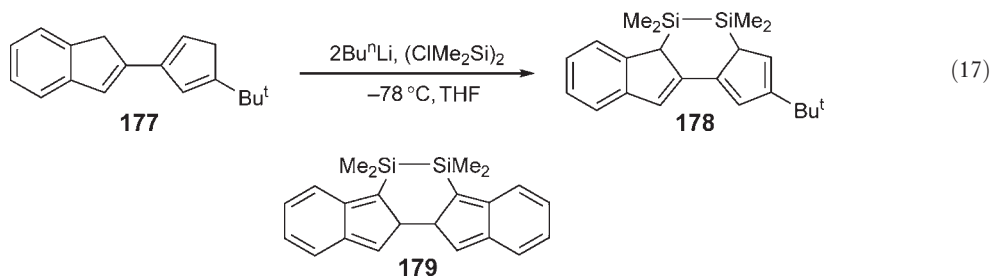
The [2.2]metacyclopheane **173** undergoes a transannular dehydrogenation to give the 4,5-disilapyrene derivative **174** in 69% yield (Equation 15) <2006JOM(691)1151>.



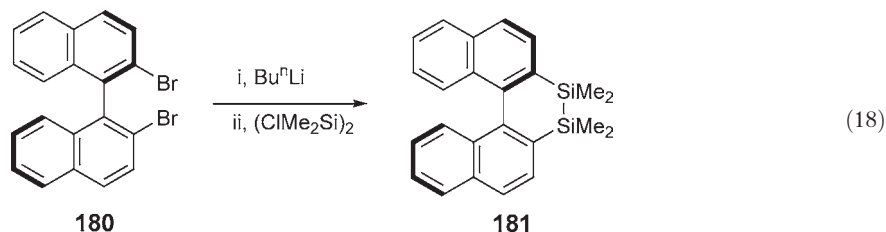
The use of silicon-bridged indenyl ligands such as **175** in transition metal chemistry has been hampered by low-yielding syntheses. However, a new synthesis using the indenyldilithium reagent **176** enables **175** to be prepared as a single isomer (other routes give a mixture of isomers) in 50% yield (Equation 16) <2006S1408>.



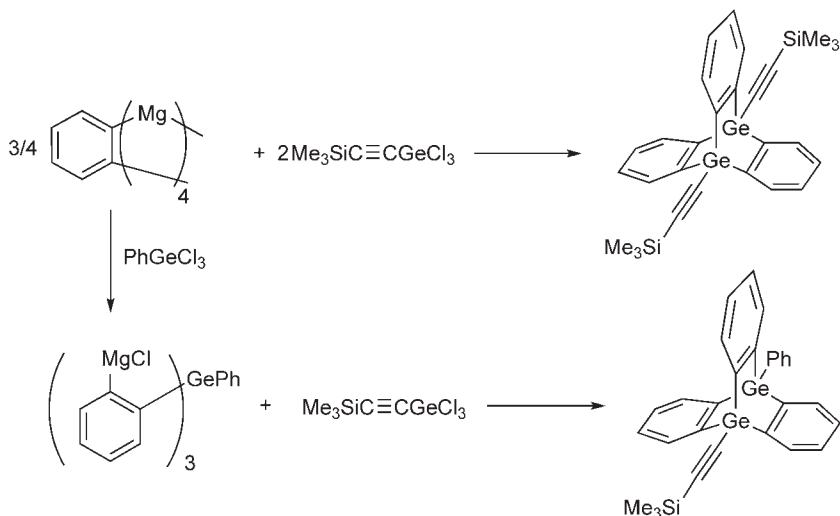
Similarly, deprotonation of **177** with BuLi gives a dilithium compound that reacts with (ClMe₂Si)₂ to give the yellow crystalline tetracyclic indenyl derivative, **178**, in 75% yield (Equation 17) <2004TL9029>. The related indenyl derivative **179** can be lithiated and treated subsequently with transition metal halides to give a range of metal complexes containing the 2,2'-disila(bisindenyl)-type ligand <2004OM968, 2001OM3869>. The related hexacyclic species **99** is also prepared via reaction between a dilithium derivative and tetrachlorodisilanes (Scheme 30) <2002JOM(642)137>.



The formation of disilaheterocycles via lithiation reactions can also be carried out with retention of optical activity. For example, dilithiation of the optically active binaphthyl species **180** followed by treatment with $(\text{ClMe}_2\text{Si})_2$ gives the disilabinaphthyl derivative **181** in 70% yield, which after two recrystallizations can be isolated enantiomerically pure (Equation 18) <2002TA2167>.

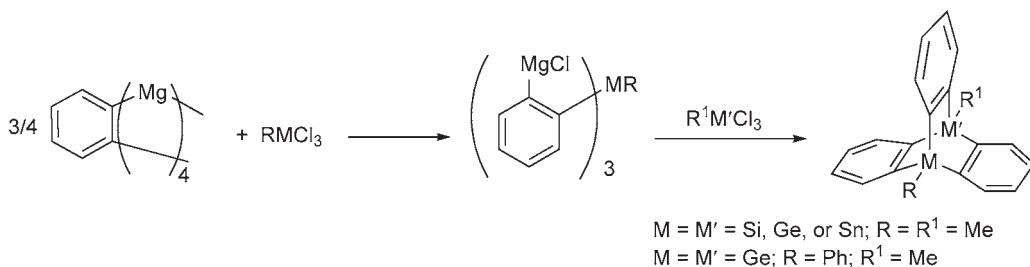


A series of 9,10-digermallatriptycenes have been prepared in good yield using the metathetical one-pot routes shown in Scheme 44, both of which rely on the reaction of $\text{Me}_3\text{SiC}\equiv\text{CGeCl}_3$ with a Grignard reagent <1998OM1762>. Desilylation using aqueous KOH affords simple ethynyl derivatives that can then be oligomerized to give novel conjugated triptycenes.



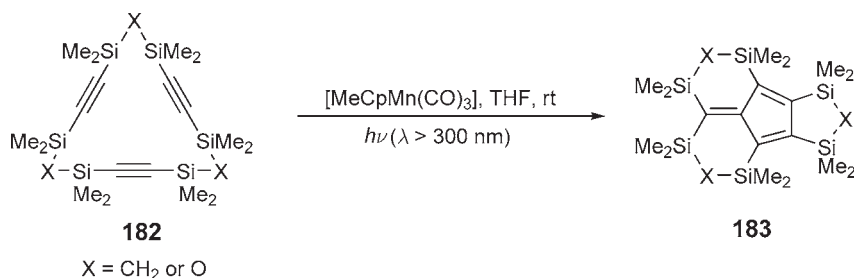
Scheme 44

A general route to dimetallatriptycenes is shown in Scheme 45 and also involves the reaction between aryl Grignard reagents and group 14 trichlorides <1996CEJ1139, 1998JOM(550)347>. In a similar manner, reaction between the *ortho*-metallated Grignard and group 15 element halides MCl_3 ($\text{M} = \text{P}, \text{As}, \text{or Sb}$) gives the mixed group 14/15 dimetallatriptycenes <1999MGM519>.



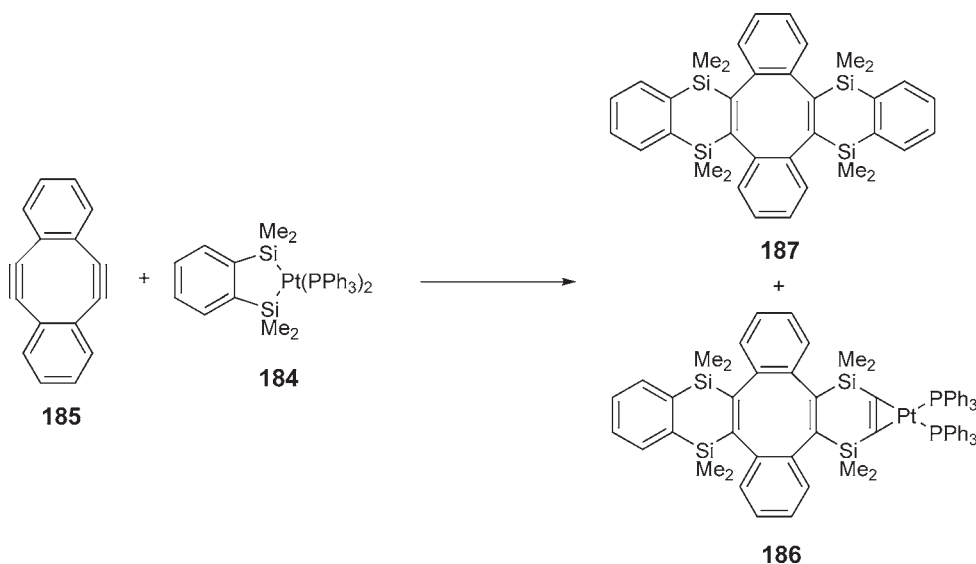
Scheme 45

The photolysis of macrocycles **182** in the presence of a manganese catalyst causes a dramatic polycyclic ring closure to give the tetracyclic species **183** (Scheme 46) <1999BCJ1115, 1998OM3143>. When treated with lithium, the hexasilafulvene derivatives **183** afford silyl-substituted fulvene dianions containing a six-center/eight-electron π -system.



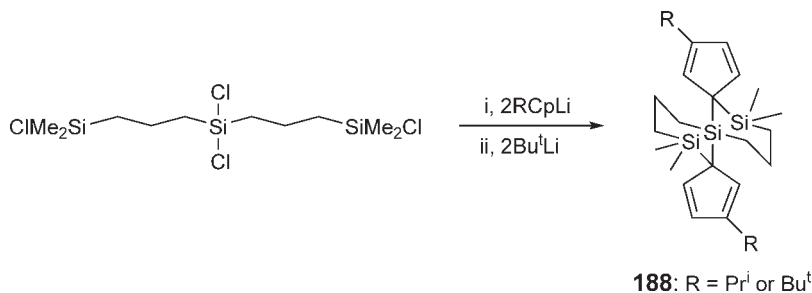
Scheme 46

The stoichiometric reaction of platinum complex **184** with the cycloalkyne **185** also gives rise to cycloaddition products, **186** and **187** (Scheme 47), but these products were not formed in the reaction of **185** with 1,2-bis(dimethylsilyl)benzene catalyzed by $[\text{Pt}(\text{CH}_2=\text{CH}_2)(\text{PPh}_3)_2]$ <1997ICA(265)1>.



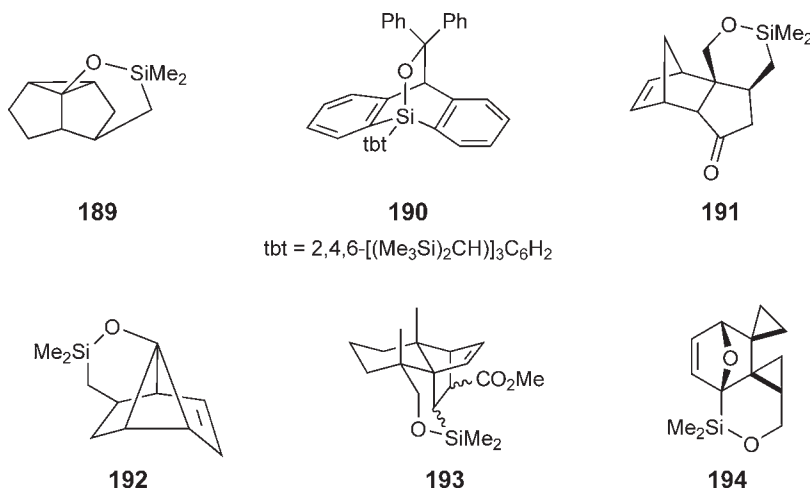
Scheme 47

The unusual spirocyclic species **188** are formed in high yield as mixtures of isomers according to Scheme 48 <1996JOM(512)225>. The initial step in the synthesis is the introduction of the two cyclopentadiene rings followed by deprotonation of these rings which undergo an intramolecular cyclization with the remaining $\text{Si}-\text{Cl}$ groups.

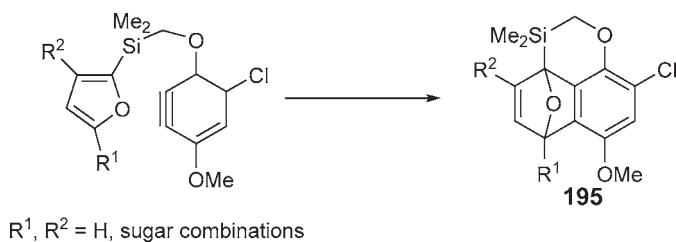


Scheme 48

A wide variety of polycyclic compounds containing Si–O bonds are known and they may be prepared via many different synthetic routes. The formation of the strong Si–O bond is often a significant driving force in such preparations. The tetracyclic species **189** forms with high regioselectivity in a photochemical reaction involving $\text{PhOSiMe}_2(\text{CH}_2\text{CH}=\text{CH}_2)$ <2001JHC1341> and the silanthracene derivative **190** is formed on addition of $\text{Ph}_2\text{C}=\text{O}$ to a 9-silaanthracene precursor <2002OM256>. The tetracyclic species **191** is an intermediate in the synthesis of (–)-iridolactone and (+)-pedicularis-lactone <2001OL679>. The polycyclic siloxane **192** can be used as a precursor to the skeleton for models of the alkaloid gelsemine <1999OL2073>. The tetracyclic siloxane **193** is formed in an intramolecular Diels–Alder reaction <1998CEJ1480> and siloxane **194** is formed in good yield from the intramolecular Diels–Alder reaction of a bis-cyclopropylidene precursor <1996T12185>.

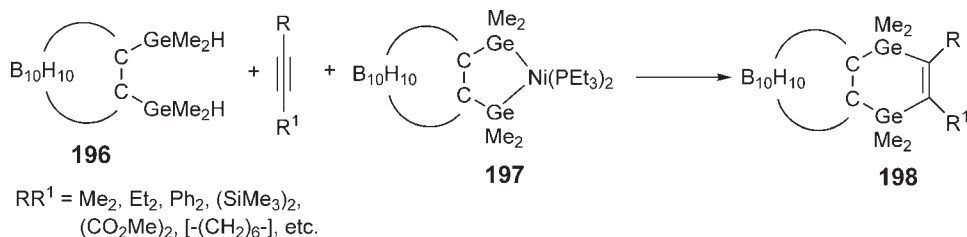


Silicon tethers can be used to bring about close proximity of cyclopentadienyl and benzyne groups such that intramolecular cycloadditions take place to give products of type **195** (Scheme 49). The linking unit can then be removed to furnish unsymmetrical *C*-aryl glycosides <2003JA12994>.



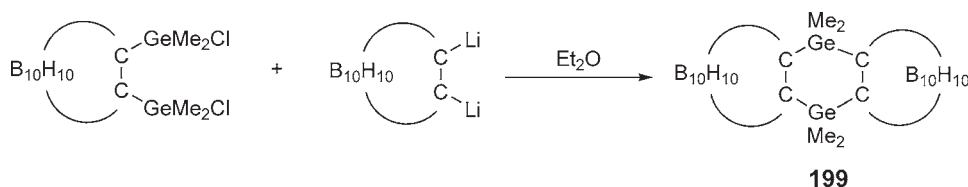
Scheme 49

The reaction of alkynes with 1,2-bis(dimethylgermyl)carborane **196** in the presence of a catalytic amount of the nickel complex **197** gives a range of carborane substituted 1,4-digermacyclohexenes **198**, in good yield, as shown in Scheme 50 <2002OM3922>.



Scheme 50

A related bis-carborane-substituted 1,4-digermacyclohexane derivative **199** can be prepared in 65% yield by the metathesis reaction shown in [Scheme 51](#) <2002IC3084>.



Scheme 51

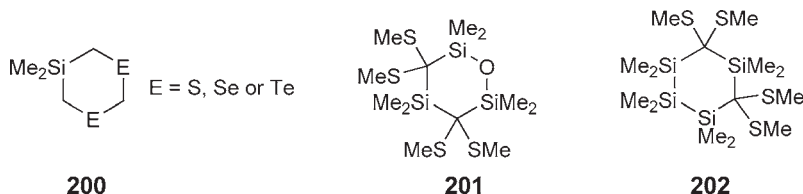
9.18.5.6 Important Compounds and Applications

Relatively few polycyclic silaheterocycles have application but porphyrin derivatives of silicon have attracted attention because of their mesogenic and electronic properties <2004LC101, 2002JA8099>.

9.18.6 Further Developments

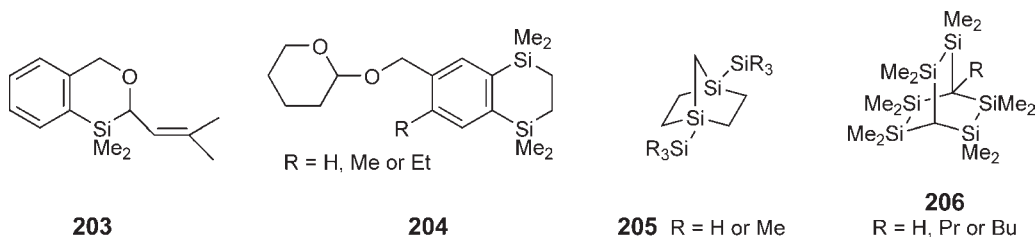
9.18.6.1 Monocyclic Compounds

Diphenylsilylene may be extruded with high stereoselectivity from 1,1,3,3-tetramethyl-2,2-diphenyl-1,2,3-trisilacycloheptane to give 1,1,2,2-tetramethyl-1,2-disilacyclohexane <2006JA14442>. A range of new mixed group 14 and 16 heterocycles such as **200** have been prepared and their chemistry and structures studied <2006JA12685, 2006JA14949>. Novel polysilacyclohexane derivatives **201** and **202** have been prepared by metathetical reactions between dilithium reagents and bifunctional chlorosilanes <2007ARK29>.



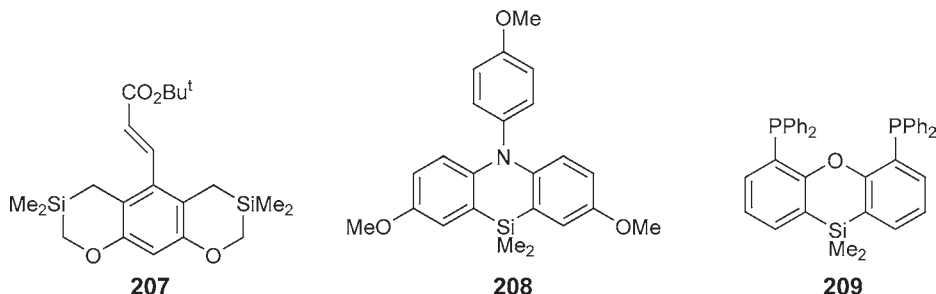
9.18.6.2 Bicyclic Compounds

The benzo-fused species **203** is formed as a byproduct in a hydrosilylation reaction <2007JOM(692)585>, and cobalt catalyzed [2+2+2] cycloadditions can give rise to 1,4-disilatetralines such as **204** <2007SL753>. Simple 1,4-disilatetralines have also been studied as analogues of the musk odorant versalide to determine their olfactory properties and their biodegradability <2007OM1295>. The 1,4-disila[2.2.1]bicycloheptanes **205** have been studied computationally to determine the effect of ring size on electronic excitations <2007JPC(A)2804> and 2,3,5,6,7,8-hexasilabicyclo[2.2.2]bicyclooctanes **206** have been found to form an unusual class of mesomorphic columnar compounds <2007AG(E)3055>.

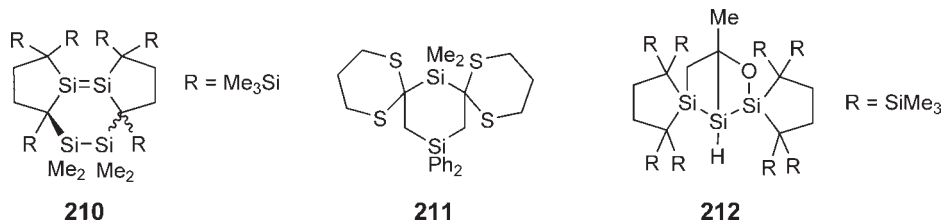


9.18.6.3 Tricyclic Compounds

The tricyclic species **207** is formed in 60% yield via a Pd-catalyzed cyclization of a bis iodomethylsilyl precursor <2007JOC775> while ESR studies on **208** have been used to study spin transfer <2007AG(E)3300> and the bis-phosphine compound **209** forms chelate complexes at Pt centers <2007JCS(D)1053>.



Novel fused tricyclic disilenes **210** have been prepared and have been structurally characterized showing that while the geometry around the double bond in the *cis* isomer is unsurprising, the *trans* isomer is significantly distorted <2006AG(E)6371>. The spirocyclic species **211** has been prepared using a route similar to that for compounds **201** and **202** <2007ARK29>, and the spirocyclic compound **212** is derived from the reaction of a trisilaallene with acetone <2007JOM(692)263>.



9.18.6.4 Higher Cyclic Rings

The formation of Si-fullerenes via plasma reactions continues to be investigated and provides access to a range of Si-heterofullerenes <2007TSF4177>. A spiro-fused analogue of **208** has also been investigated by ESR to investigate spin transfer mechanisms <2007AG(E)3300>.

References

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Biographical Sketch



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9.19

Six-membered Rings with Two or More Heteroatoms with at least One Boron

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9.19.1 Introduction

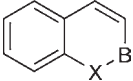
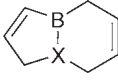
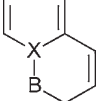
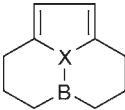
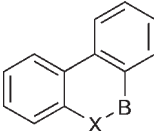
The literature on boron-containing heterocycles that have at least one other heteroatom within the six-membered ring system was documented in CHEC(1984) and CHEC-II(1996) <1984CHEC(1)629, 1996CHEC-II(6)1155>, and the subject of the present work is the progress of the field since 1995. A search of the literature since the publication of CHEC-II(1996) revealed that there are about 60 different ring systems that come under the title of this chapter. Most of them are presented in [Tables 1–3](#), which aim to provide the reader with leading references to as wide a range as possible

Table 1 Rings containing the C–B–C linkage

Ring type	References
<i>1,3-Substituted rings</i>	
X = B	1998EJI459, 1994ZNB465, 1992CB23, 1990ZNB985
X = B	2004ZNB782, 2001EJI1949, 2000AGE1276, 1997ZNB823, 1995AGE681, 1994ZNB465
X = B	1992AGE1384
X = B	1997JMT65
<i>1,4-Substituted rings</i>	
X = O	1998JA1705
X = S	2004CC1284
X = N	1995JMT109
X = B	1994ZNB1677, 1994CB813, 1995CB183
X = Sn	1999JOM93, 1994CB333, 1993CB1361
X = B	1995CB183
X = O	1998JA1705, 1996JA259
X = N	2005OL4373, 1997T8599, 1997TL6281
X = B	2002OM4159, 2000AGE1312, 1996JOM41, 1995ZNB1476, 1995SM1109, 1995JOM235, 1998EJI761
X = S	2004CC1284
X = P	2005OL4373

of structural types. For clarity, divisions have been made for C–B–C, C–B–X, and Y–B–X ring fragments, where X and Y represent any element other than carbon. The most common systems reported were the 1,3,2-dioxa-, 1,3,2-oxaza-, and 1,3,2-diazaborinanes **A** (X, Y = O or/and N) containing 1,3-diheteroatom substitution. 1,2-Oxaborinanes and 1,2-azaborinanes **B** with the C–B–X linkage (X = O or N) are also very common and they are extensively covered in the literature. Other systems, such as heterocycles **C** and **D** containing the X–C–B–C and X–C–C–B–C fragments, 1-hetera-4-boracyclohexa-2,5-dienes **E**, and boratabenzenes **F** are considerably less common. Nevertheless, in the last decade, ingenious use of new reactions and reagents has made these structures much more readily available for investigation. Particularly noteworthy in this period are reports of functionalized 1,3-dibora- and 1,3,5-triboracyclohexanes, 10-boraanthracenes containing 9-heteroatom substitution, and boron-containing polyheteroatom π -electron systems.

Table 2 Rings containing the C–B–X linkage

<i>Ring type</i>	<i>References</i>
<i>Rings with two heteroatoms</i>	
 X = O X = N X = P	2004JFC975, 2001JOC7148, 1999JA450, 1996OM152, 1996CL539, 1996CL537 2004ZFA2641, 1997JOM297, 1996CB1541 1997JOM323
 X = O	1998EJI459
 X = O X = N	2002AGE152 2003OM3748
 X = N	2001OM5413, 2000OL2089
 X = N X = O	2004ZFA2632 2004ZFA2632
 X = N	2002OM4578
 X = N	1997JOM181, 1997JOM71
 X = N	1998JOM247
 X = O X = N	2004JOC5147, 2000JOM168 2004JOC5147, 1999CC2279, 1997T8599, 1997TL6281

(Continued)

Table 2 (Continued)

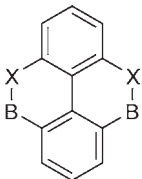
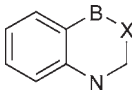
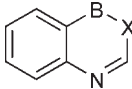
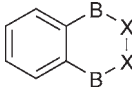
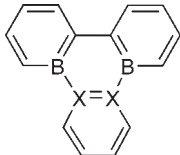
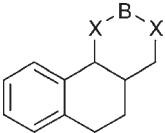
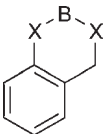
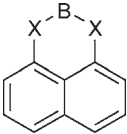
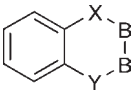
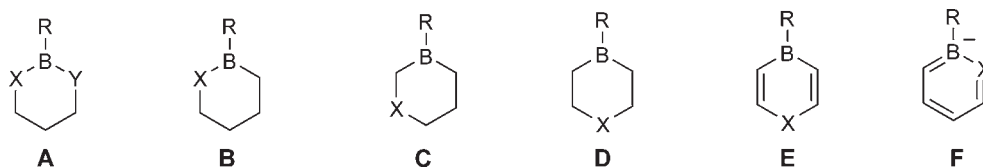
<i>Ring type</i>	<i>References</i>
 X = N	2001J(P2)2166
<i>Rings with three heteroatoms</i>	
 X = N	1996IZV183
 X = N	1997OM5321
 X = N	1996AXC2826
 X = O X = N	2002SL477, 1997JOC4492, 1996JOC4510 2002TL3255, 1999JOC9566, 1998JHC887, 1997JOC4492, 1996JOC4510
 X = N	1999JOC9566, 1997JOC4492
<i>Rings with four heteroatoms</i>	
 X = O, N, P, or S	1997ZNB823
 X = N	2003AGE1252
 X = N	2003AGE1252

Table 3 Rings containing the X–B–Y linkage

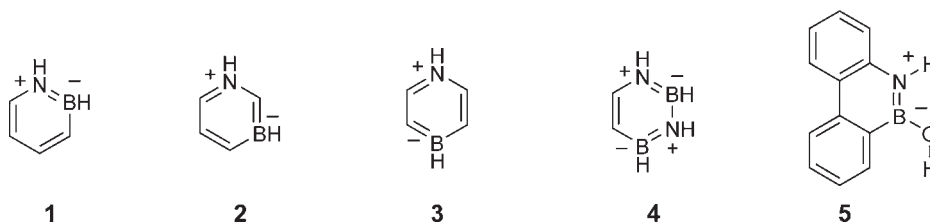
Ring type	References
<i>Rings with three heteroatoms</i>	
 X=Y=O X=O; Y=N X=Y=N	2005TL5647, 2005TL5109, 2004JOC695, 2003TL7645, 2002JA13644, 2002TL2317, 1998TL6483 2005JOM469, 2001POL1053, 2001OL1391 2005JA12162, 2005JOC5545, 2005JA8185, 2005T2683, 2005JOC2075, 2004JOC2070, 2004JA3357, 2004TL1949, 2004JA1772, 1999POL2405, 1999JOC7813, 1999CC1889, 1999TL5199, 1999TL1471, 1998IC5131, 1998JA10001
 X=O	2001BMCL3143, 2001EJOC4259, 1995IC1507
 X=O X=N	2005T1765, 2004JA13196, 2002TA1965, 2002JOM194, 2000J(P1)567, 1998TL6483, 1996JOC3218 2005JA8185, 2003CEJ4156, 2000POL165, 1999EJOC2501, 1998TL4733, 1998TL2643, 1997JOC6682, 1997CC229
 X=O X=N	2005T1765, 2000J(D)3136, 1995IC1507 2005JA8185, 2003CEJ4156, 1997JOC6682, 1999EJO2501, 1998TL4733, 1997CC229
 X=Y=N	2005JA8185, 2005JOC2075, 2005ZAAC(631)518, 2004IC7162, 1998IC5131, 1998TL2643, 1996JOC3061
 X=Y=N	2005JA8185
<i>Rings with four heteroatoms</i>	
 X=Y=O X=Y=N X=Y=P	2004IS(34)1, 2001AGE4182, 2000NJC115, 1997POL2325 1998POL4139 1997CB1677
<i>Rings with five heteroatoms</i>	
 X=N	1995CB1037



A *Chemical Abstracts* search between 1995 and the end of 2005 revealed about 180 relevant publications, which were screened for inclusion in this chapter. Reviews related to the topic include those on B–C–B compounds <2003AOM327>, boron macrocycles based on self-assembly of Schiff bases <2001JOM259>, naphthalene derivatives *peri*-substituted by group 13 elements <2002CCR93>, cyclic boronic esters <1998T10555> and functional group compatibilities in boronic ester chemistry <1999JOM(581)51>. 1,3,2-Dioxaborinane chemistry has been given wide coverage in the book by Matteson <1995MI1>.

9.19.2 Theoretical Methods

Theoretical treatments of the six-membered cyclic π -electron systems with BN bonds continue to appear <1997JMT65, 1998T14913>. The replacement of a pair of carbon atoms in benzene by B and N leads to a series of heterocyclic molecules. Of the three structural isomers **1–3**, 2-azaborine **1**, where B and N atoms are adjacent, is found to be most stable by modified neglect of diatomic overlap (MNDO) and *ab initio* calculations. MNDO has also been used to compare ring isomers of diazadiborine, where two CC units are replaced by two BN pairs. These studies indicate that the 1,3,2,4-diazadiborine **4** is the most stable isomer. In general, when multiple pairs of BN are present, these pairs prefer to be consecutive with one another. On the other hand, in the case of fused rings such as naphthalene, a single BN pair is most favorably disposed on the α - and β -positions, avoiding the fused ring locations <1997JMT65>. The aromaticity of the 10-hydroxy-9-aza-10-boraphenanthrene **5** has been described in the past in the context of experimental observations such as its chemical stability, reactivity, and spectroscopic properties <1996CHEC-II(6)1155>. More recently, the aromatic character of **5** was supported also by *ab initio* calculations utilizing the HF/6-31G(d,P) basis set. The calculated N–B Löwdin bond order (1.31) suggests that this bond has significant π -character. This point is illustrated further by examining the calculated highest occupied molecular orbital (HOMO) of **5** which shows clearly the N–B π -orbital overlap. Interestingly, in contrast to the bond polarization that is conventionally written as $N^+ = B^-$, the calculated electrostatic potential surface of **5** (in kcal mol^{−1}) is negative (−14.9) around the nitrogen atom and positive (+17.7) around boron. This observation is consistent with calculations on borazines, which have demonstrated that, although there is considerable $N \rightarrow B$ charge transfer in the π -system, it is outweighed by $B \rightarrow N$ charge transfer within the σ -framework <1997T8599>. Structural aspects of 10-hydroxy-9-aza-10-boraphenanthrene and related compounds also have received attention <1997TL6281, 1999CC2279, 2001J(P2)2166>.

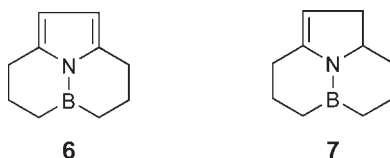


Computational results were reported on the stabilization and on the nucleus-independent chemical shifts (NICSs) of the isoelectronic, all-hydrogen-substituted trishomoaromatic set $[(CH_2)_3(BH)_3]^{2-}$, $[(CH_2)_3(CH)(BH)_2]^-$, $[(CH_2)_3(CH)_2(BH)]$, and $[(CH_2)_3(CH)_3]^+$. The computed NICS values prove the strong homoaromatic character of the reduced triboracycles <2001EJI1949, 2000AGE1276>. Analysis of the electronic structure of zwitterionic boron–carbon mono- and bis-homoaromatics containing positively charged NMe_2 , PPh_2 , or $AsPh_2$ bridges and anionic three-center two-electron (3c2e) delocalized boron heterocyclic units gives insight into the origin of the trend of increasing effectiveness of BC_2 , B_2C , and B_3 3c2e bonds: higher electronegativity of carbon versus boron prevents symmetric delocalization in rings with B_2C and especially BC_2 centers. Additionally, a dianionic trishomoaromatic with an oxygen homobridge was studied. The high

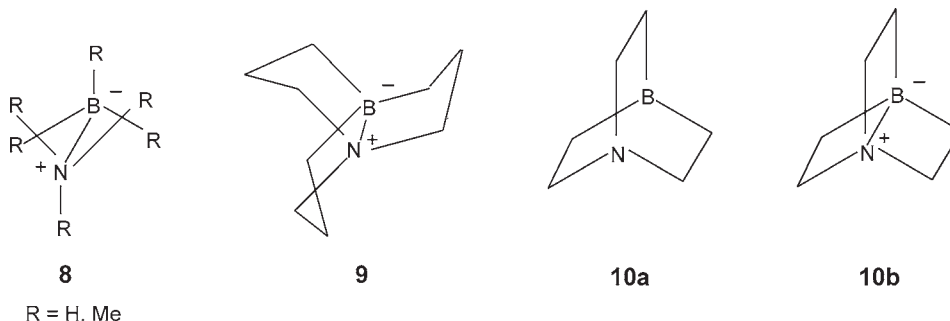
electronegativity of oxygen precludes effective cyclic electron delocalization (aromaticity) in 1-oxa-2,4,6-triboracyclohexanediide, the isostere of the aromatic pyrylium cation <2003JOM244>.

1,3,2-Dioxaborines with fluorine and other substituents at boron were calculated by methods based on density functional theory (DFT: B3-LYP) or many-body perturbation theory at the second order (MBPT(2): MP2). According to quantum-chemical calculations, 2,2-difluoro-1,3,2-dioxaborines are of puckered structure with a low barrier to inversion. The calculated charge distribution does not reflect well the traditional formula description. The boron atom carries a positive rather than a negative charge. Some compounds have a pronounced zwitterionic character accompanied by relatively high dipole moments. The calculated electron affinities (EAs) classify 1,3,2-dioxaborines as electron-acceptor compounds <2004JPO359>. The applicability of the MM+ molecular mechanics method and MINDO/3, MNDO, and AM1 semi-empirical methods to calculation of the optimal geometries, formation heats, and free conformation energies of substituents in different six-membered cyclic boron esters with oxygen and nitrogen atoms was examined <1999RJC403, 2000RJO285, 2001MI494>. AM1 is mostly preferable for bond length and angle calculations, while MM+ and AM1 are applicable to intracyclic torsion angle calculations. The latter two are also quite reliable for determination of the enthalpy difference or the free conformation energies of substituents at C-5 of the ring in 1,3,2-dioxa- and 1,3,2-oxazaborinanes <2001MI819-01>. Both empirical (MM2) and semi-empirical (AM1, MNDO) methods were used to calculate the energy of unsubstituted and 2-, 3-, 5-, 3,5-, and 2,3,5-substituted 1,3,2-oxazaborinanes with complete geometrical optimization <1999CHE928>. A semi-empirical (AM1) study allowed calculations of the energy for all possible stereoisomers of 2-phenyl-6-aza-1,3-dioxa-2-borabenzocyclononones, showing that the stabilization increases as the tetrahedral character of the boron atom increases and also as the NB bond distance decreases, in agreement with the experimental results <2002JOM194>.

A theoretical consideration of *N*-pyrrolylborane **6** and related tricyclic enaminoborane **7** has concluded that the BN(pp) π -bonding in **6** is significantly reduced with respect to enaminoborane **7**. The π -bond occupancy is 1.899 for **7** and only 1.748 for **6**. This is in accordance with calculated and experimental ^{11}B , ^{13}C , and ^{14}N shielding data for the title compounds. Further, the results of the molecular orbital (MO) calculations are supported by the pronounced Lewis-acidic character of **6** <1998JOM247>.



Ab initio quantum chemical investigations have been used to compare the borazane molecules **8**, whose B–N bonds incontrovertibly exist, and propellane-like structures **9** and **10** <1995JMT109>. It was found that boraza[3.3.3]propellane **9** resembles hexamethylborazane in its bond length, dipole moment, and BN bond critical point. In contrast, boraza[2.2.2]propellane **10b** does not exist as such but rather has the open form, 1-aza-4-borabicyclo[2.2.2]octane **10a**. The HF/6-31G* BN bond lengths (R_{BN}) in hexamethylborazane and boraza[3.3.3]propellane **9** are 1.836 and 1.768 Å, respectively. The dipole moment of **9**, 3.345 D, directed along the threefold axis with the positive end toward nitrogen, is similar to that calculated for hexamethylborazane, 4.577 D. Calculations of **10** yielded a C_{3v} structure with large values of R_{BN} (2.359 Å). The HF/6-31G* charge density has no bond critical point along the BN axis, only a cage critical point. This molecule also has a small dipole moment (0.85 D in MP2/6-31G*), the negative end of which is directed toward nitrogen.



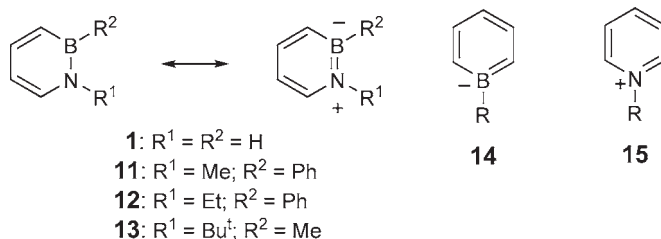
MO calculations have been carried out for the [4+2] Diels–Alder-like cyclization of aminoboranes $\text{R}_2\text{B}=\text{NR}^1_2$ with substituted *cis*-1,3-butadienes <2003OM3748>, and for the [4+2] ene-type reactions between iminoboranes

$\text{RB}\equiv\text{NR}^1$ and alkynes <2004OM5048>. The structure and stereochemistry of the novel bora derivatives of 1-[(2-hydroxy-1-naphthyl)methyl]proline were elucidated by means of two-dimensional nuclear magnetic resonance (2-D NMR) spectra as well as AM1 semi-empirical calculations <2005TA2019>.

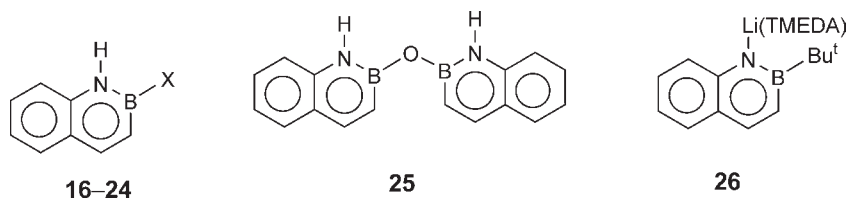
9.19.3 Experimental Structural Methods

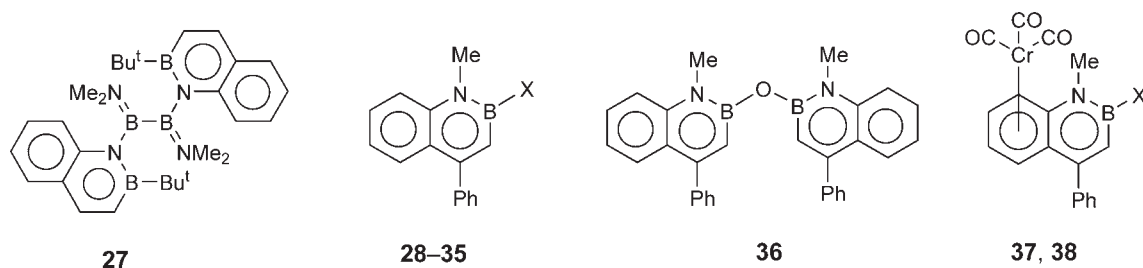
Because of the diverse nature of the six-membered polyheteroatom boracycles comprising this chapter, a detailed treatment of their structural properties is outside the scope of this review, and therefore the emphasis here will be on a small number of ring systems that have been systematically studied and fully characterized. **Tables 1–3** provide more comprehensive references, which should be consulted for further information.

A number of papers have been published, which are concerned with the study of the structure and physical properties of boron–nitrogen heteroaromatic compounds <1997TL6281, 1997T8599, 1999JOC9566, 2001OM5413, 2004OM5626, 2004ZFA2632>. Ashe and co-workers have reported the ^1H , ^{13}C , and ^{11}B NMR spectra of a series of 1,2-dihydro-1,2-azaborines (also to be formulated as 1,2-azoniaboratabenzenes) <2001OM5413>. The ^1H NMR signals for the four nonequivalent ring protons of the 1,2-dihydro-1,2-azaborines **11–13** show a first-order pattern in the range δ 6.15–7.75 (all δ values are given in ppm). The chemical shift values of the protons that are α (H-3) and γ (H-5) to boron are approximately 1 ppm upfield from those β (H-4, H-6) to boron. In the ^{13}C NMR spectra, the signals for ring carbon atoms that are α or γ to boron are shielded, while those that are α or γ to nitrogen are deshielded. The same pattern of shielding and deshielding is shown for boratabenzenes **14** and pyridinium salts **15**. The ^{11}B NMR shift values of compounds **11–13** (δ 35.2–37.7) are in agreement with the calculated chemical shift of the parent ring **1** (δ 34.4).



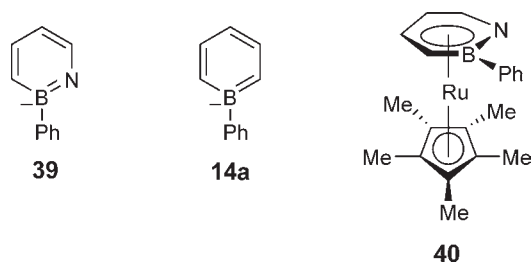
A structural study of the 1-azonia-2-boratanaphthalenes (**16–38**) also confirms the aromaticity of these compounds <2004ZFA2632>. The vicinal coupling constants of the aromatic protons H-3–H-8 are found at $^3J = 11\text{--}12\text{ Hz}$ for H-3/H-4 (**16–27**) and $^3J = 7\text{--}8\text{ Hz}$ for H-5/H-6, H-6/H-7, and H-7/H-8 (**16–35**). The coupling patterns appear as a doublet with the signals for H-3 (**16–26**), H-5, and H-8, and as a pseudotriplet with the signals for H-6 and H-7. Long-range couplings of $J = 1\text{--}2\text{ Hz}$ are observed as multiplets with the signals for H-5, H-6, and H-7 (**16–36**), H-3 (**16–26**), and H-8 (**28–36**). The signal for H-3 certainly appears as a singlet for **28–36**. The ^{11}B NMR signals for **16–36** are found in the range $\delta = 27.1\text{--}41.4$. The shift values are influenced by the ligand X in a known manner: $\delta = 27.1\text{--}29.2$ for $\text{X} = \text{OR}$; $\delta = 31.0\text{--}33.3$ for $\text{X} = \text{Cl, Br}$; $\delta = 36.3$ for $\text{X} = \text{Ph}$; $\delta = 37.3\text{--}41.4$ for $\text{X} = \text{alkyl}$. The crystal structures of **25** and **38** show that the NBC_8 skeletons are planar within experimental error. The B–N distances of 1.424(5) **25** and 1.428(5) Å **38** are comparable to analogous distances in borazines (e.g., 1.435 Å for $\text{B}_3\text{N}_3\text{H}_6$ in the gas phase). The longest distances in the ring skeletons are the B–C(3) bond lengths (1.524 and 1.540 Å). Nevertheless, these bond lengths are distinctly shorter than the B–C single bond distance for BMe_3 (1.578 Å) and thus indicate a considerable contribution from boron to the aromatic π -electron delocalization.



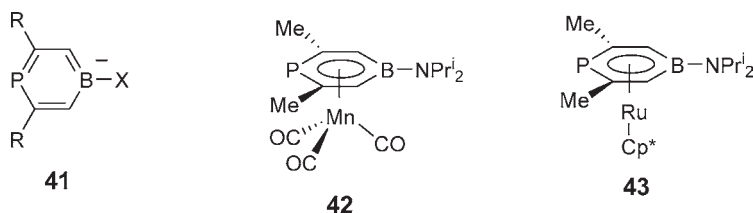


X = Cl (**16**), Br (**17**), Prⁱ (**18**), Bu^t (**19**), OMe (**20**), OBu^t (**21**), Me (**22**), (CH₂)₃NMe₂ (**23**), OH (**24**), Cl (**28**), N(SiMe₃)₂ (**29**), Me (**30**), Et (**31**), Prⁱ (**32**), Bu^t (**33**), CH₂SiMe₃ (**34**), Ph (**35**), Et (**37**), CH₂SiMe₃ (**38**)

Noteworthy are the observations that 1-phenyl-1,2-azaboratabenzene anion **39** is a heteroaromatic π -ligand with an adjustable basicity for nitrogen. It was shown that ¹H, ¹³C, and ¹¹B NMR chemical shift values for the 1,2-azaboratabenzene salt K–**39** are quite similar to those found for the boratabenzene salt Li–**14a**. The spectra of K–**39** and Li–**14a** exhibit high-field ¹¹B chemical shifts (δ 34.9 and 32.2 ppm, respectively) that are in agreement with the existence of a π -conjugated ring system. An X-ray analysis of the sandwich complex **40** synthesized in this study shows that the C₄BN ring is η^6 -coordinated to the Ru atom. As expected, the NMR signals for the C₄BN atoms are shifted upfield relative to those of K–**39**, supporting π -complexation of the metal to the heteroaromatic ring. Potentiometric titration of **40** in 80% CH₃OH/H₂O gave a p*K*_a of 9.21 ± 0.10. Thus, the basicity of **40** is comparable with that of 4-dimethylaminopyridine (DMAP; p*K*_a = 9.0) under the same conditions <2004OM5626>.

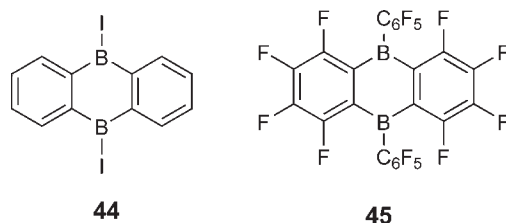


1,4-Phosphaboratabenzenes **41**, heteroaromatic compounds containing boron and phosphorus, have been known since 1983 <1983JOM33>. More recent results have extended their chemistry to late transition metal complexes, which closely resemble those of the related boratabenzene. In the Mn(CO)₃ complex **42**, the heterocycle is coordinated to the Mn(CO)₃ group in a piano-stool fashion. The boron and phosphorus atoms are displaced out of the BC₄P ring away from Mn by 0.335(4) and 0.061(3) Å, respectively, which gives the ligand a boat-like geometry. There is also a strong slip distortion away from boron so that the bonding of the metal to the ring approaches η^5 . The B–N distance (1.408(3) Å) is short and indicates strong B–N π -bonding. The molecular structure of the ruthenium complex **43** is that of a classical sandwich compound. Again, the boron is strongly displaced out of the plane of the four carbon atoms (0.284(3) Å), while phosphorus is only displaced by 0.052(3) Å. However, the B–N distance (1.443(2) Å) is longer in **43** than in **42**, indicating weaker B–N π -bonding <2003OM910>.

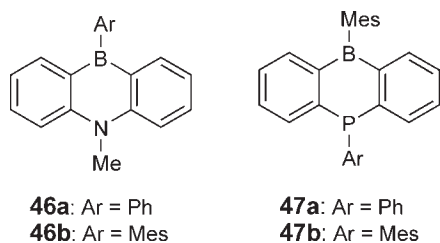


Further interesting examples of six-membered heteroaromatic systems including boron atoms are boranthracene derivatives, the basic structure of which consists of a 9,10-dihetero-substituted anthracene skeleton. The details of the structural analysis of such compounds are reported in a series of papers <1995ZNB1476, 1995SM1109,

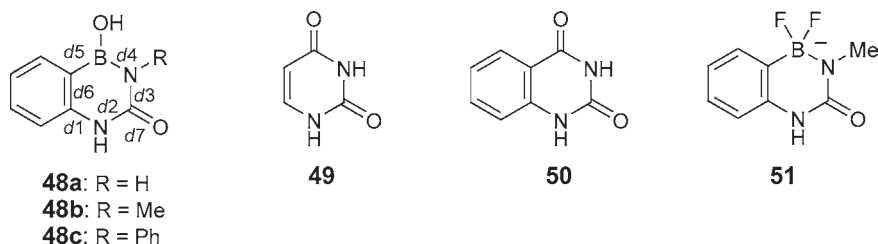
1996AXC991, 1998EJI761, 2002OM4159, 2005OL4373>. X-Ray structure determination and multinuclear NMR studies of **44** indicate that the π -conjugated system spreads over the whole molecule including the planar six-membered ring, which contains two boron atoms. This conclusion is supported by the observed B–C bond length of 1.518(13) Å, being significantly shorter than the B–C single bond lengths of 1.571(3)–1.589(5) Å, for BMe₃ or BPh₃. In the perfluorinated 9,10-diboraanthracene **45**, the C₁₂F₈B₂ core is also planar. However, the C₆F₅ rings are rotated 75° out of the plane, hindering π -communication between the pendant C₆F₅ substituents and the C₁₂F₈B₂ core. The results are consistent with the ¹⁹F NMR data, which reveal significant upfield displacements of the C₆F₅ *ortho*, *meta*, and *para* signals versus B(C₆F₅)₃, while the C₆F₄ signals are shifted downfield of those in B(C₆F₅)₃ <2002OM4159>. Interestingly, the 9,10-diboraanthracenes absorb in the visible spectrum (yellow) and exhibit their ¹¹B NMR signals shifted considerably upfield ($\delta < 70$), a situation attributable to a more shielded boron nucleus, than those of PhBEt₂ or *o*-(Et₂B)₂C₆H₄ ($\delta = 78$ –80). Thus, both the electronic and the ¹¹B NMR spectral data are consistent with the interaction of the 2p_z-orbital of boron with the adjacent π -clouds <1998EJI761>.



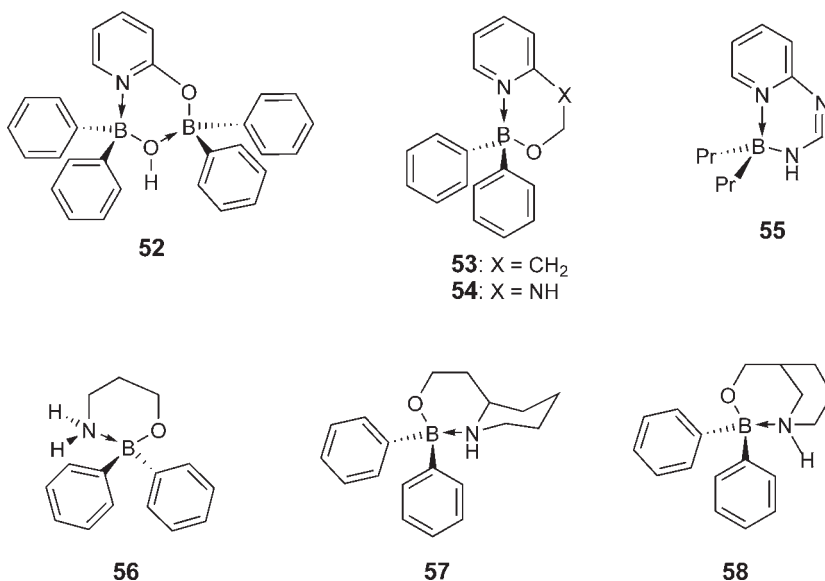
A structural comparison of the 9,10-azaboranthracenes **46** and 9,10-phosphaboranthracenes **47** has revealed weak delocalization of the phosphorus lone pair into the π -system. Unlike the azaborine ring, the phosphaborin ring of **47** deviates from planarity due to pyramidalization at the phosphorus atom. The sums of the bond angles around the phosphorus atom (307°) and the boron atom (360°) are similar to those of ordinary triarylphosphanes and triarylboranes. In the ³¹P NMR spectra, the signals for **47a** ($\delta_P = 13.3$) and **47b** ($\delta_P = 22.2$) were shifted upfield compared with those of the parent triarylphosphanes. The ultraviolet–visible (UV–Vis) spectra for **47** showed absorption maxima in the near-UV region ($\lambda_{\max}$ 368 nm for **47a**, 393 nm for **47b**). These absorptions are derived from intramolecular charge transfer as predicted by density functional calculations on model compounds <2005OL4373>.



The structures of several 1-hydroxy-1*H*-2,4,1-benzodiazaborin-3-ones **48a–c** were studied by ¹H, ¹³C, and ¹¹B NMR spectroscopy, mass spectrometry, and X-ray crystallographic analyses <1999JOC9566>. An X-ray diffraction study shows that the fused benzene ring and heterocyclic ring systems in **48b** and **48c** are essentially coplanar. The dihedral angle between the benzene ring and heterocyclic ring is 2.0(3)° and 3.7(6)° for **48b** and **48c**, respectively. The bond lengths of the urea moiety (*d*1, *d*2, *d*3, and *d*7) in the boracyclic system are comparable to the related bonds in uracil **49** and benzouracil **50** and are essentially identical to those observed for the tetracoordinated anion **51**. The C–B bond lengths, *d*5 (**48b**: 1.543(4) Å; **48c**: 1.531(3) Å) are slightly shorter than those observed for phenylboronic acid (1.565(3) Å) and tetracoordinated anion **51** (1.576(6) Å). The B–N bond lengths, *d*4 (**48b**: 1.451(3) Å; **48c**: 1.464(2) Å) are considerably shorter than the B–N single bond (1.57–1.63 Å). They are very close to those observed for borazines (1.44(2) Å) and (dimethylamino)dimethylborane (1.42(3) Å). This suggests a partial double bond character of the B–N bond in the benzoborauracils **48**. The sum of the bond angles around the B and the N atoms in both compounds **48b** and **48c** is exactly 360°, meeting the requirement of the sp² hybridization. The ¹¹N signal for the benzoborauracils **48a–c** was observed at ca. 30 ppm (referenced to Et₂O·BF₃) in agreement with the existence of an sp²-hybridized boron atom in the heterocyclic system. Thus, 1-hydroxy-1*H*-2,4,1-benzodiazaborin-3-ones **48** may be viewed as boron isosteres of naturally occurring pyrimidines.



A summary of the most important structural data for six-membered (N $\rightarrow$ B)-borinanes **52–58** has been presented recently by Höpfl *et al.* <1999KGS1041>. The N $\rightarrow$ B bond lengths in the BOBOCN heterocycle **52** (1.612(8) Å) and the BNCNCN heterocycle **55** (1.599(9) Å) are comparable, while the bonds are significantly longer in **53** (1.685(6) Å) and **54** (1.642(3) Å). A similar divergence has been determined for the primary and secondary 1,3-amino alcohol derivatives **56–58**, whose N $\rightarrow$ B bond lengths range from 1.638(3) to 1.674(5) Å. The covalent bond between the 2-pyridyloxy group and the second boron atom is shorter (1.532(7) Å) than the corresponding bond with the bridging hydroxyl group (1.558(8) Å), thus confirming its coordinative character.



9.19.4 Thermodynamic Aspects

Quantum structure–property relationships (QSPRs) have been determined to predict the melting point temperatures for 1,2,3-diazaborine compounds. Electronic and topological descriptors were computed from molecular structures and a QSPR model was generated by linear multiple regression using reported melting point temperatures as the dependent variable. The most accurate prediction results were obtained using the Levenberg–Marquardt neural network algorithm <2003JCI1513>.

Systematic conformational studies on 1,3,2-dioxaborinanes and 1,3,2-oxazaborinanes have been reported <2001MI494, 1999CHE928, 1999RJC403, 1997CHE1362>. Pseudorotation and barriers to inversion of 1,3,2-dioxaborinane rings have been studied theoretically employing empirical, semi-empirical, and nonempirical methods <2003CHE263>. According to ¹H NMR spectroscopic data, 2,4-disubstituted 1,3,2-dioxaborinanes exist in the preferred sofa conformation with equatorial alkyl groups at C-4 <1997CHE1362>. The potential energy surfaces for unsubstituted, as well as 2-, 5-, and 2,5-substituted, 1,3,2-dioxaborinanes revealed a global minimum corresponding to the sofa conformer, and also minima corresponding to half-chair and 1,4- and 2,5-twist forms <1999RJC403, 1999CHE935>. The conformational composition of *cis*- and *trans*-2-isobutyl-5-methyl-4-phenyl-1,3,2-dioxaborinane stereoisomers has been studied by ¹H NMR spectroscopy as well as by MM2 and AM1 calculations of the optimal geometry <2000MI692>. Analysis of conformational composition of tetra- and pentamethyl-substituted

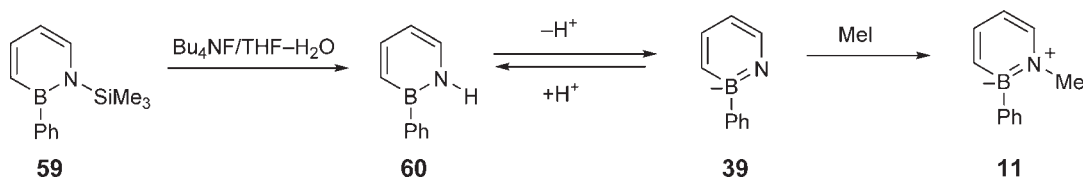
1,3,2-dioxa(oxaza)borinanes showed that the sofa and semi-chair conformers were highly populated, with the latter predominant <2000RJO285>. With the help of ^1H and ^{13}C NMR spectroscopy it was demonstrated that the formation of the stereoisomers of 2-alkyl-4,5-dimethyl-1,3,2-dioxa borinanes from 2-methyl-1,3-butanediol and acyclic boric acid esters occurs stereospecifically. This conclusion was confirmed by calculations of the relative energies of the *cis*- and *trans*-isomers of model 4,5-dimethyl-1,3,2-dioxaborinanes <1998CHE367>. The conformational equilibrium of 2,5-disubstituted 1,3,2-dioxaborinane molecules, including two sofa forms, is shifted toward the equatorial conformer. The values of ΔG° for a number of substituents on the C-5 ring atom have been established <2003CHE379>. 4-Methyl-2,5-disubstituted 1,3,2-dioxaborinanes are conformationally inhomogeneous due to the internal rotation of the substituent at the C-5 atom <2002RJC400>. The conformational composition for stereoisomers of 2-alkyl-5-isopropyl-4-methyl-1,3,2-dioxaborinanes was studied by ^1H and ^{13}C NMR spectroscopy and MM+ and AM1 calculations. The results indicate high conformational flexibility of the *cis*- and *trans*-forms, which exist in an equilibrium mixture of sofa and half-chair conformers <2002CHE1283>.

9.19.5 Reactivity of Fully Conjugated Rings

There has been very little study of the reactivity of fully π -conjugated six-membered rings containing boron. The known reactions of such heterocycles include protonation, alkylation, and complexation with transition metal derivatives.

9.19.5.1 Protonation and Alkylation Reactions

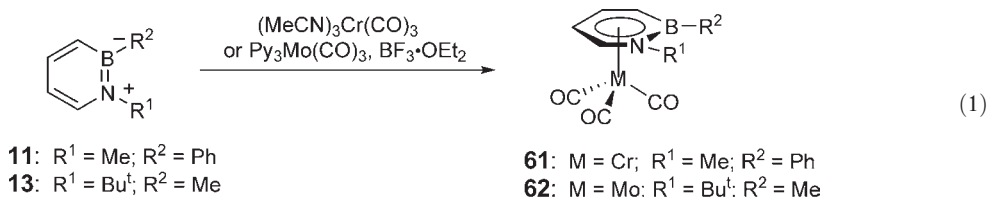
The heteroaromatic 1-phenyl-1,2-azaboratabenzene anion **39** is formed easily by deprotonation of its conjugate acid, 1,2-dihydro-1,2-azaborine **60**. Treatment of **60** with potassium bis(trimethylsilyl)amide in toluene gave 1,2-azaboratabenzene derivative K-**39**, which could be isolated as a white powder. Deprotonation of **60** is reversible in either tetrahydrofuran (THF) or dimethyl sulfoxide (DMSO). Bracketing experiments in DMSO indicate that the acidity of **60** is comparable with pentamethylcyclopentadiene ($\text{p}K_a \sim 26$). Quenching the solution of K-**39** with excess methyl iodide afforded the *N*-methyl derivative **11** (Scheme 1) <2004OM5626>.



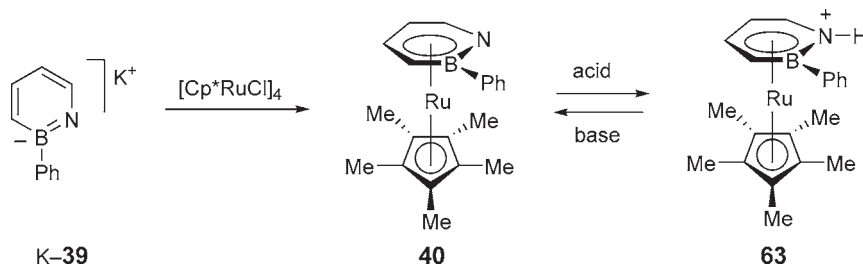
Scheme 1

9.19.5.2 Complexation with Transition Metal Derivatives

The reaction of 1,2-dihydro-1,2-azaborine **11** with $(\text{MeCN})_3\text{Cr}(\text{CO})_3$ affords tricarbonyl chromium complex **61**, while the reaction of **13** with $\text{Py}_3\text{Mo}(\text{CO})_3$ and $\text{BF}_3 \cdot \text{OEt}_2$ affords molybdenum complex **62** (Equation 1). X-Ray structures of **61** and **62** show that the metals are η^6 -bound to the 1,2-dihydro-1,2-azaborine rings <2001OM5413>.

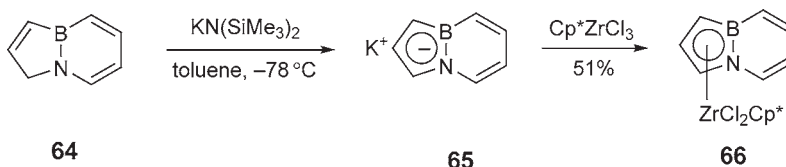


1,2-Azaboratabenzene salt K-**39** reacts with $[\text{Cp}^*\text{RuCl}]_4$ to form the π -coordinated Ru(II) complex **40**. Addition of 1 equiv of HOAc to the THF solution of **40** affords salt **63** (Scheme 2) <2004OM5626>.



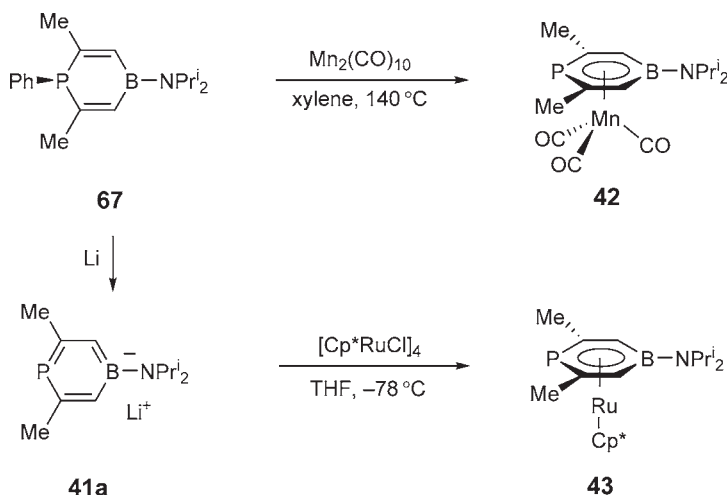
Scheme 2

It has proved possible also to obtain 3*a*,7*a*-azaborindenyl zirconium complex **66** starting from the diheteroaromatic 3*a*,7*a*-azaborindenyl salt **65** and Cp^*ZrCl_3 (Scheme 3). The sequential reaction of the azaborindene **64** with $\text{KN}(\text{SiMe}_3)_2$ and Cp^*ZrCl_3 in toluene affords complex **66**. The molecular structure of the latter closely resembles that of $\text{Cp}^*(\text{Ind})\text{ZrCl}_2$. The C_3BN portion of the azaborindenyl unit is η^5 -bound to Zr, while the carbocyclic portion of the C_4BN ring is not coordinated. The C_3BN ring is completely planar but is unsymmetrically bound to Zr. The $\text{C}(1)\text{C}(2)\text{C}(3)$ unit is closer to Zr (2.47–2.50 Å) than are the bridgehead B (2.713 Å) and N (2.612 Å) <2002OM4578>.



Scheme 3

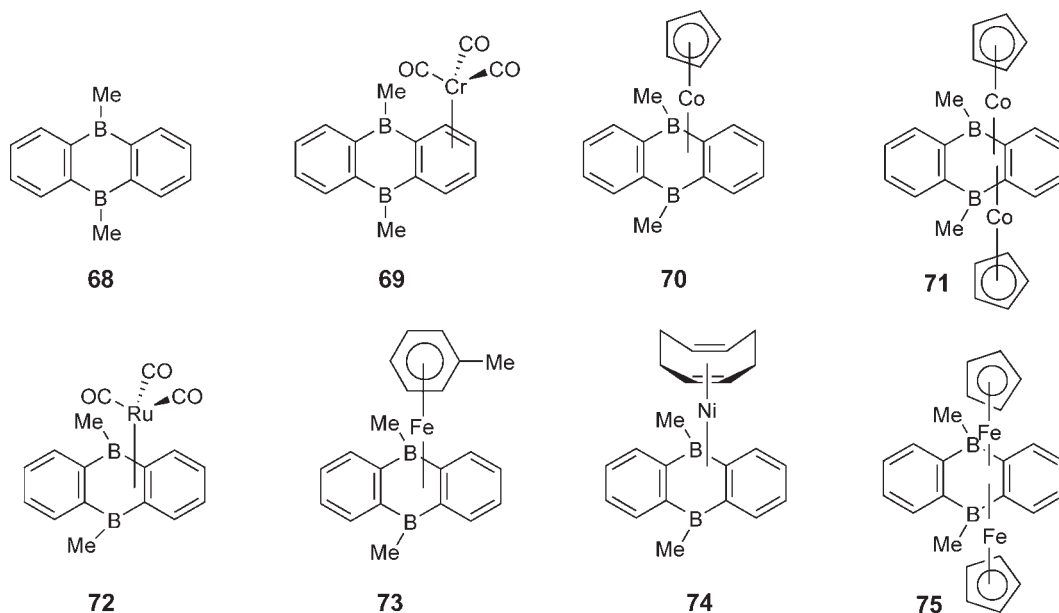
The first successful attempt to prepare phosphoratabenzene–transition metal complexes is shown in Scheme 4. The *P*-phenyl group of 1,4-dihydro-1-phenyl-1,4-phosphaborin **67** is easily cleaved. Thus, treatment of **67** with $\text{Mn}_2(\text{CO})_{10}$ in xylene at 140°C gave the $\text{Mn}(\text{CO})_3$ complex **42** in 71% yield. Further, the reaction of stabilized anion **41a**, generated from **67** and lithium powder in ether, with $[\text{Cp}^*\text{RuCl}_4]$ gave a good yield of the $\text{Cp}^*\text{Ru}^{\text{II}}$ complex **43** <2003OM910>.



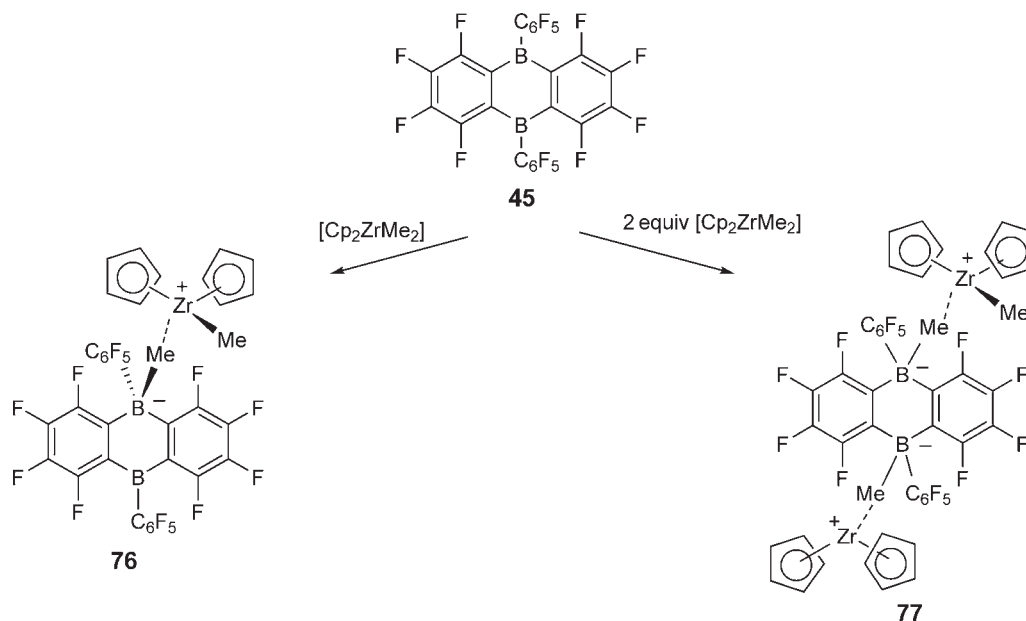
Scheme 4

Various complexation reactions of 9,10-dihydro-9,10-dimethyl-9,10-diboraanthracene **68** have been described <1995JOM235>. With $(\text{CO})_3\text{Cr}(\text{MeCN})_3$, complexation takes place at the carbocyclic moiety of **68** to give **69**.

Neither reduction nor carbonylation of **69** at CO pressure results in a migration of the chromium carbonyl group toward the heterocyclic part of **69**. The reaction of **68** with an excess of $[\text{CoCp}(\text{C}_2\text{H}_4)_2]$ yields the sandwich complex **70** and the paramagnetic triple decker complex **71**. Reactions with the isolobal metal complex fragments $\text{Ru}(\text{CO})_3$, $\text{Fe}(\text{C}_7\text{H}_8)$, and $\text{Ni}(\text{C}_8\text{H}_{12})$ yield the complexes **72**, **73**, and **74**. Two equivalents of $[\text{FeCp}(\text{C}_8\text{H}_{12})]$ and **68** yield the diamagnetic complex **75**. In addition, other mono- and polynuclear complexes of **68** have been reported [<1996JOM41, 2004JOM429>](#).



Perfluorodiboraanthracene **45** was shown to be a potent Lewis acid which is able to abstract alkide groups (e.g., CH_3^-) from organotransition metal complexes, forming highly reactive cationic complexes [<2000AGE1312, 1999AGE3695>](#). For example, reaction of **45** with $[\text{Cp}_2\text{ZrMe}_2]$ in a 1:1 molar ratio proceeds with instantaneous methyl anion abstraction to generate the stable ion pair **76**. Addition of 2 equiv of $[\text{Cp}_2\text{ZrMe}_2]$ to a solution of compound **45** results in the formation of symmetrical bis-borate **77** (Scheme 5).



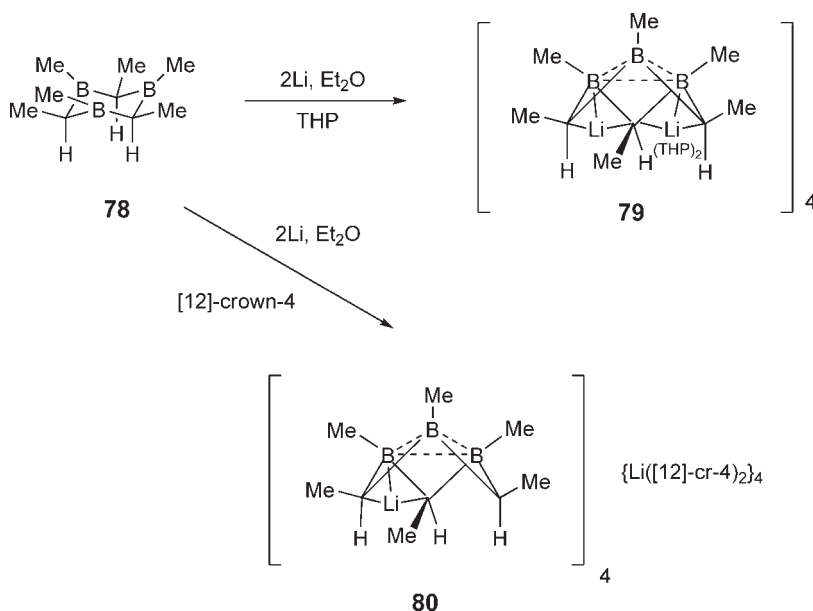
Scheme 5

9.19.6 Reactivity of Nonconjugated Rings

The body of information related to the reactivity of nonconjugated six-membered polyheteroatom boracycles is rather limited. A few typical reactions of 1,2-azaborines, 1,3,2-oxazaborinanes, and 1,3,2-dioxaborinanes were discussed in CHEC-II(1996) <1996CHEC-II(6)1155>. They involve, for example, insertion of isocyanates into the B–N bond of benzoxazaborinones, the ZnCl_2 -catalyzed conversions of 1,3,2-dioxaborinanes to 1,3-dioxanes, and the reductive conversion of 1,3,2-dithiaborinanes to 1,3-dithianes through a tin(II)-mediated process. Herein, some more recent examples of the reactivity of nonconjugated boracycles are presented.

9.19.6.1 Boracycles with the C–B–C Linkage

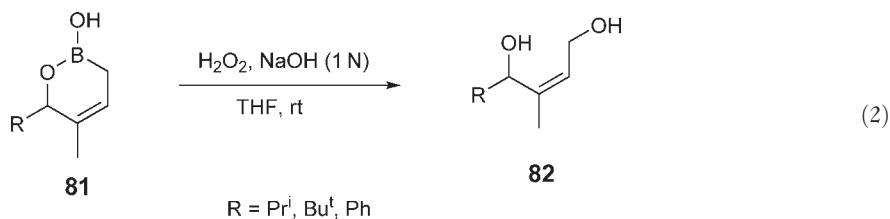
1,3,5-Triboracyclohexane **78** reacts with Li powder in ether in the presence of tetrahydropyran (THP) or 12-crown-4 to give tetrameric aggregates of cyclotriborate compounds **79** and **80** (Scheme 6) <2000AGE1276>. Two electrons are added to the combination of p-orbitals at the B centers forming trishomoaromatic dianions. The ^{11}B NMR signals of the products were at extremely high field ($\delta = -29.2$) and indicated multiple connectivity at the boron atoms. To study the reaction with other alkali metals, **78** was reduced with sodium, potassium, rubidium, and cesium. X-Ray structure analyses show a variety of arrangements, depending on the alkali metal. The various dianions show characteristic NMR chemical shifts in the high-field region, but do not obey a monotonous order with counterions Li^+ to Cs^+ <2001EJI1949>.

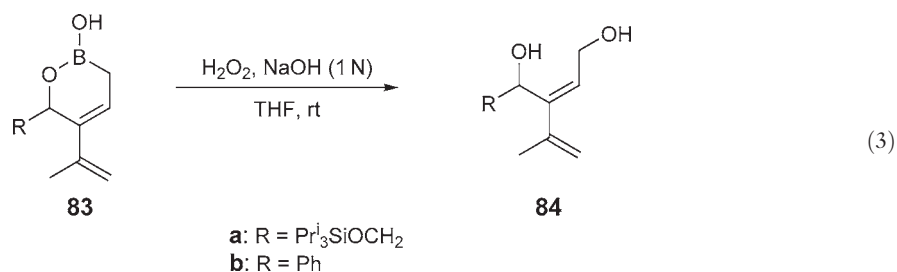


Scheme 6

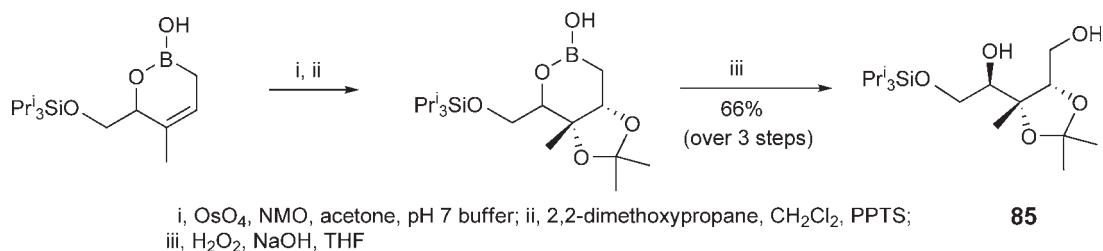
9.19.6.2 Boracycles with the C–B–X Linkage

The cyclic allylboronic acids **81** provided the trisubstituted (Z)-olefins **82** when treated with alkaline hydrogen peroxide (Equation 2). If, instead of boracycles **81**, the cyclic dienylic boronic acids **83** are used in the previous reaction, the stereodefined, trisubstituted dienylic carbinols **84** are formed (Equation 3) <2002AGE152>.



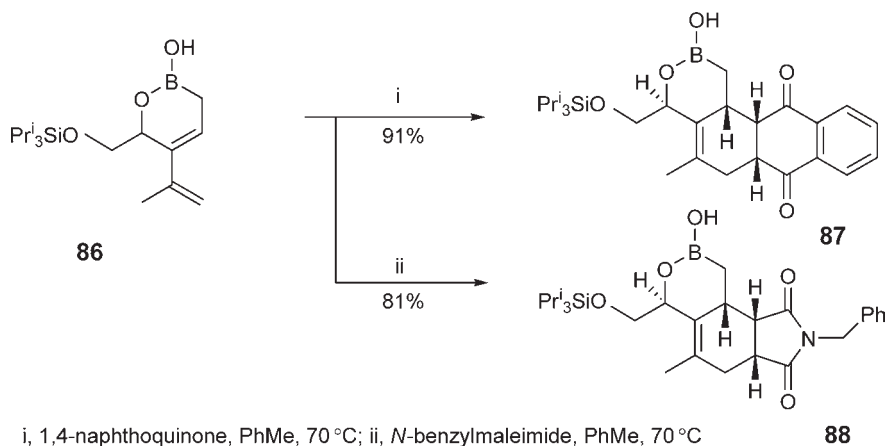


The cyclic allylboronic acids are excellent substrates also for diastereoselective dihydroxylation. [Scheme 7](#) demonstrates the utility of this reaction in preparing functionalized xylitol derivative **85** with >20:1 diastereoselectivity [\(<2002AGE152>](#).



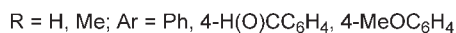
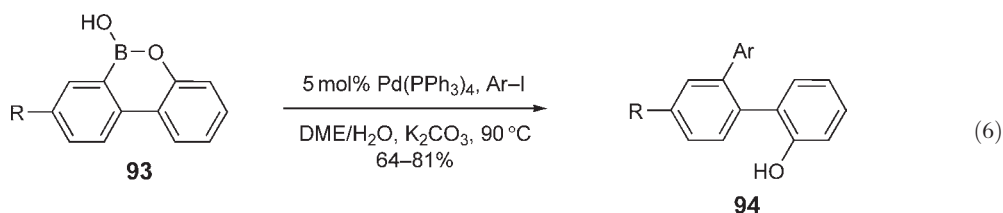
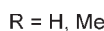
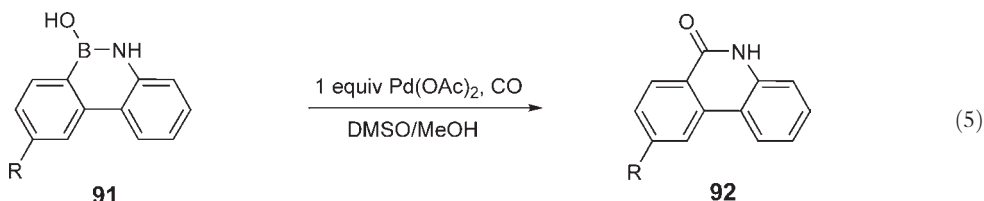
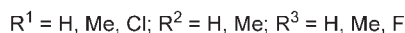
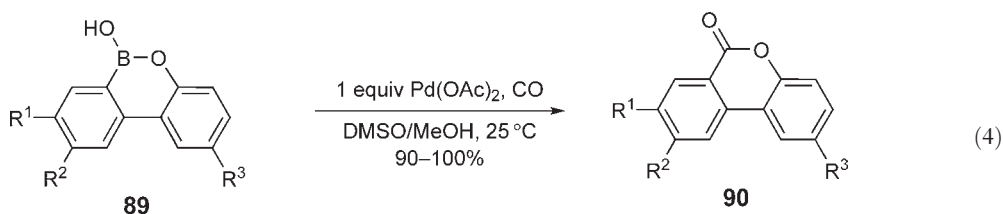
Scheme 7

Diels–Alder cycloaddition of the dienyl boronic acid **86** provided stereoselective access to the tetracyclic and tricyclic heterocycles **87** (de ≥ 13:1) and **88** (de ≥ 20:1) ([Scheme 8](#)) [\(<2002AGE152>](#).

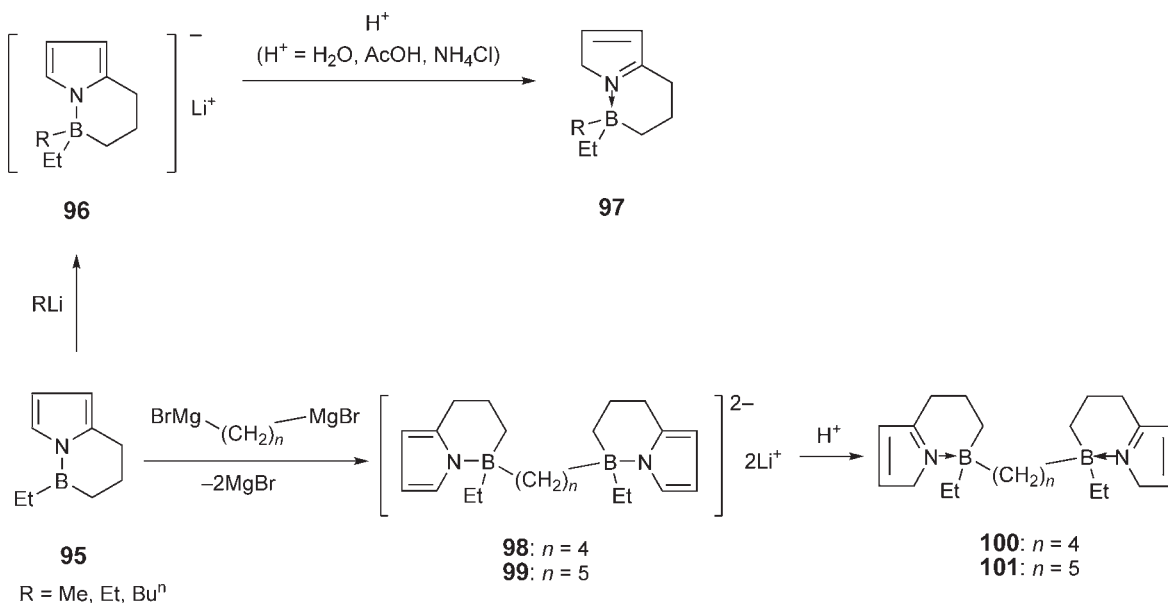


Scheme 8

10-Hydroxy-10,9-boroxaphenanthrenes **89** undergo Pd-catalyzed carbonylation readily to give the 3,4-benzocoumarins **90**. When 1 equiv of Pd(OAc)₂ was used, the reaction was essentially complete within 2–4 h, affording products **90** in excellent yields and with high regioselectivity ([Equation 4](#)). Considerable generality has been found in this approach and the related lactams **92** have been obtained through appropriate substrate modifications ([Equation 5](#)). The same authors have shown that the Pd-catalyzed Suzuki coupling of boroxaphenanthrenes **93** with aryl iodides also occurs under mild conditions and gives triaryls **94** in good yields ([Equation 6](#)) [\(<2004JOC5147>](#).

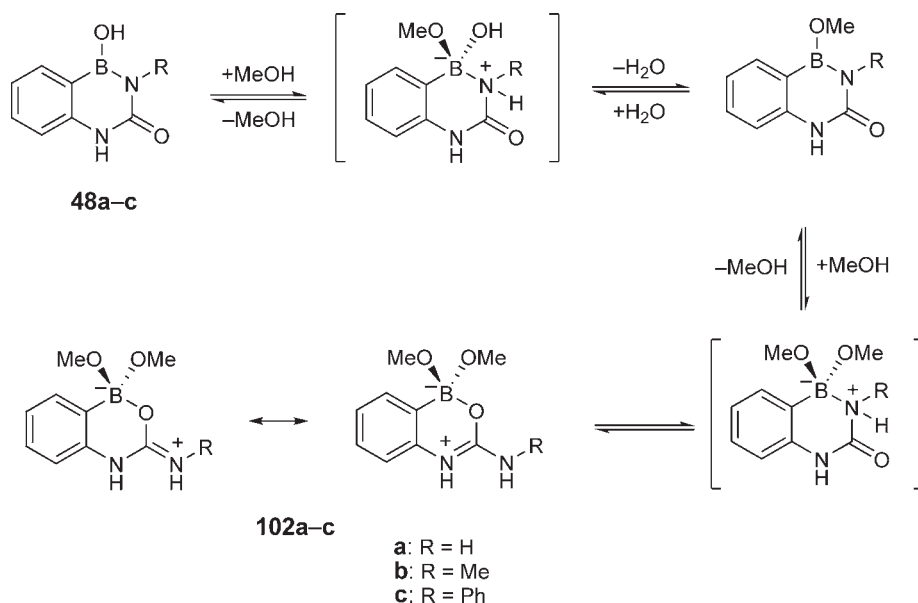


Some aspects of the reactivity of bicyclic *B*-alkyl-*N*-pyrrolylboranes have been reported <1997JOM297>. Reaction of **95** with alkyllithium reagents affords *N*-pyrrolylborates **96**, which can be protonated to give the 2*H*-pyrrole-borane adducts **97**. Compound **95** reacts also with 1,4-di(bromomagnesium)butane or 1,6-di(bromomagnesium)hexane to give the coupled borates **98** and **99** as mixtures of diastereomers, and these can be protonated also to give the corresponding 2*H*-pyrrole-borane adducts **100** and **101** (Scheme 9).

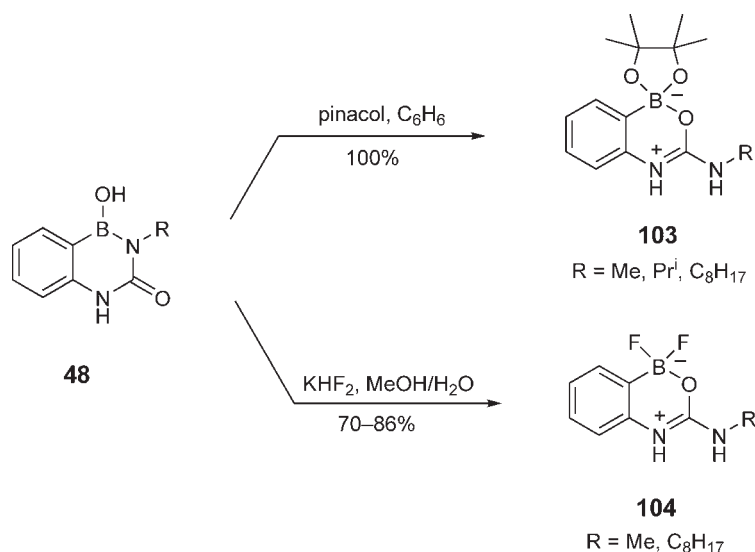


Scheme 9

^{11}B NMR spectral analysis of the methanolic solutions of benzo-fused boron-containing heterocycles (benzoborauracils) **48** confirmed the formation of the corresponding bis-methanol adducts **102** (Scheme 10). The equilibrium is dependent upon the solvent systems used and the substituent at the nitrogen atom. In $\text{MeOH-}d_4$ solution, the methyl-substituted benzoborauracil **48b** contains 85% of the bis-methanol adduct **102b**, whereas the unsubstituted analog **48a** forms only 30% of the adduct **102a**. Phenyl-substituted benzoborauracil **48c** is completely converted to the bis-methanol adduct **102c** in $\text{DMSO-}d_6/\text{MeOH}$ (1:1) solution <1999JOC9566>. On interaction with pinacol the benzoborauracils **48** gave the zwitterionic heterocycles **103**, whereas treatment of **48** with KHF_2 gave the difluoro analogs **104** (Scheme 11) <1997JOC4492>.



Scheme 10

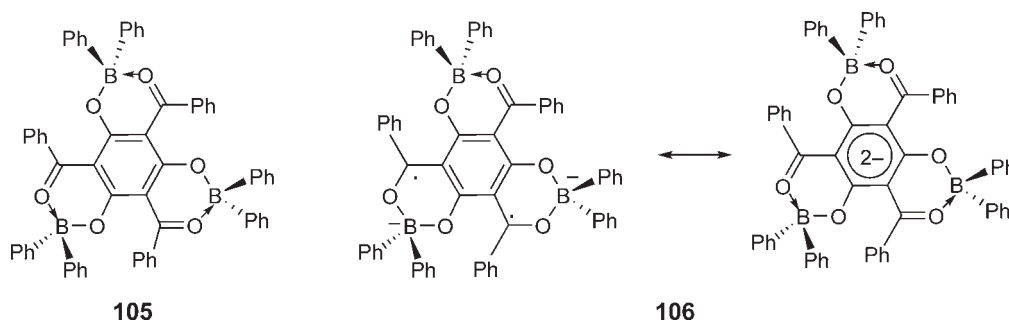


Scheme 11

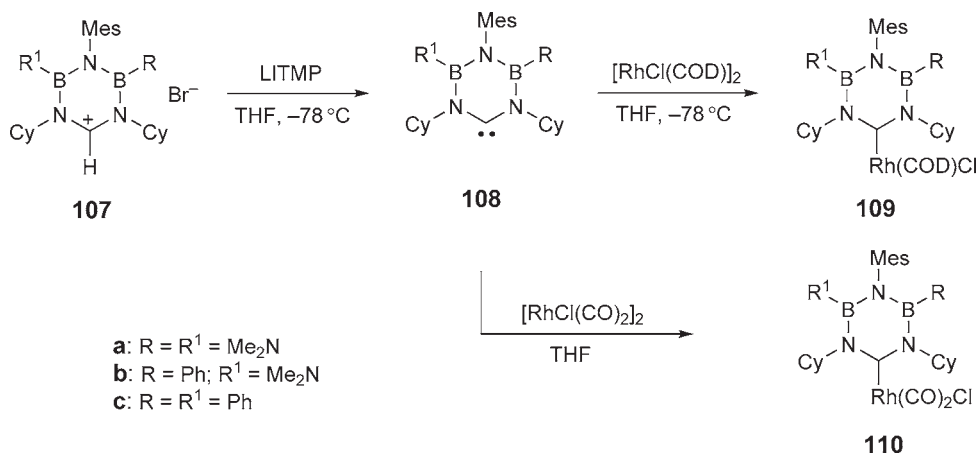
9.19.6.3 Boracycles with the Y–B–X Linkage

Broad overviews of the chemical properties of 1,3,2-dioxa-, 1,3,2-oxaza-, and 1,3,2-diazaborinanes covering the literature up to 1995 have been presented in CHEC(1984) <1984CHEC(1)629> and CHEC-II(1996) <1996CHEC-II(6)1155>. The title compounds have been demonstrated to be suitable protective groups for 1,3-diols, useful intermediates for orchestrating Diels–Alder cycloadditions, and the ligands of choice for the generation of α -boryl carbanions and transmetalation reactions including B/Hg exchange. Additionally, the Suzuki–Miyaura coupling of boronic acid derivatives, including 1,3,2-dioxaborinanes, to acyl and vinylic halides provides a very useful method for the construction of C–C bonds. In the last decade, the chemistry of 1,3,2-dioxaborinanes and related compounds continues to be an active area. The stereochemical features of reactions of 1,3,2-dioxaborinanes with aldehydes leading to 1,3-dioxanes have received further study <2001CHE131, 2001RJO1359>. Interest has continued in the chemistry of 1,3,2-dioxaborinanes bearing exocyclic phosphine fragments <1999RJC413, 1995ZOB1979>. Properties of compounds containing a P–C–O–B fragment, for example, 1,3,2,5-dioxaboraphosphorinanes, have been studied <1997RJC349>. Also, the reaction between 4,5-dimethyl-1,3,2-dioxathian-2-oxide and diisobutyl isobutylborate yielding 2-isobutyl-4,5-dimethyl-1,3,2-dioxaborinane and diisobutyl sulfite has been investigated <2000RJO292>. A simple synthesis of 2-(1-trimethylgermyl-1-alkyl)- and 2-(1-trimethylgermyl-1-alkenyl)-1,3,2-dioxaborinanes, and their selective oxidation, has been described <2005TL5647>.

In order to obtain insight into the stability of the anion radical of borane chelates, Okada and co-workers examined the reduction of the 2,4,6-tribenzoyl-1,3,5-tris(diphenylboryloxy)benzene **105** <1998TL6483>. Treatment of **105** with an Na–K alloy in THF produced the dianionic species **106** whose ground state was shown to be a triplet.



Derivatives **107** are prone to form remarkably stable six- π -electron, six-membered N-heterocyclic carbenes. Treatment of **107** with lithium 2,2,6,6-tetramethylpiperide in THF solution at -78°C cleanly gives carbenes **108** which react with 0.5 equiv of bis(μ -chlorocyclooctadienyl)rhodium to give complexes **109**. The corresponding complexes **110** were prepared by the addition of carbenes **108** to 0.5 equiv of bis(μ -chlorodicarbonyl)rhodium (Scheme 12). A single crystal X-ray study of **108c** and **109c** reveals, in both cases, the planar six-membered ring



Scheme 12

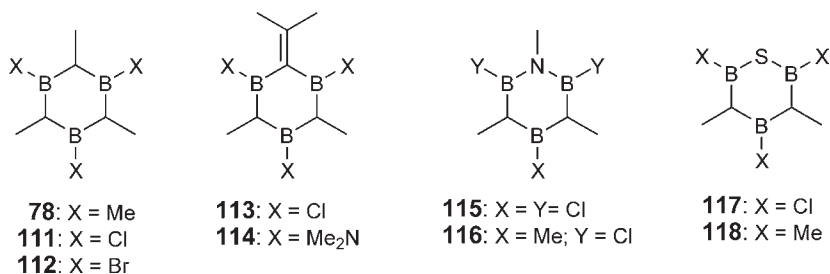
skeleton with a propeller-like arrangement of substituents <2005JA10182>. A similar approach to a stable five-membered N-heterocyclic carbene with a B₂-backbone was described earlier by Roesler and co-workers <2005JA4142>.

9.19.7 Reactivity of Substituents Attached to Ring Carbon Atoms

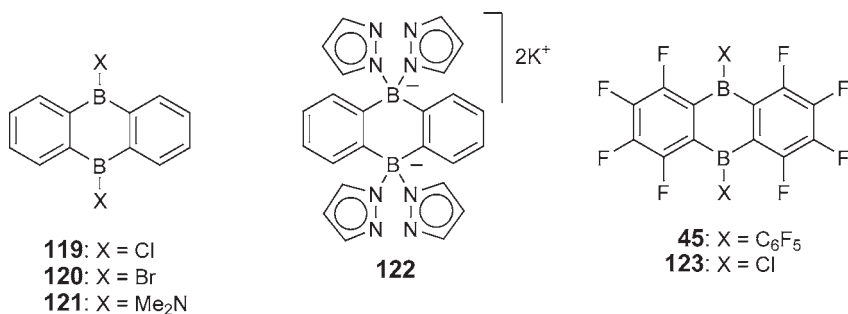
To our knowledge, no systematic studies concerning this area have appeared in the literature.

9.19.8 Reactivity of Substituents Attached to Ring Heteroatoms

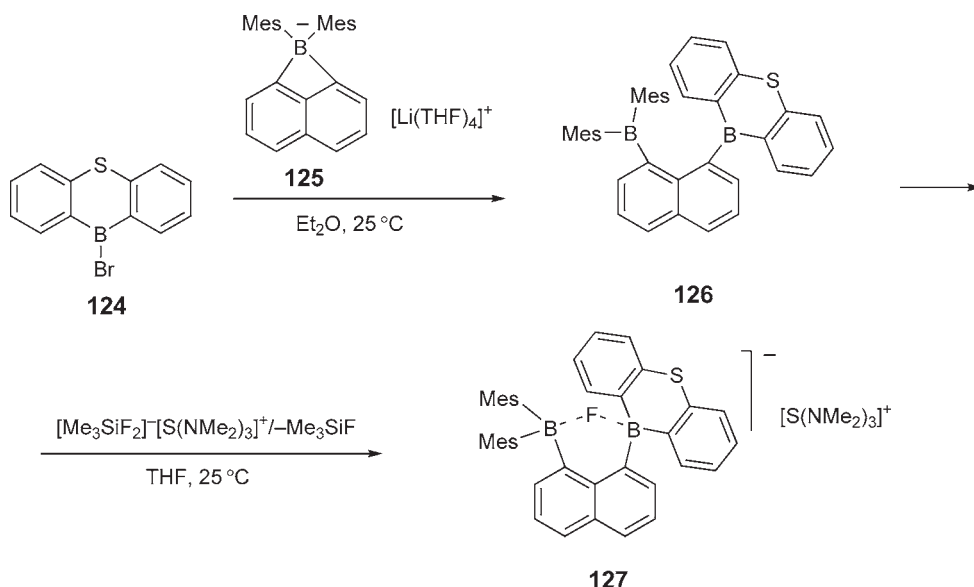
The original synthesis of 1,3,5-tribromo-1,3,5-triboracyclohexane **112** involves the reaction of 1,3,5-trichloro-1,3,5-triboracyclohexane **111** with BBr₃ <2004ZNB782>. Methylation of **111** with AlMe₃ affords 1,3,5-trimethyl-1,3,5-triboracyclohexane **78**. The amino derivative **114** was formed from **113** and 3 equiv of Me₂NSiMe₃ in hexane with elimination of chlorotrimethylsilane <1997ZNB823>. The boron–nitrogen heterocycle **115** could be monomethylated with MeLi in the 4-position to give **116**. The other B–Cl bonds remained unreactive toward methylation even when higher temperatures and other methylation reagents (AlMe₃, SnMe₄) were applied. In contrast to the N-heterocycle **115**, reaction of the boron–sulfur heterocycle **117** with Me₄Sn leads to compound **118** <1997ZNB823>.



Alkyl, aryl, and amino derivatives of the tricyclic system 9,10-dihydro-9,10-diboraanthracene were synthesized by the reactions of dichlorodiboraanthracene **119** with 2 equiv of a suitable nucleophile. The same type of reactivity was observed with dibromodiboraanthracene **120**. For example, treatment of the dibromo derivative **120** with Me₂NSiMe₃ affords the aminoborane **121**, which in turn reacts readily with 2 equiv of Kpz (pz = pyrazolyl) and 2 equiv of Hpz in toluene to give the discorpionate ligand **122** <2004OM2107>. The 9,10-boraanthracene compound **123** has been converted smoothly into the perfluorophenyl-substituted analog **45** by the use of Zn(C₆F₅)₂ as a C₆F₅-transfer agent <1998CJC513>.

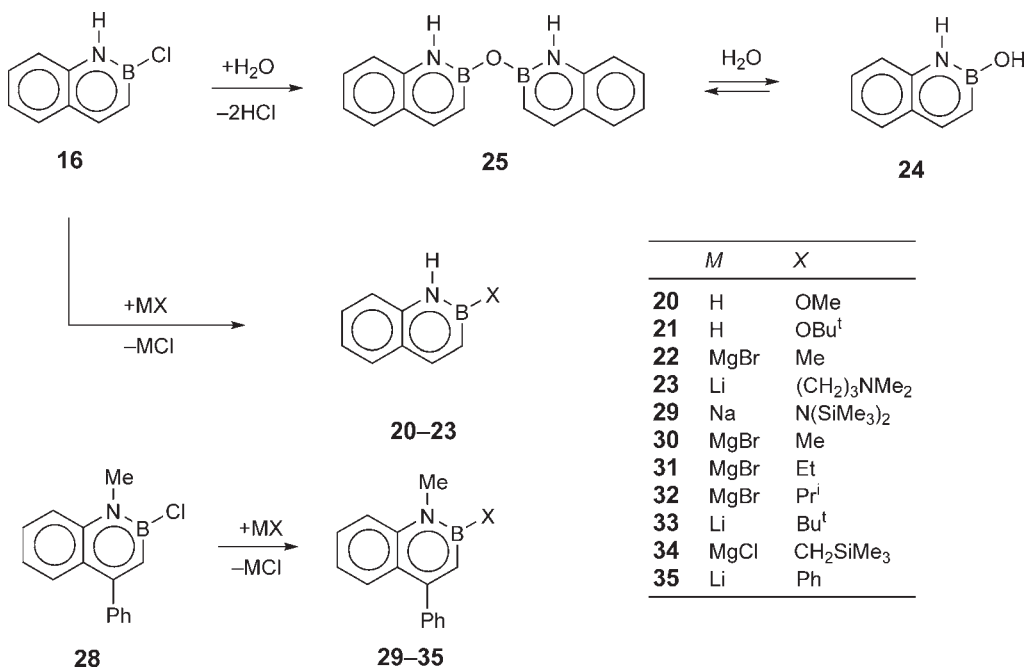


Reaction of 10-bromo-9-thia-10-boraanthracene **124** with dimesityl-1,8-naphthalenediylborate **125** provides a facile route to the bright yellow bidentate diborane **126** (Scheme 13). The ¹H NMR spectrum of **126** indicates the existence of a rigid structure since four aryl protons and six distinct methyl groups are observed for the mesityl substituents. Treatment of **126** with [Me₃SiF₂][−] [S(NMe₂)₃]⁺ gave the anionic chelate complex **127**. As confirmed by single crystal X-ray analysis, the fluorine atom is bound to both boron centers via B–F bonds of comparable lengths (F–B(1) 1.633(5), F–B(2) 1.585(5) Å) <2004CC1284>.



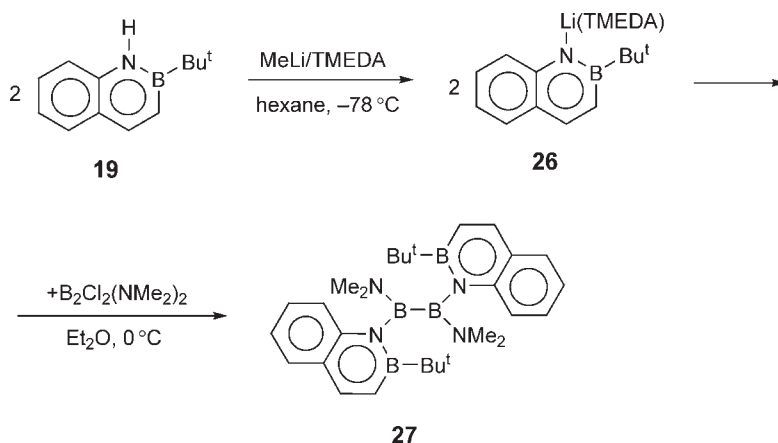
Scheme 13

The boron-bound chloro ligand in 1-azonia-2-boratanaphthalene **16** can also be replaced by anionic ligands. The hydrolysis of **16** with aqueous THF gives an equilibrium mixture of the bis(azoniaboratanaphthyl) oxide **25** and the 2-hydroxy derivative **24**. With alcohols, Grignard reagents, and organolithium compounds, reactions of **16** give the corresponding 2-alkoxy- and 2-alkyl-1-azonia-2-boratanaphthalenes **20–23**. The replacement of Cl in **28** by the bis(trimethylsilyl)amino group, alkyl groups, and the phenyl group gave access to compounds **29–35** (Scheme 14) <2004ZFA2632>.



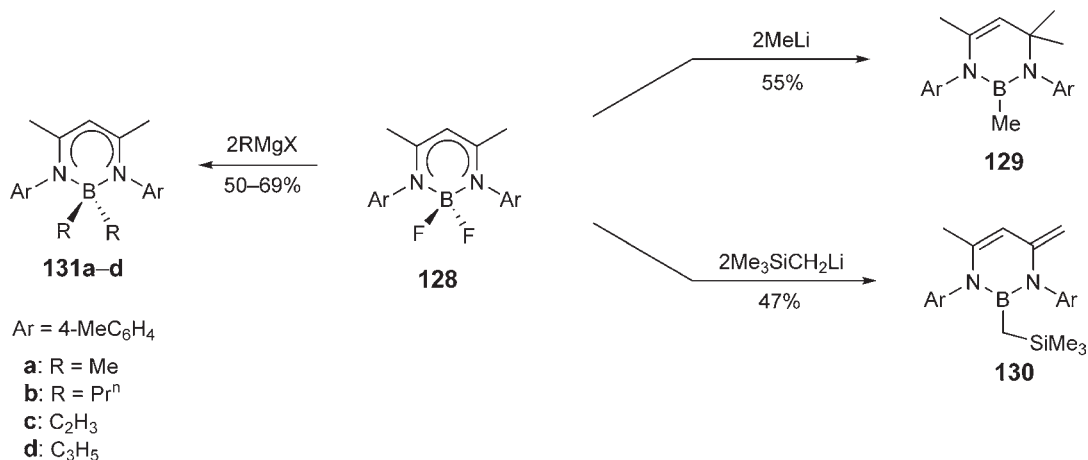
Scheme 14

The nitrogen atom of azoniaboratanaphthalenes can be lithiated when the boron atom is protected by an alkyl group. Thus, lithiation of the *B-tert*-butyl derivative **19** with MeLi in the presence of tetramethylethylenediamine (TMEDA) produces *N*-lithio derivative **26**, which reacts with the diborane Cl-B(NMe₂)-B(NMe₂)-Cl to give the corresponding 1,2-bis(azoniaborata-1-naphthyl)diborane **27** (Scheme 15) <2004ZFA2632>.

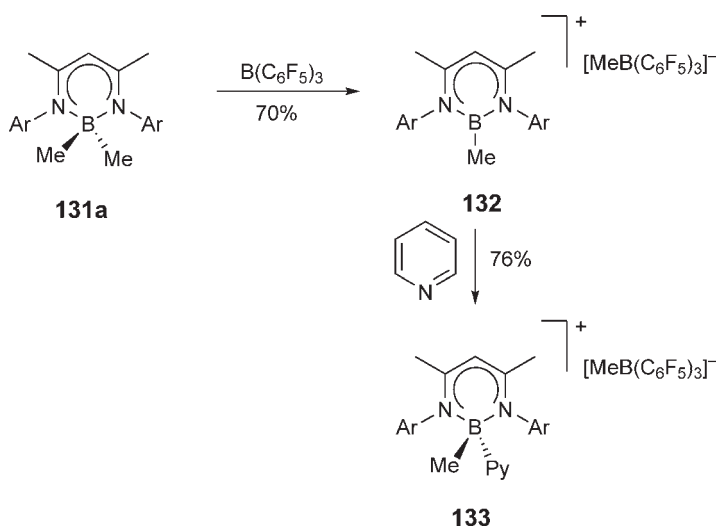


Scheme 15

In the reaction of β -diketiminato boron(III) difluoride complex **128** with alkyllithium or Grignard reagents the products depend on the nature of the organometallic compound. Thus, for example, when **128** was treated with 2 equiv of MeLi in ether, the desired dimethyl boron derivative could not be detected in the crude reaction mixture. Instead the heterocycle **129** was isolated in 61% yield. The reaction formally involves alkylation at boron followed by nucleophilic addition to the imine carbon and subsequent LiF elimination. For Me₃SiCH₂Li, deprotonation of the diketiminato ligand afforded the compound **130**. However, when compound **128** was treated with 2 equiv of alkyl Grignard reagent in ether, the dialkyl products **131** were isolated (Scheme 16) <1999POL2405>. In an effort to generate a cationic boron center, the reactivity of **131a** toward B(C₆F₅)₃ was also investigated. Interaction of these compounds leads to the ionic product **132**, which adds pyridine to form the stable adduct **133** (Scheme 17). The molar conductivity for a CH₂Cl₂ solution of compound **132** was similar to that for [Bu₄N]⁺Br⁻ <1999POL2405>.

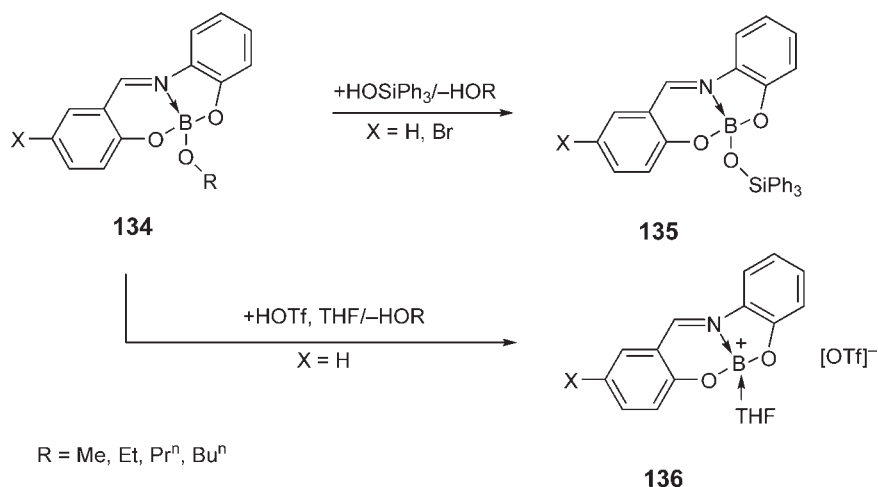


Scheme 16



Scheme 17

A specific example of the process, useful for the synthesis of boracycles containing a single B-O-Si linkage, is shown in [Scheme 18](#). The RO/Ph₃SiO exchange was performed for the chelated borates **134**. Strong acids such as HOTf and HOTs can be used to remove an alkoxide from a suitable boron-containing starting material. For example, the reaction of **134** with HOTf leads to the charged species **136** [<1998IC4934>](#).



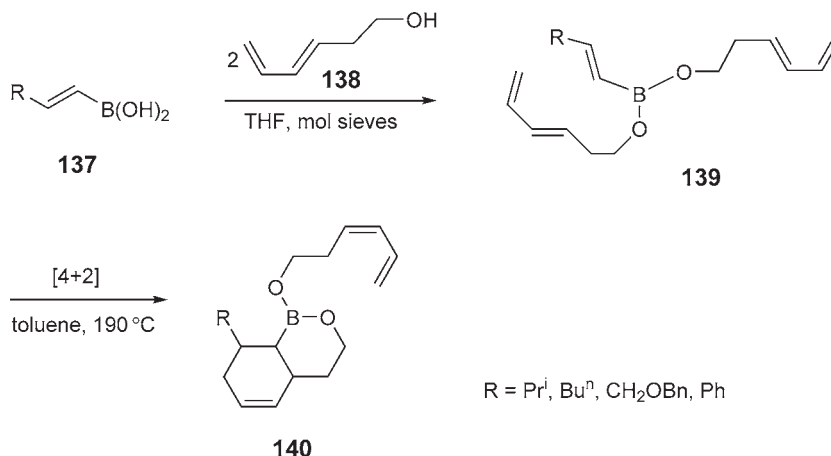
Scheme 18

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

Due to the great number of ring systems covered in this chapter, few of the methods employed in their preparation can be discussed in detail. Some of the new syntheses will be described briefly and [Tables 4 and 5](#) provide more comprehensive references, which should be consulted for further information.

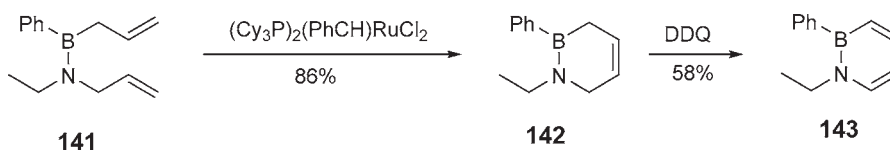
9.19.9.1 One-Component Synthesis

A boron-tethered (C–B–O) intramolecular Diels–Alder (IMDA) approach has been used to prepare cyclic alkenyl boronic esters **140** (Scheme 19). Thus, reaction of 2 equiv of the dienyl alcohol **138** with **137** in THF, in the presence of molecular sieves, provides the corresponding IMDA precursors **139**. The IMDS reaction was then accomplished at 190 °C in a toluene solution, with 5 mol% of 2,6-di-*tert*-butyl-4-methylphenol as a free radical inhibitor. Transformation of the carbon–boron bond in **140**, using standard organoborane reactions, can then afford a variety of functionalized cyclohexene derivatives <1999JA450>.



Scheme 19

The ring-closing metathesis (RCM) process has been applied recently to organoboron heterocycles. Upon treatment of aminoborane **141** with 5 mol% of Grubbs catalyst in CH₂Cl₂ at 25 °C for 10 h, cyclization occurred smoothly to give the ring-closed product **142** in 86% yield. Reaction of **142** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in pentane gave azaborine **143** in 58% yield (Scheme 20) <2000OL2089>.



Scheme 20

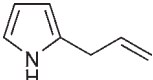
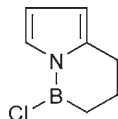
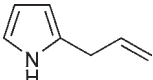
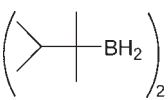
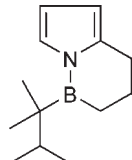
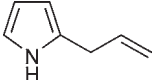
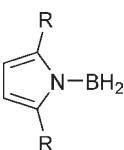
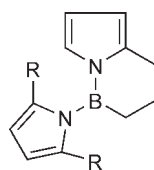
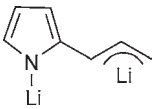
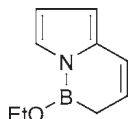
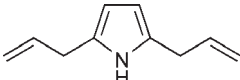
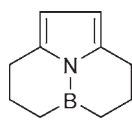
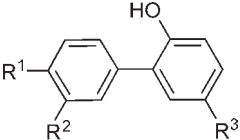
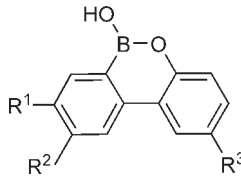
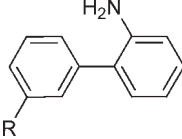
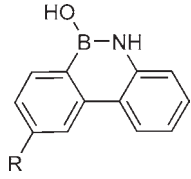
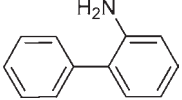
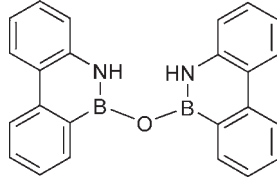
9.19.9.2 [5+1] Two-Component Synthesis

The main methods available to prepare six-membered boracycles containing C–B–X and Y–B–X linkages are of this type and were covered in CHEC-II(1996) <1996CHEC-II(6)1155>. However, many new examples of such syntheses have been described and these are summarized in Table 4.

9.19.9.3 [4+2] Two-Component Synthesis

These reactions provide convenient routes to six-membered boracycles containing C–B–X, B–B–X, and B–C–C–B linkages (Table 5).

Table 4 Two-component synthesis of polyheteroatom six-membered boracycles from 5+1 atom fragments

Entry	Substrate	Boron reagent	Boracycle	Reference
1		$\text{BH}_2\text{Cl} \cdot \text{Et}_2\text{O}$		1997JOM181
2				1997JOM181
3				1997JOM181
4		$\text{B}(\text{OEt})_3$, then Me_3SiCl		1997JOM71
5		$\text{Et}_2\text{BH}/\text{Et}_3\text{B}$		1998JOM247
6		$\text{BCl}_3/\text{AlCl}_3$		2004JOC5147
7		$\text{BCl}_3/\text{AlCl}_3$		2004JOC5147
8		$\text{BCl}_3/\text{AlCl}_3$		1997T8599

(Continued)

Table 4 (Continued)

Entry	Substrate	Boron reagent	Boracycle	Reference
9		$\text{BCl}_3/\text{AlCl}_3$		2001J(P2)2166
10		BCl_3		2002TL3255
11				1997ZNB823
12	$(\text{Me}_3\text{Si})_3\text{P}$			1997ZNB823
13	$(\text{Me}_3\text{Si})_2\text{S}$			1997ZNB823
14	PhPH_2			2003OM910
15		$\text{MesB}(\text{OMe})_2$		2005OL4373
16	$\text{HO}(\text{CH}_2)_3\text{OH}$			2005TL5109
17	$\text{HO}(\text{CH}_2)_3\text{OH}$			2005TL5647

(Continued)

Table 4 (Continued)

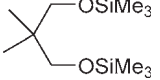
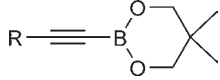
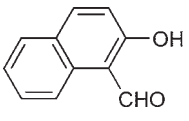
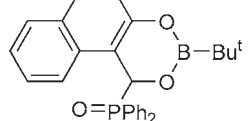
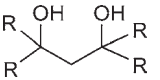
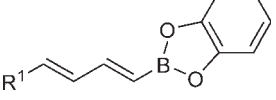
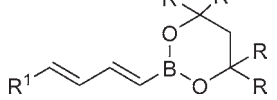
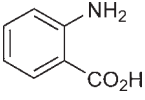
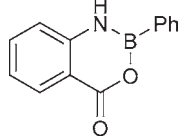
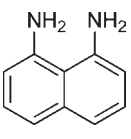
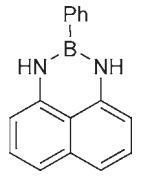
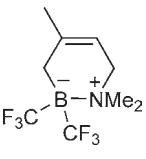
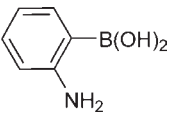
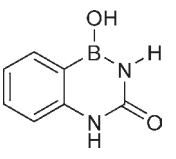
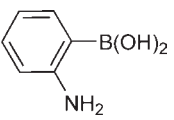
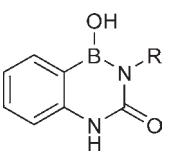
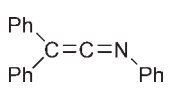
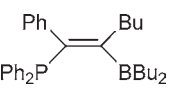
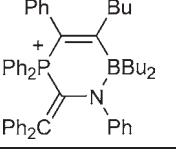
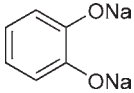
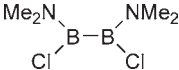
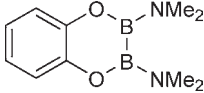
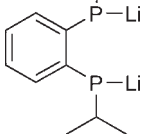
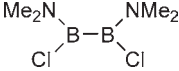
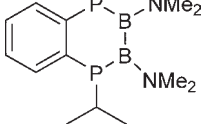
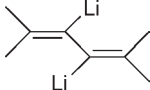
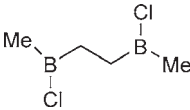
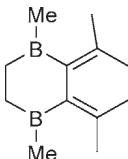
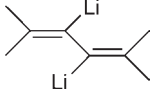
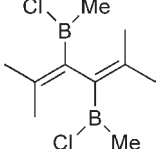
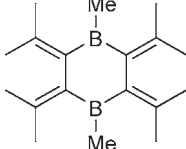
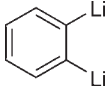
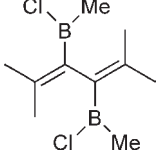
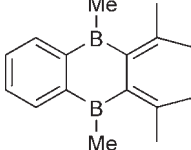
Entry	Substrate	Boron reagent	Boracycle	Reference
18		$R-C\equiv C-B(NPr^i)_2$		1996S45
19	 , Ph_2PH	$(OBu^t)_3$		1995ZOB1979
20				2002TL2317
21		$PhB(OH)_2$		2003CEJ4156
22		$PhB(OH)_2$		2003CEJ4156

Table 5 Two-component synthesis of polyheteroatom six-membered boracycles from 4+2 atom fragments

Entry	Substrate	Boron reagent	Boracycle	Reference
1		$F_3C-B=NMe_2 + F_3C$		2003OM3748
2	KCNO/aq. AcOH			1999JOC9566
3	RNCO			1996JOC4510 1997JOC4492
4				1996IZV183

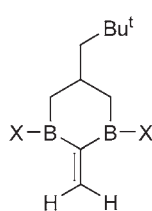
(Continued)

Table 5 (Continued)

Entry	Substrate	Boron reagent	Boracycle	Reference
5				2000NJC115
6				1997CB1677
7				1994ZNB1677
8				1994ZNB1677
9				1995CB183

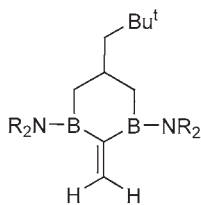
9.19.9.4 [3+3] Two-Component Synthesis

The highly reactive neopentyldiborinane **144** has been obtained from the reaction of $\text{H}_2\text{C}=\text{C}(\text{CH}_2\text{SnMe}_3)_2$ with $(\text{Cl}_2\text{B})_2\text{CHCH}_2\text{Bu}^t$ in toluene. Amination of **144** with $\text{Me}_2\text{NSiMe}_3$ or Pr^i_2NH gave the more stable aminoborinanes **145** <1990ZNB985>. Borylation of trimethylenemethane dianion, $\text{Li}_2[\text{C}(\text{CH}_2)_3]$, provides a versatile starting point for the synthesis of five-, six-, seven-, and eight-membered ring systems including diborinane derivatives **146** <1992CB23>. A similar cyclocondensation reaction of $\text{Me}_2\text{C}=\text{C}(\text{CH}_2\text{SnMe}_3)_2$ with 1,3-bis(dichloroboryl)propane leads to 1,3-dichlorodiborinane **147**, in which the chlorine atoms can be substituted by dimethylamino or methyl groups to yield **148** <1994ZNB465>.

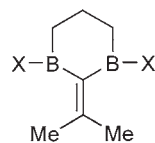


144: X = Cl

145: X = Me_2N , Pr^i_2N



146: R = Me or Et



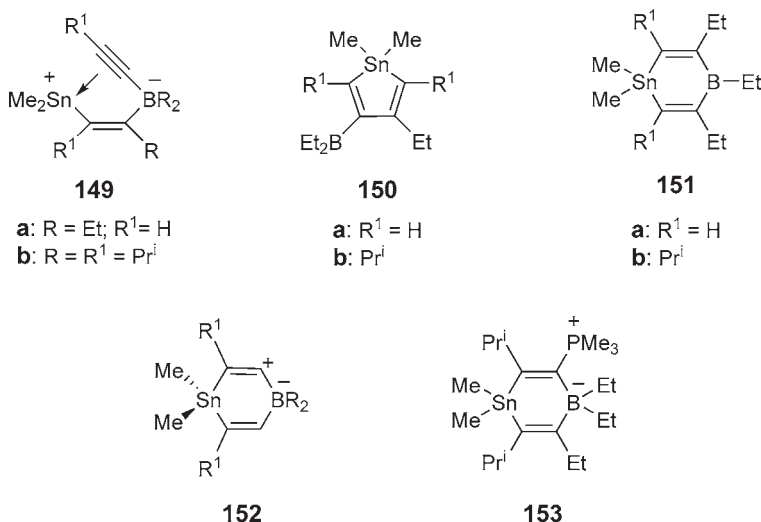
147: X = Cl

148: X = Me or Me_2N

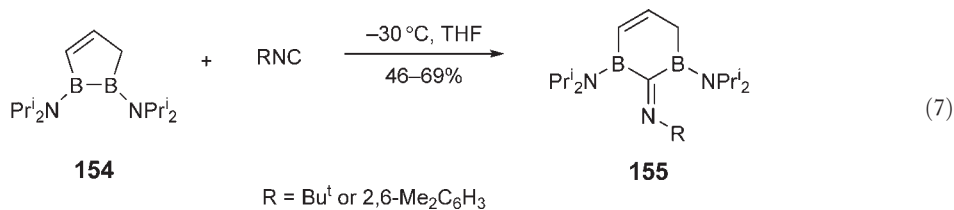
9.19.10 Ring Syntheses by Transformation of Another Ring

The typical approach to 4-borins containing 1-heteroatom substitution involves transmetalation of the corresponding 1-stannacyclohexa-2,5-dienes by dibromo- or dichloroboranes. For example, the use of the tin/boron exchange reaction has been applied successfully to the synthesis of 4-methyl-1,4-thiaboron from 1-thia-4-stannacyclohexa-2,5-diene and dibromomethylborane <1995OM3141>. The radical addition of H_2S , H_2PR , H_2SiR_2 , H_2GeR_2 , and H_2SnR_2 to di-1-alkynylboron compounds $(\text{RC}\equiv\text{C})_2\text{BX}$ provides an alternative method for the preparation of 4-heteroatom-substituted borins <1996CHEC-II(6)1155>.

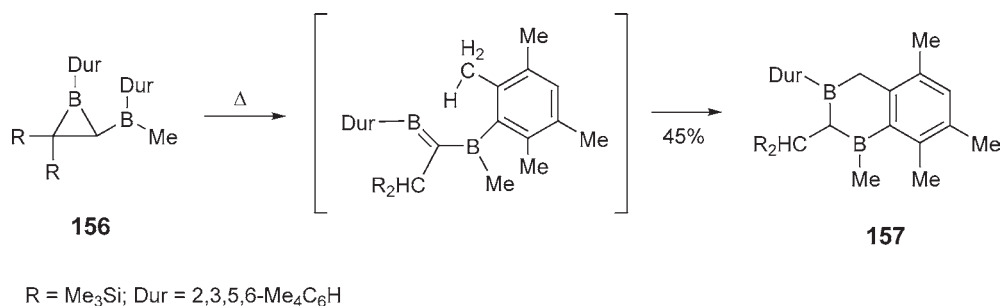
Di-1-alkynyltin derivatives such as $\text{Me}_2\text{Sn}(\text{C}\equiv\text{CR}^1)_2$ react with triorganoboranes R_3B ($\text{R} = \text{Et}$, Pr^i) to give the zwitterionic η^2 -(alkyn-1-ylborate)alkenyltin derivatives **149** in which a cationic three-coordinate tin center is stabilized by intramolecular side-on coordination to the $\text{C}\equiv\text{C}$ triple bond. Without an excess of Et_3B , intramolecular 1,1-vinylboration leading to the stannoles **150** competes with 1,1-ethylboration leading to 1-stanna-4-bora-2,5-cyclohexadienes **151** <1993CB1361, 1994CB333>. Interestingly, the dynamic NMR spectra of compounds **149** are in accordance with an equilibrium in which the alkynyl group migrates between the boron and tin atoms. In the dynamic process, structure **152** represents an extreme case of bridging alkynyl groups. In fact, the reversible reaction of the vinyl cation **152** ($\text{R} = \text{Et}$; $\text{R}^1 = \text{Pr}^i$) with PMe_3 leads to the novel heterocycle **153**, which can be identified by its NMR data as a derivative of **152** containing a vinyl cationic fragment stabilized by C–P coordination <1999JOM93>.



The insertion of isonitriles into the B–B bond of 1,2-diboroles **154** represents a convenient approach to six-membered cyclic organo-1,3-diboranes (Equation 7). The steric demand of the 1,2-diborole **154**, and that of the isonitrile's substituent, both prevent further dimerization of the 2-imino-1,3-diboracyclohex-4-enes **155**. Also reported in this study is rearrangement of **155** into 1-boracyclopent-3-enes in the presence of water <1998EJI459>.

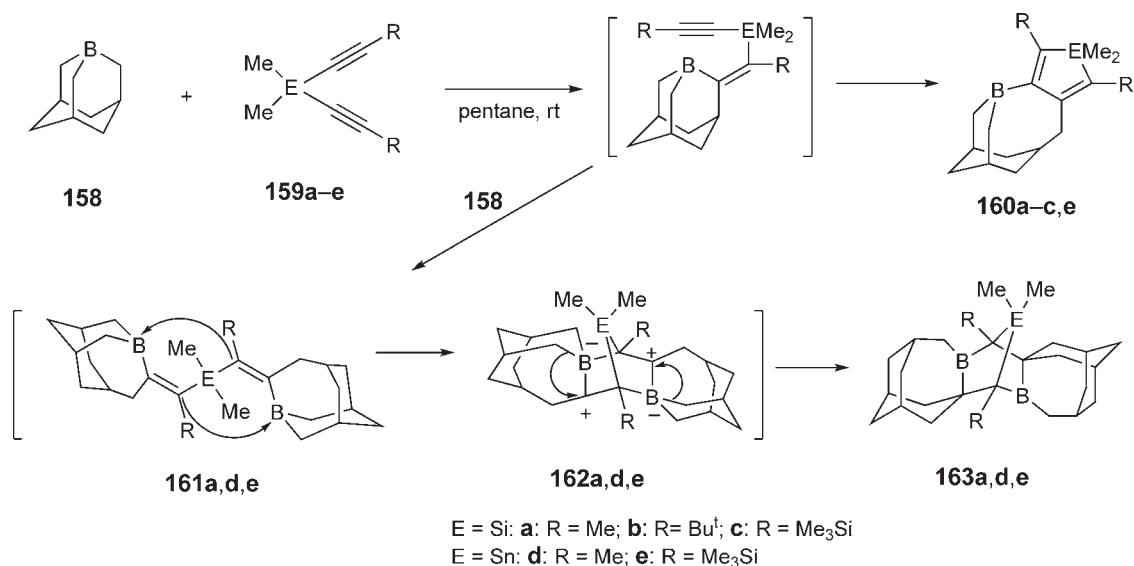


Borylborirane and methyleneborane derivatives also are important substrates in ring expansion reactions leading to 1,3-diboracyclohexanes. Berndt's group has demonstrated that borirane **156** undergoes thermal B–C cleavage to give tetrahydrodiboranaphthalene **157** (Scheme 21) <1992AGE1384>. The precise mechanism of this transformation is unknown but likely involves an intramolecular C–H bond addition to the $\text{C}=\text{B}$ bond.



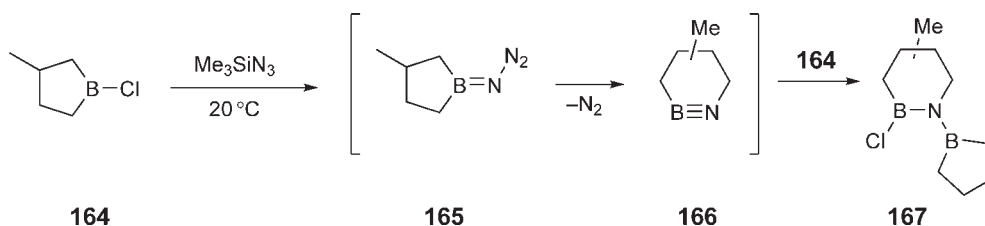
Scheme 21

First access to the novel octacyclic 7-metalla-2,5-diboranorbornane derivatives **163**, based on reactions of 1-boraadamantane **158** with di-1-alkynylsilicon **159a–c** and tin **159d** and **159e** compounds, was disclosed recently by Wrackmeyer *et al.* <2001CEJ775>. As shown in Scheme 22, there is competition between the 1:1 and 2:1 reactions and, depending on the reaction conditions, a mixture of the silole or stannole derivatives **160** and octacyclic compounds **163** is formed. Thus, when di-1-alkynylsilane **159a** was added to 1-boraadamantane at room temperature, a 40:60 mixture of the silole **160a** and the diboranorbornene **163a** was formed. The presence of a bulky group such as Bu^t or Me₃Si on the C≡C groups makes the second intermolecular 1,1-organoboration slower than the intramolecular reaction. Therefore, the reactions of **159b** and **159c** with **158** give the siloles **160b** or **160c**, exclusively. However, since the 1-alkynyltin compounds are much more reactive toward trialkylboranes than their silicon analogues, 7-stanna-2,5-diboranorbornane derivative **163d** is formed selectively from **159d**, and the reaction of **159e** with **158** affords a mixture of **160e** and **163e** in a 60:40 ratio. According to semi-empirical AM1 calculations, **163a** is more stable than **161a** by 18.9 kcal mol⁻¹ and **162a** is higher in energy than **161a** by 28 kcal mol⁻¹.



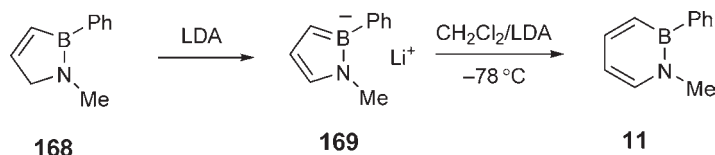
Scheme 22

The only product that is formed from the reaction of 1-chloro-3-methylboracyclopentane **164** with Me₃SiN₃ at room temperature is the six-membered 1,2-azaborinane **167**. Its formation can be rationalized by assuming that the azidoborane **165** is an intermediate; the latter decomposes rapidly into **166**, which is chloroborated by excess **164** (Scheme 23) <2004ZFA2641>.



Scheme 23

Reaction of *in situ*-generated chlorocarbene with substituted 1,2-azaborolides is an important method for the production of 1,2-dihydro-1,2-azaborines. An example is the preparation of compound **11** from lithium 1,2-azaborolide **169**. The optimized method involves the addition of excess CH_2Cl_2 to solid **168** at -78°C followed by treatment with 1 equiv of lithium diisopropylamide (LDA) in ether. On workup, **11** was isolated in 64% yield (Scheme 24) <2001OM5413>. A similar ring expansion route was used to prepare 1-phenyl-1,2-azaboratabenzene <2004OM5626>.



Scheme 24

The [2+2] cycloadducts **171a** and **171b**, accessible from the reaction of aminoborane **170** with the corresponding isocyanates, are transformed easily into the stable four-membered heterocycles **172a** and **172b**. In contrast, the initially formed [2+2] cycloadducts **171c–e**, bearing aromatic substituents ($\text{R} = 4\text{-XC}_6\text{H}_4$, $\text{X} = \text{H}, \text{Me}, \text{OMe}$), undergo two different rearrangements. While one pathway is the same as that for **171a** and **171b** and leads to species of type **172**, the other route leads to bicyclic heterocycles of type **173** (Scheme 25) <1997OM5321>.

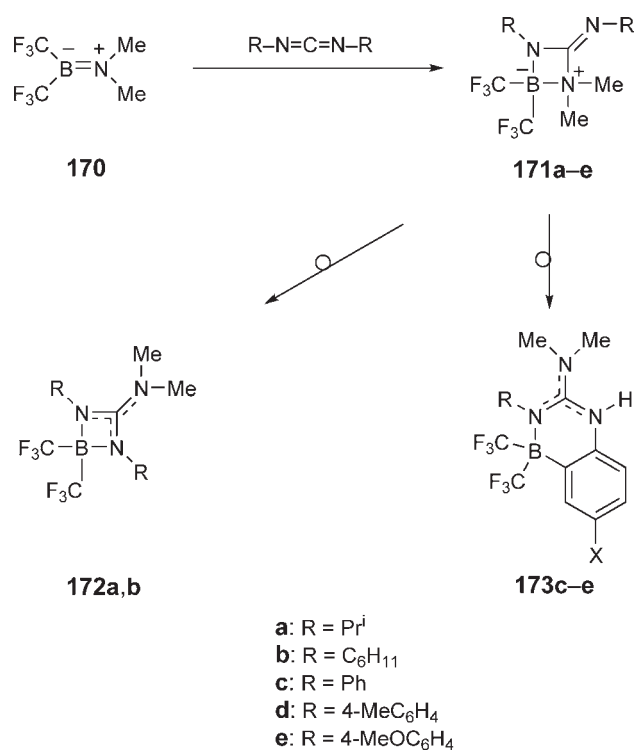
Ring opening of 1,3-dioxanes **174** by boronate esters, followed by ring closure of the resultant bipolar derivatives, is a potentially attractive route to 1,3,2-dioxaborinanes (Scheme 26) <1995KGS160, 1996ZOB270>. Reactions between boronate esters and 1,3-dioxo-2-silacyclohexane **175** <1997RJO1674>, 1,3-dioxo-2-germacyclohexane **176** <1999RJC1842>, 1,3-dioxo-2-arsenacyclohexane 2-oxide **177** <2000RJC812>, and 1,3,2-dioxathian 2-oxide **178** <2000RJO292> lead to the corresponding 1,3,2-dioxaborinanes in low yields.

9.19.11 Synthesis of Particular Classes of Compounds

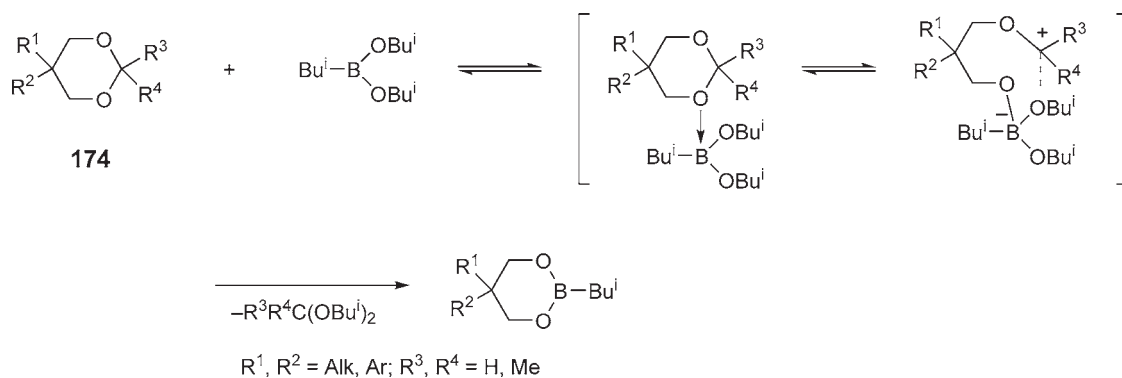
9.19.11.1 1,3,5-Triboracyclohexanes

Compounds of this class were not reviewed in CHEC(1984) and CHEC-II(1996) and, accordingly, for completeness, this section includes references to older work. In general, six-membered heterocycles containing the C–B–C–X fragment (X is any heteroatom) in which the C–B bonds are simple two-center two-electron bonds are rare; much more common are the polyhedral carboranes where multicenter bonding predominates. Nevertheless, several stable representatives of 1,3,5-triboracyclohexanes are known.

More than 40 years ago Köster and Benedikt <1964AG650> published the synthesis of the 1,3,5-triboracyclohexane, *cyclo*-(EtBCH₂Et)₃, and some years later Kromer and Goubeau <1971CB1347> reported chloro- and dimethyl-amino-substituted 1,3,5-triboracyclohexanes, *cyclo*-(ClBCH₂Me)₃ and *cyclo*-(Me₂NBCH₂Me)₃. More recently, Siebert and co-workers have carried out systematic studies of the synthesis of 1,3,5-trihalogeno-1,3,5-triboracyclohexanes <1997ZN823>. Attempts were made to obtain *cyclo*-(ClBCH₂Me)₃ by the hydroboration of acetylene with

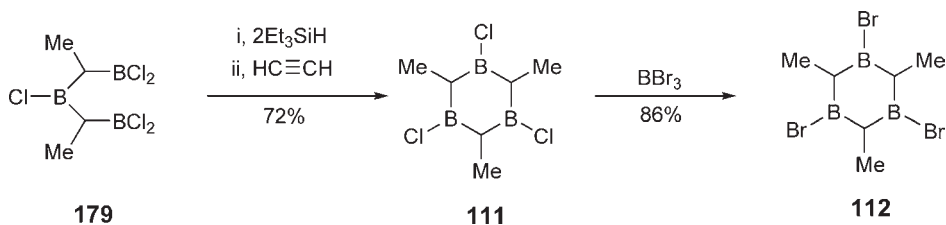


Scheme 25

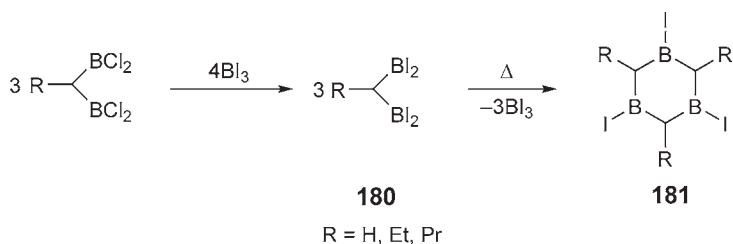


Scheme 26

$\text{HSiMe}_3/\text{BCl}_3$ at -78°C in hexane, but the yields were low. However, this compound can be prepared readily from the reaction of the triborapentane **179** with 2 equiv of triethylsilane, followed by double hydroboration of acetylene. Reaction of **111** with BBr_3 provides the corresponding bromo derivative **112** (Scheme 27) <1997ZNB823>. The iodo derivatives **181** are available by heating 1,1-bis(diiodoboryl)alkanes **180** under reduced pressure (Scheme 28) <2004ZNB782>. Starting with bis(dichloroboryl)- and bis(dibromoboryl)methane, only small amounts of the trimerization cyclic products $(\text{H}_2\text{CBCl})_3$ and $(\text{H}_2\text{CBBr})_3$ were obtained, which could not be separated from by-products.



Scheme 27

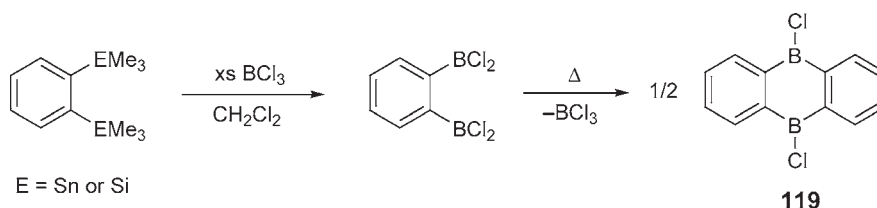


Scheme 28

The reactivity of 1,3,5-triboracyclohexanes has also seen some development. Methylation of compound **110** with Al_2Me_6 yields hexamethyl-1,3,5-triboracyclohexane, $\text{cyclo}-(\text{MeBCHMe})_3$ <1997ZNB823>. This compound undergoes reduction with alkali metals in donor solvents to form the trishomoaromatic cyclotriborate derivatives <2001EJI1949, 2000AGE1276>. Treatment of 2-isopropylidene-1,3,4,5,6-pentamethyl-1,3,5-triboracyclohexane with $\text{CpCo}(\text{C}_2\text{H}_4)_2$ gives the $\mu\text{-}\eta^6\text{-}\eta^6$ -1,3,5-triboratabenzene bis(cyclopentadienylcobalt) triple-decker complex <1995AGE681>.

9.19.11.2 9,10-Dihydro-9,10-diboraanthracenes

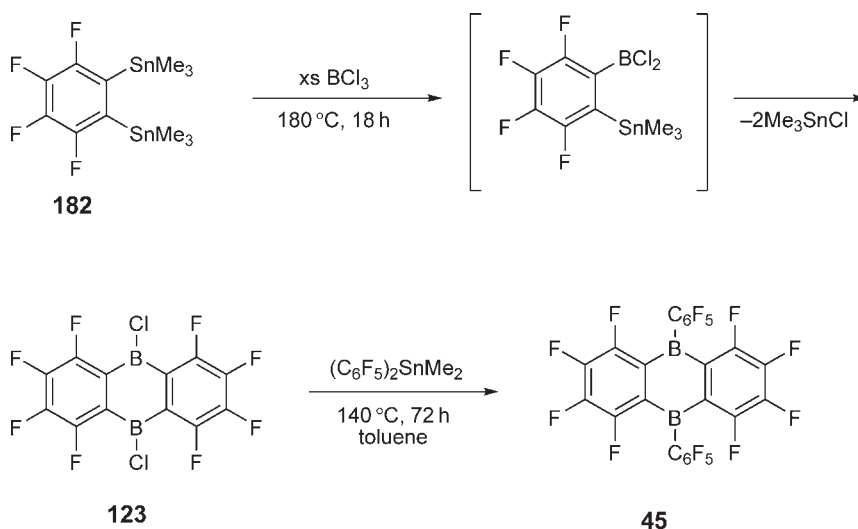
Many reports have appeared in the literature since 1995 featuring compounds of this class. The thermolysis of 1,2-bis(boryl)benzenes was, and still is, the most common procedure for the synthesis of 9,10-dihydro-9,10-diboraanthracenes. Scheme 29 demonstrates the utility of this route in preparing diboraanthracene **119** bearing chlorine substituents. The precursors, containing two Me_3Sn or Me_3Si groups, can be obtained from the corresponding organyl dibromides or dichlorides via organomagnesium intermediates in the presence of Me_3SnCl or Me_3SiCl <1998EJI761>. The iodo analogue of **119**, 9,10- $\text{I}_2\text{C}_{12}\text{B}_2\text{H}_8$, is formed in the direct reaction of 1,2-diiodobenzene with BI_3 , and its molecular structure was determined by X-ray analysis <1995SM1109>. The nearly planar skeleton of the molecule suggests that the central six-membered boron-containing ring is conjugated with the outer two benzene rings. Thus, the $2p_z$ -orbitals of two boron atoms should act as electron acceptors <1996AXC991>.



Scheme 29

The reactivity of the 9,10-dichloro- and 9,10-diiodo-diboranthracenes toward organic nucleophiles has been explored [\[1995ZNB1476, 1995SM1109\]](#).

The synthesis, characterization, and unusual properties of perfluorodiboranthracene **45**, including significantly enhanced Lewis acidity and cocatalytic olefin polymerization activity, has been described independently by Marks and co-workers [\[2000AGE1312, 2002OM4159\]](#) and Collins and co-workers [\[1999AGE3695\]](#). Parent dichlorodiboranthracene **123** was prepared by reaction of distannyl precursor **182** with BCl_3 . Treatment of **123** with 1 equiv of $(\text{C}_6\text{F}_5)_2\text{SnMe}_2$ [\[2000AGE1312\]](#) or $\text{Zn}(\text{C}_6\text{F}_5)_2$ [\[1998CJC513\]](#) yields the diboranthracene **45** as a pale yellow, air-sensitive crystalline solid (Scheme 30). X-Ray diffraction analysis of **45** reveals a nearly planar $\text{C}_{12}\text{F}_8\text{B}_2$ core with C_6F_5 rings rotated 75° out of the plane, hindering π -conjugation between the pendant C_6F_5 substituents and the $\text{C}_{12}\text{F}_8\text{B}_2$ core, and thereby enhancing Lewis acidity of the boron centers. In regard to the Lewis acidity of **45**, equilibration studies with $\text{CH}_3\text{CN} \cdot \text{B}(\text{C}_6\text{F}_5)_3$ indicate that **45** is a stronger Lewis acid than $\text{B}(\text{C}_6\text{F}_5)_3$ [\[2002OM4159\]](#).



Scheme 30

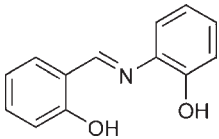
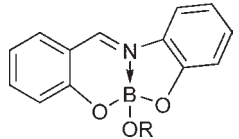
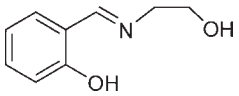
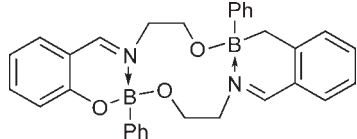
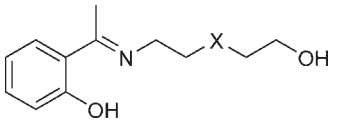
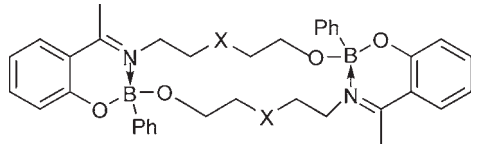
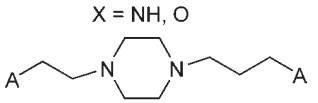
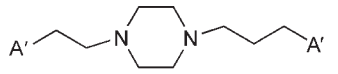
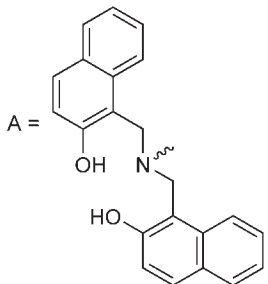
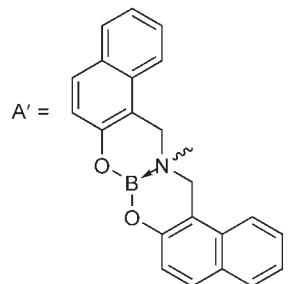
9.19.11.3 Chelate Ring Systems

There are hundreds of compounds known containing six-membered chelate boracycles. The methods to prepare them have not developed much beyond those described in CHEC-II(1996) [\[1996CHEC-II\(6\)1155\]](#), but some new variations of reagents and experimental conditions have been described. Table 6 provides references that should be consulted for further information.

Table 6 Synthesis of six-membered ring chelates containing boron

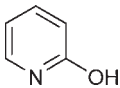
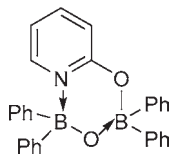
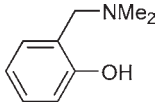
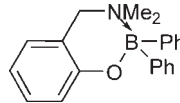
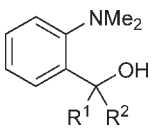
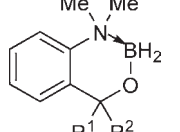
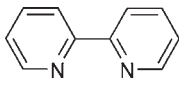
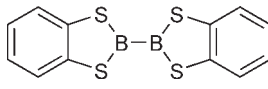
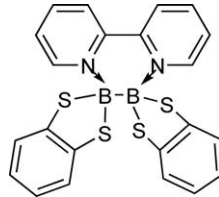
Entry	Substrate	Boron reagent	Boracycle	Reference
1		9-BBN, alk. H ₂ O ₂		2004JFC975
2		KHF ₂		1996JOC4510
3		9-BBN		1997JOM323
4		NaBO ₂		2005T1765
5		BF ₃ ·OEt ₂		2004RCB1924
6		BF ₃ ·OEt ₂		2001RJC1562

(Continued)

13		$B(OR)_3$		1998IC4934
14		$ArB(OH)_2$		1997JOM71 1999JOM70 2000JOM273
15		$PhB(OH)_2$		2004ICA2593
16	$X = NH, O$ 	$B(OMe)_3$		2000JOM215
	$A =$ 		$A' =$ 	

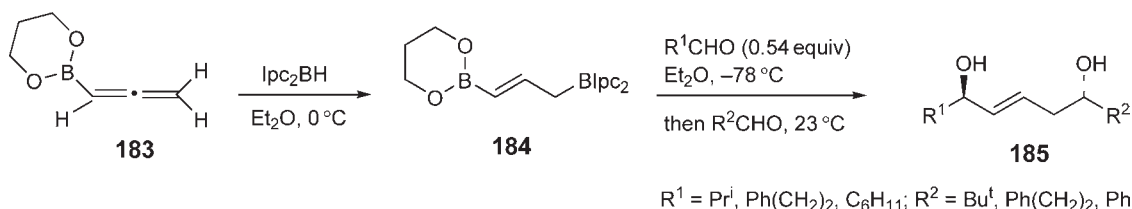
(Continued)

Table 6 (Continued)

Entry	Substrate	Boron reagent	Boracycle	Reference
17		Ph ₂ BOH		1999KGS1041
18		Ph ₂ BOH		2000JOM27
19		BH ₃ ·THF		2004IC7162
20				1998POL4139

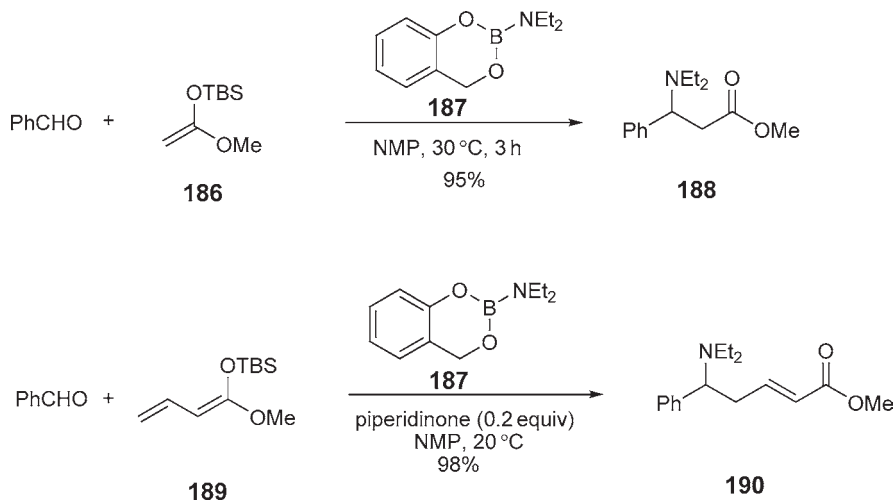
9.19.12 Important Compounds and Applications

The utility of 1,3,2-dioxaborinanes and related boracycles in organic synthesis is well established and several recent reviews cover parts of the literature [\[2001JOM259, 1999JOM\(581\)51, 1998T10555\]](#). Most of the work in this area in the decade 1995–2005 has centered on the use of boronic esters in stereoselective synthesis, often with the goal of preparing enantiomerically pure compounds. Thus, the synthetic potential of the 1,3,2-dioxaborinanyl group was demonstrated further by enantioselective synthesis of (*E*)-1,5-*anti*-diols **185** using a highly diastereoselective one-pot double allylboration reaction sequence. Coupling of two different aldehydes with (*E*)-[γ -(1,3,2-dioxaborinanyl)allyl]-diisopinocampheylborane **184**, generated by hydroboration of 2-allenyl-1,3,2-dioxaborinane **183** with diisopinocampheylborane, [(Ipc)₂BH]₂, gave diols **185** in 65–87% yield with 89–96% ee and $\geq 20:1$ diastereoselectivity ([Scheme 31](#) [\[2002JA13644\]](#)).



Scheme 31

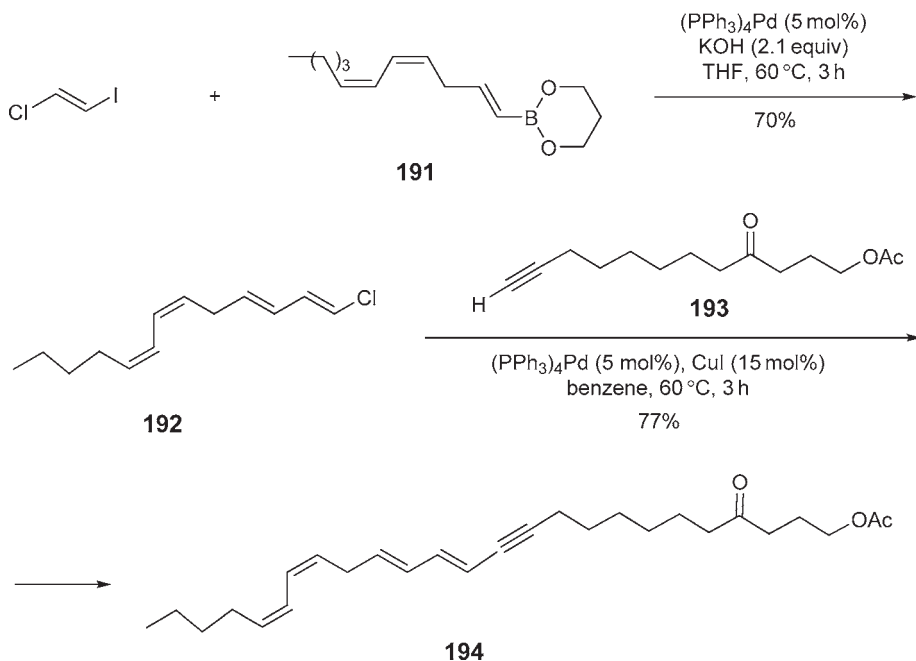
1,3,2-Dioxaborinanes are highly efficient and mild iminium ion generators in the Mannich-type aminative coupling of aldehydes with silyl ketene acetals. For example, a three-component reaction of silyl ketene acetal **186** with benzaldehyde in the presence of 1,2,3,4-tetrahydro-1,3,2-dioxaboranaphthalene **187** gives the corresponding product **188** in high yield. The vinylogous Mannich reaction with silyl ketene acetal **189** was also examined. In this case, only the γ -addition product **190** with *trans*-geometry was obtained ([Scheme 32](#) [\[2004JA13196\]](#)).



Scheme 32

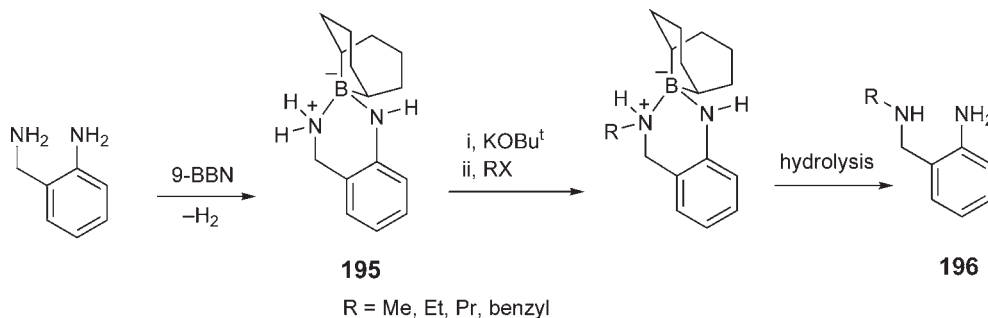
The Suzuki coupling of 1,3,2-dioxaborinanes to aryl and vinyl halides provides a very useful method for the construction of C–C bonds [\[1996CHEC-II\(6\)1155\]](#). This process has been applied recently in the synthesis of

naturally occurring ant venom (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacos-13,15,18,20-tetraen-11-yn-4-one 1-acetate **194** <2004JOC695>. Selective Suzuki coupling of (*E*)-1-chloro-2-iodoethylene with dioxaborinane **191** gave tetraene **192**, which then underwent Sonogashira coupling with **193** to give the target product (**Scheme 33**).



Scheme 33

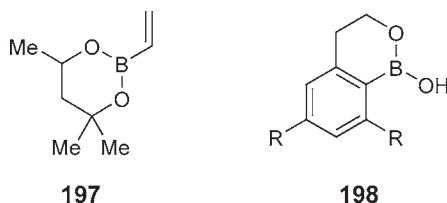
A convenient synthesis of 2-amino-*N*-alkylbenzylamines **196** by direct mono alkylation of 2-aminobenzylamine has been achieved by a potassium *tert*-butoxide/alkyl halide treatment of the 9-borabicyclo[3.3.1]nonane (9-BBN) aminoborane derivative **195**. This method relies on formation of a stable chelate, which serves in the dual roles of protecting and activating the amino group (**Scheme 34**) <1998TL2643>. A similar approach has been used for selective mono-*N*-alkylation of 1,8-diaminonaphthalene <1997JOC6682> and amino alcohols <2004OL3549>.



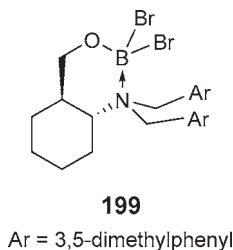
Scheme 34

4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane **197** was found to be a superior reagent in terms of stability and reactivity in comparison to the vinylboronate pinacol ester. It gave improved selectivity for Heck versus Suzuki

coupling with both aryl iodides and bromides <2003TL7645>. The same compound was proposed as a genuine two-carbon vinyl-dianion building block in stereocontrolled polyene syntheses <2005OBC3167>. 1-Hydroxy-1,2,3,4-tetrahydro-2-oxa-1-boranaphthalenes **198** have been used for the purpose of controlling the stereochemistry of organic reactions. These boronic acids recognize α - and β -anomers of 2-deoxyribofuranosides and have been employed for stereoselective reduction of acyclic and cyclic β -hydroxy ketones <1996CL537>.



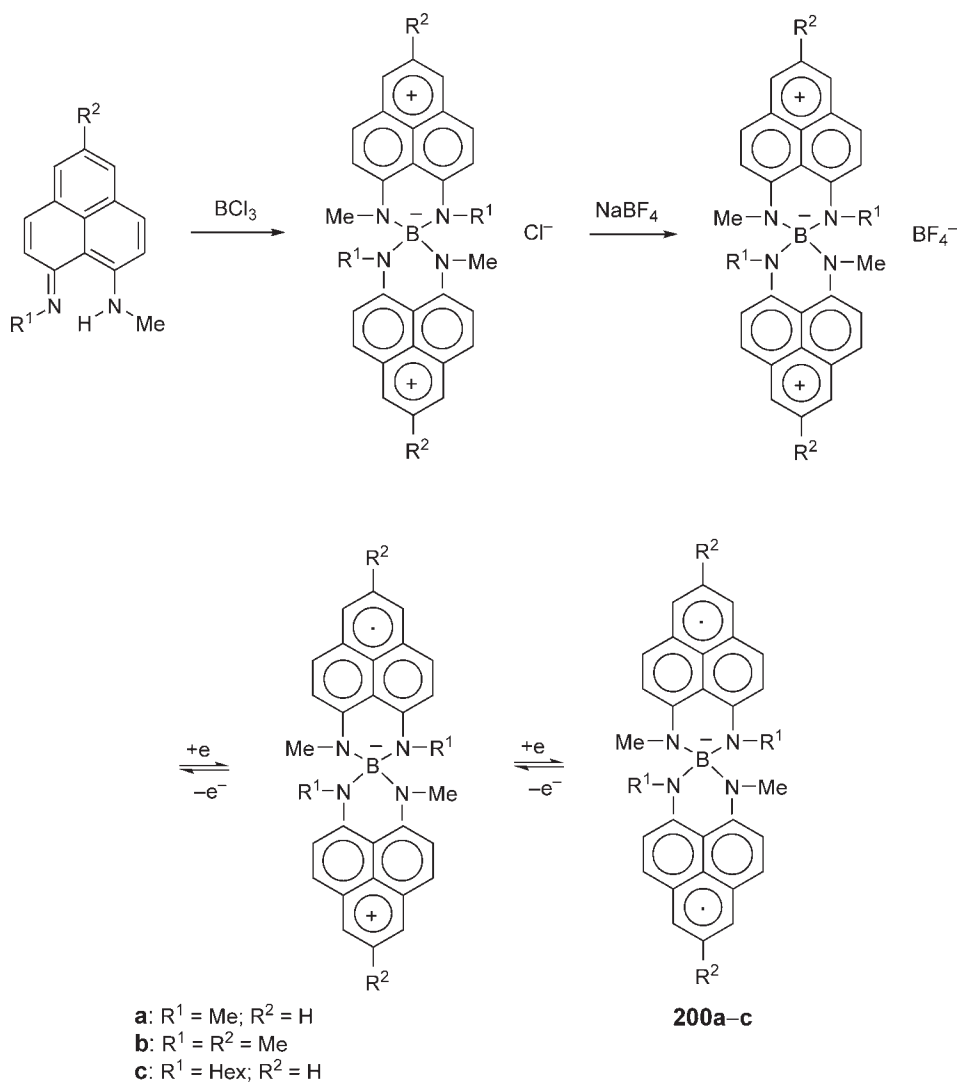
Lewis acid properties and single-site olefin polymerization characteristics of catalyst systems utilizing the binuclear organo-Lewis acid cocatalyst 9,10-bis(pentafluorophenyl)-9,10-diboraoctafluoroanthracene **45** have been studied <2002OM4159, 1999AGE3695>. When **45** is paired with di-Me organo-group 4 catalyst precursors, it affords extremely efficient single-site olefin polymerization systems in both laboratory and large-scale reactors. In all cases, **45** forms polymerization systems with higher activities than those utilizing $B(C_6F_5)_3$ as the cocatalyst. 1,3,2-Oxazaborinane **199** is another example of very strong chiral Lewis acid. Its utility has been demonstrated in Diels-Alder reactions with both reactive and unreactive 1,3-dienes <1996JA5502>.



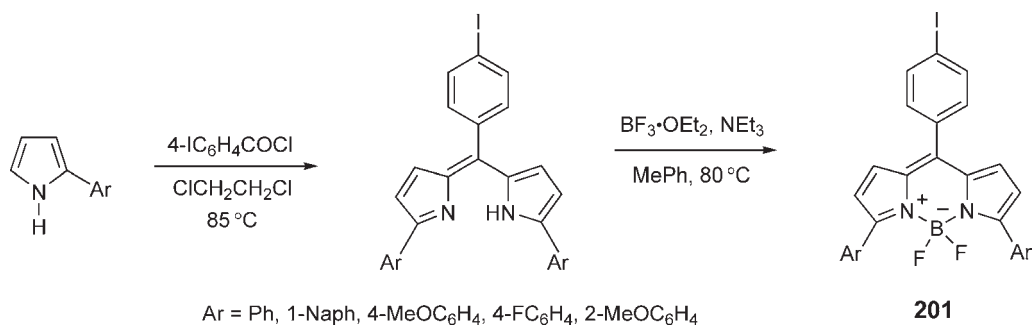
1,3,2-Dioxaborines are potential components in advanced materials. The EAs of various substituted 1,3,2-dioxaborines are of the same order of magnitude as those of quinones and close to the EAs of strong organic acceptor compounds such as tetracyanoethylene <2004JPO359>. A new family of spiro-bis(1,9-disubstituted-phenalenyl)-boron neutral radicals **200** based on the N,N'-ligand system has been developed (Scheme 35) <2005JA8185>. Two of these radicals are among the most highly conducting neutral organic solids, with room temperature conductivities reaching $\sigma_{rt} = 4 \times 10^{-2} \text{ S cm}^{-1}$.

The bidentate diborane **126** selectively complexes fluoride anion (see Scheme 13) with an association constant $>5 \times 10^9 \text{ M}^{-1}$ in THF, and can serve as a colorimetric anion sensor <2004CC1284>. Four-coordinate boron N-heterocycle complexes (L-N,N')BPh₂ exhibit luminescence and electroluminescence in a broad range of visible wavelengths depending on the substituents on the chelate heterocycle <2005MI143>.

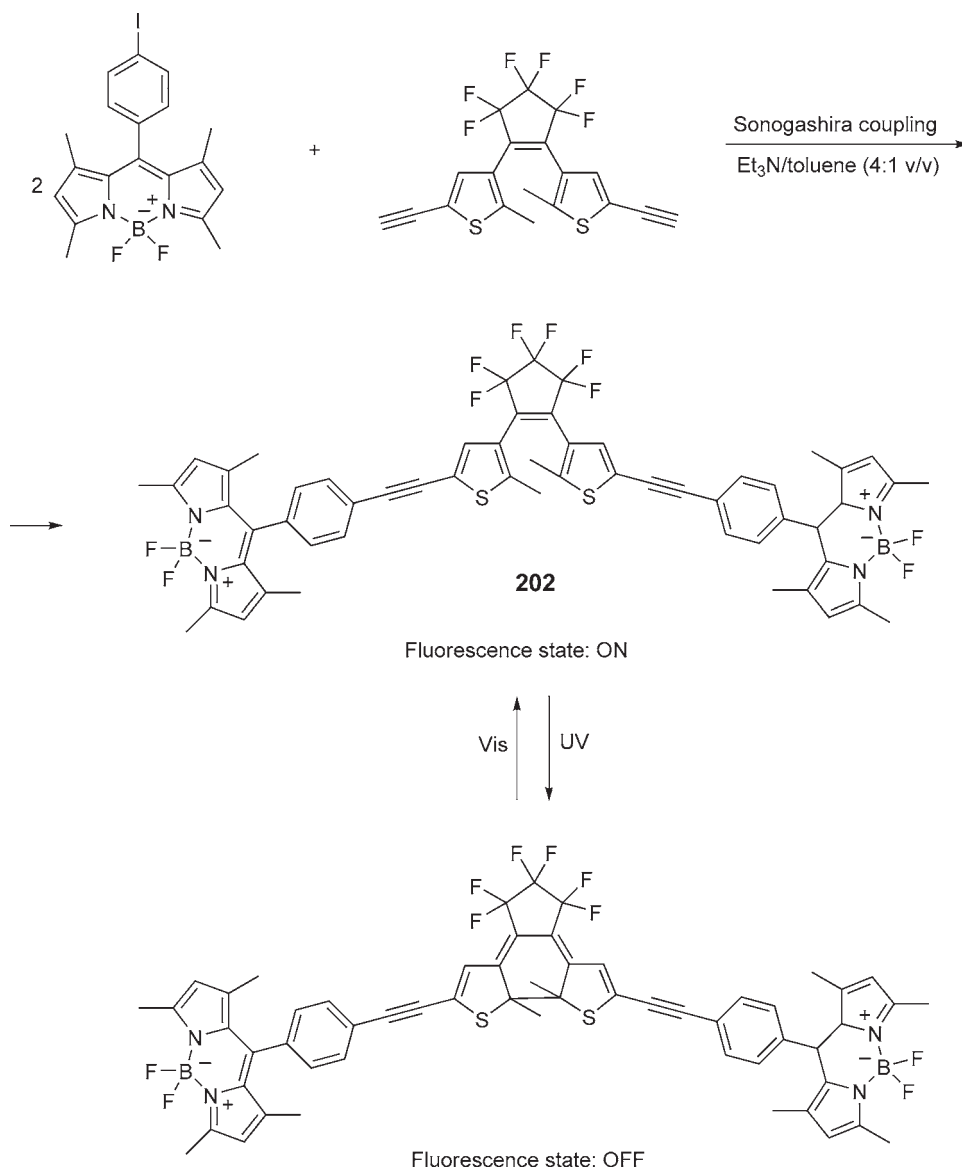
4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY dye) and its derivatives are highly fluorescent materials that have found numerous applications in molecular biology as well as in the development of molecular devices <2005T2683, 2004JA1772, 2004TL1949, 2004JA3357, 2004JOC2070, 1999TL1471, 1999TL5199, 1999CC1889, 1999JOC7813, 1998JA10001, 1998SL1276>. The attractive properties of these dyes include high molar extinction coefficients, high fluorescence quantum yields, insensitivity to solvent polarity, and a tunable emission range. Scheme 36 depicts the synthetic route that was used for the preparation of 3,3-diaryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene dyes **201** <1999JOC7813>. It is easy to modify BODIPY chemically for the preparation of compounds with potential technical utility. For example, the fluorescent switch **202** containing photochromic dithienylethene units linked to derivatized 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene was synthesized from 4,4-difluoro-8-(4'-iodophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene and dithienylethene by Sonogashira coupling. Covalently linking BODIPY dyes to photochromic dithienylethenes allows formation of new photoswitches that are highly emissive as open-ring isomers and in which the fluorescence is significantly quenched in the closed-ring isomers (Scheme 37) <2005JOC5545>.



Scheme 35



Scheme 36



Scheme 37

Many other compounds with modified BODIPY structures have been prepared to provide highly sensitive fluorescence probes for nitric oxide [\[2004JA3357\]](#), fluorescence-labeled lipid A analogues [\[1999TL5199\]](#), new water-soluble amine reactive reagents for labeling biomolecules [\[1999TL1471\]](#), stable and highly luminescent pyridine-, bipyridine-, phenanthroline-, bipyrimidine-, and terpyridine-based ligands [\[2004JOC2070, 2004TL1949\]](#), photostable photosensitizers [\[2005JA12162\]](#), and dialkynyl borane complexes for ‘cascadelle’ energy transfer and protein labeling [\[2005AGE3694\]](#). Two fluorescence off-on Ca^{2+} indicators based on *o*-aminophenol-*N,N,O*-triacetic acid (APTRA) as a low-affinity ligand for Ca^{2+} and BODIPY as a fluorophore have been developed [\[2005OBC2755\]](#). Novel dyads in which a porphyrin ring is directly fused through two β -pyrrolic carbons to a BODIPY moiety were prepared using a stepwise approach starting from the Cu(II) complex of pyrrolo[2,3-*c*]-5,10,15,20-tetraphenylporphyrin. Luminescence spectra displayed a very intense band around 700 nm, making these species suitable as near-infrared dyes and sensors in biological media [\[2004T1099\]](#).

Finally, new cyclic oligoboronates were prepared and their possible applications in supramolecular host–guest chemistry were discussed [\[1997JOM71, 1999JOM70\]](#).

9.19.13 Further Developments

Computational studies of [2+2] and [4+2] pericyclic reactions between phosphinoboranes X_2BPY_2 and alkenes have been reported. Phosphinoborane $(F_3C)_2BPBu^t_2$ is predicted to undergo facile [4+2] cyclization with *cis*- C_4H_6 and ϵ - C_5H_6 with barriers of $<10 \text{ kcal mol}^{-1}$ and exothermicities of $>30 \text{ kcal mol}^{-1}$. It thus represents a candidate for synthesis and subsequent reactions <2007OM2672>.

Ab initio and DFT calculations on 1,2-dihydro-1,2-oxaborine suggested that this boron–oxygen heterocycle has considerable aromatic stabilization <2001MC43>. To test this hypothesis experimentally, a new synthesis of 1,2-dihydro-2-phenyl-1,2-oxaborine has been developed. Preliminary investigation of the chemistry of this compound suggests that the 1,2-dihydro-1,2-oxaborine ring is aromatic, as had been predicted by calculations <2007OM1563>.

Although the aromatic nature of Dewar's BN-phenanthrene has been contested in the literature, Piers group has employed recently nucleus independent shift calculations (NICS) as effective means of evaluating the aromaticity of various heterocyclic rings <2006JA10885>. Thus, the resulting NICS(1) values determined for 4a-aza-4b-boraphenanthrene suggested reasonably high aromatic character for both the C_5N (−9.5) and C_5B (−8.7) rings, whereas the outer C_4BN ring (−6.3) was observed to possess slightly reduced aromaticity. Similar trends were observed for the isomeric Dewar's BN-phenanthrene (C_6 , −10.0 and −10.4; C_4BN , −4.6) as well as for the all-carbon phenanthrene (inner, −10.7; outer, −8.2), which suggests similar aromatic behavior for all three phenanthrene species. The incorporation of B–N moieties into polycyclic aromatic hydrocarbons (PAHs) such as triphenylene, pyrene or phenanthrene can dramatically alter the photophysical properties of the resulting materials. For example, phenanthrene analogues with internalized B–N moieties were found to afford blue light emission with good quantum efficiencies, whereas the isomeric species with peripheral B–N moieties displayed only UV emission behavior, like the all-carbon framework <2007OL1395>.

The reaction of borane methyl sulfide with 2-amino-2-methylpropan-1-ol has been studied. Instead of the expected five-membered oxazaborolidine derivatives, two polycyclic structures with NBN and OBN moieties were obtained, and their structures were determined by X-ray crystallography <2006JOM1993>.

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Biographical Sketch



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